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Micormedex NeoFax Essentials 2020

Acetaminophen
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
Intravenous
Fever
Gestational age 32 weeks or more: 12.5 mg/kg/dose IV every 6 hours up to a MAX 50
mg/kg/day of all routes of administration [1].
Fever/Pain
Oral
Preterm infants less than 32 weeks Postmenstrual Age: 20 to 25 mg/kg orally; then
12 to 15 mg/kg/dose every 12 hours as needed or around-the-clock.
Preterm infants greater than or equal to 32 weeks Postmenstrual Age: 20 to 25

mg/kg orally; then 12 to 15 mg/kg/dose every 8 hours as needed or around-the-clock.
Term infants: 20 to 25 mg/kg orally; then 12 to 15 mg/kg/dose every 6 hours as needed or around-the-clock.
Rectal
Preterm infants less than 32 weeks Postmenstrual Age: 30 mg/kg rectally; then 12 to 18 mg/kg/dose every 12 hours as needed or around-the-clock.
Preterm infants greater than or equal to 32 weeks Postmenstrual Age: 30 mg/kg rectally; then 12 to 18 mg/kg/dose every 8 hours as needed or around-the-clock.
Term infants: 30 mg/kg rectally; then 12 to 18 mg/kg/dose every 6 hours as needed or around-the-clock.
Closure of Patent Ductus Arteriosus
Oral
Preterm infants: 15 mg/kg/dose orally every 6 hours for 3 days [2]; a second course may be required [3].
Uses
Closure of patent ductus arteriosus (PDA): NSAIDs (indomethacin and ibuprofen) are the standard drugs for closure of PDA. However, there are risks to NSAIDs and there is a high rate of spontaneous closure; therefore, treatment should be limited to select preterm newborns with symptomatic PDA [7][8]. Acetaminophen may be a treatment option in those having NSAID failure or contraindications to NSAIDs [9]. IV acetaminophen may be an option in those who have a contraindication to feeding, or who have feeding intolerance [10][3].
Oral acetaminophen appears as effective as ibuprofen, but long-term safety trials are needed [2].
IV acetaminophen vs. placebo: More preterm infants experienced closed ductus arteriosus in the acetaminophen group compared with placebo group (HR 0.49 (95% CI, 0.25 to 0.97)) in a double-blind, randomized, phase I to II study (n=48). Ductal closure was observed at a mean postnatal age of 177+/-338 hours for the acetaminophen group and 336+/-517 hours for the placebo group. The mean gestational age and birth weight were

28.4 weeks and 1.22 kg in the acetaminophen group and 28.3 weeks and 1.12 kg in the placebo group. The dosage was 20 mg/kg IV for 1 dose, followed by 7.5 mg/kg/dose IV every 6 hours for 4 days of acetaminophen [11].

Acetaminophen vs Ibuprofen vs Indomethacin: Acetaminophen IV is as effective as indomethacin IV and ibuprofen (at standard doses) IV in the closure of PDA in preterm infants (gestational age less than 28 weeks) with hemodynamically significant PDA in a randomized study (n=300). After the first treatment course, the closure rates were 80%, 77%, and 81% for acetaminophen, ibuprofen, and indomethacin, respectively. Adverse effects (increase in serum creatinine and serum BUN and decrease in platelet count and urine output) were significantly more with ibuprofen and indomethacin than acetaminophen. Bilirubin significantly increased with ibuprofen. The mean weights were 1.1 kg, 1 kg, and 1.1 kg in the infants treated with acetaminophen, ibuprofen, and indomethacin, respectively [12].

Oral acetaminophen vs. oral ibuprofen: In an open-label, randomized trial (n=80), there was no difference in ductal closure rate (72.5% vs 77.5%) in preterm infants (30 weeks or less gestational age; 1250 g or less) administered a first course of oral acetaminophen compared with oral ibuprofen within 48 to 96 hours after birth with hemodynamically significant PDA. The doses were 15 mg/kg/dose every 6 hours for 3 days of acetaminophen and 10 mg/kg followed by 5 mg/kg/dose 24 and 48 hours later of ibuprofen; each dose was administered via an orogastric tube and flushed with 1 to 2 mL of sterile water. Reopening and subsequent closure with a second course occurred in 24.1% versus 16.1% of patients. Bilirubin levels and renal and liver function tests before and after the first and second course of each drug did not differ significantly within or between groups [3].

Case-series: Several case-series demonstrate ductal closure in preterm infants (n=30; 23 to 36 weeks gestational age; 590 to 990 g birth weight). Dose regimens were either 15 mg/kg/dose every 6 hours for 3 days or 10 mg/kg/dose every 8 hours for 3 days. Treatment durations were extended up to 7 days for persistent hemodynamically PDA [10][13][9][14].

Fever reduction and treatment of mild to moderate pain: The decision to use acetaminophen should be weighed against the epidemiological evidence of an association between acetaminophen use and asthma, atopy, rhinoconjunctivitis, or eczema; although causality has not been established [15][16][17]. The IV route may be considered when the oral or rectal route is not possible [18].

Routine prophylactic use of acetaminophen at the time of vaccination is not recommended

because of a potential reduction in antibody response.
FDA Pediatric Approval
Intravenous
Management of mild to moderate pain and moderate to severe pain with adjunctive opioid analgesics in children 2 years or older. Indicated in fever in neonates or older [1].
Administration
Intravenous: Administer IV over 15 minutes (10 mg/mL). Withdraw appropriate dose and administer in bottle, bag, or IV syringe; dose should be administered within 6 hours [1].
Exercise caution when calculating the dose in milligrams and administering the dose in milliliters [4][5][6]. The administered volume in a neonate should always be 7.5 mL or less [6].

MEDICATION SAFETY
Contraindications/Precautions
Intravenous formulation contraindicated in patients with severe hepatic impairment or severe active liver disease. Hypersensitivity reactions, including life-threatening anaphylaxis, have been reported [20].
Rare but serious skin reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, and acute generalized exanthematous pustulosis, have been associated with the use of acetaminophen. Reactions may occur after one use or at any time. Discontinue use immediately if rash or other hypersensitivity symptoms occur [21].
Use with caution in patients with hepatocellular insufficiency, severe renal insufficiency, glucose 6 phosphate dehydrogenase deficiency, chronic malnutrition, or dehydration/hypovolemia [18].
A modest reduction in blood pressure and heart rate may occur in neonates (preterm and full-term) after IV administration of acetaminophen. Neonates with pre-existing low arterial pressure may be at greater risk for hypotension [22].
Epidemiological evidence demonstrated an association between acetaminophen use and asthma [17], rhinoconjunctivitis, eczema [16] and atopy [15]. Confirmatory studies are needed; however, in a meta-analysis, the odds ratio (OR) was 1.6 (95% CI, 1.48 to 1.74) for the risk of asthma in children among users of acetaminophen in the year prior to asthma diagnosis and the first year of life and 1.96 (95% CI, 1.5 to 2.56) for the risk of wheezing

and acetaminophen use in the previous year of life [17]. In 2 observational studies, the OR was 3.61 (95% CI, 1.33 to 9.77) for atopy and acetaminophen exposure before the age of 15 months [15], and up to 2.39 (95% CI, 2.24 to 2.55) for rhinoconjunctivitis symptoms or 1.99 (95% CI, 1.82 to 2.16) for eczema symptoms and acetaminophen exposure in the previous 12 months in adolescents [16]

Adverse Effects

Injection site events (pain and site reactions; 15%) and vomiting (5%) occur with IV acetaminophen [18]. Rash, fever, thrombocytopenia, leukopenia, and neutropenia have been reported in children [20][23][24][25][26]. Serious skin reactions have been reported from patients who were rechallenged with acetaminophen and had a recurrence of a serious skin reaction [21].

Hypothermia did not develop in 99 neonates (93 normothermic and 6 with fever) administered IV acetaminophen [27].

Although data are limited for neonates, in children liver toxicity occurs with excessive doses [18][20] or after prolonged administration (greater than 48 hours) of therapeutic doses. Hepatotoxicity occurred in less than 0.01% of children administered therapeutic doses of acetaminophen, in a systemic review (n=32,424; studies=62). The estimated risk for minor or major hepatic events was 0.031% (95% CI, 0.015% to 0.057%) [28]. No significant increases in liver enzymes were observed after a median duration of 60 hours (6 to 480 hours) and a median of 9 (2 to 80) doses of IV acetaminophen (20 mg/kg loading dose; 10 mg/kg (every 6 hours for more than 36 weeks postmenstrual age (PMA), every 8 hours for

31 to 36 weeks PMA, and every 12 hours for less than 31 weeks postmenstrual age) in 189 infants (1 day to 182 days of age; 30 to 55 weeks PMA), in a retrospective analysis [29].

Acute liver failure occurred in an 11-month-old boy who received therapeutic doses of oral acetaminophen for a prolonged duration (10 days) [30].

Black Box Warning

Prevent acetaminophen injection dosing errors, which may result in accidental overdose and death, by confirming that doses in milligrams (mg) are not confused with doses in milliliters (mL); that patients under 50 kg receive weight-based doses; that infusion pumps are

programmed correctly; and that the total dose of acetaminophen from all routes and from all sources does not exceed daily limits. Life-threatening cases of acute hepatic failure leading to liver transplant or death have been linked with acetaminophen use. In most cases of hepatic injury, acetaminophen doses exceeded maximum daily limits and often involved the use of more than 1 acetaminophen-containing product [19].

Solution Compatibility

D5W; NS.

Terminal Injection Site Compatibility

Acetaminophen 10 mg/mL

Cimetidine 12 mg/mL, dextrose 5% in lactated Ringer solution, dextrose 5% in normal saline, dextrose 10%, dexamethasone 10 mg/mL, diphenhydramine 50 mg/mL, dolasetron 20 mg/mL, fentanyl 50 mcg/mL, granisetron 0.1 mg/mL, heparin 100 units/mL, hydrocortisone 50 mg/mL, hydromorphone 4 mg/mL, ketorolac 15 mg/mL, lactated Ringer solution, lidocaine 20 mg/mL, lorazepam 0.5 mg/mL, mannitol 150 mg/mL (15%), methylprednisolone 125 mg/mL, metoclopramide 5 mg/mL, midazolam 5 mg/mL, morphine 15 mg/mL, nalbuphine 20 mg/mL, ondansetron 2 mg/mL, potassium chloride 0.1 mEq/mL.

Terminal Injection Site Incompatibility

Diazepam.

Compatibility information refers to physical compatibility and is derived from Trissels 2 Clinical Pharmaceutics Database. The determination of compatibility is based on concentrations for administration recommended herein. Drug compatibility is dependent on multiple factors (eg, drug concentrations, diluents, storage conditions). This list should not be viewed as all-inclusive and should not replace sound clinical judgment. The user is referred to Trissels 2 for more complete details. Trissels 2 Clinical Pharmaceutics Database, version updated on 06/15/2013.

Monitoring

Assess for signs of pain. Monitor temperature. Assess liver function. Serum acetaminophen concentration is obtained only to assess toxicity.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Nonnarcotic analgesic and antipyretic. Peak serum concentration occurs approximately 60 minutes after an oral dose. Absorption after rectal administration is variable and prolonged.

Extensively metabolized in the liver, primarily by sulfation with a small amount by glucuronidation. Metabolites and unchanged drug are excreted by the kidney. Elimination half-life is approximately 3 hours in term neonates, 5 hours in preterm neonates greater than 32 weeks gestation, and up to 11 hours in more immature neonates. Elimination is prolonged in patients with liver dysfunction.

IV: A dose of 12.5 mg/kg/dose IV administered to a neonate (greater than 32 weeks gestational at birth) provided similar concentrations as those achieved in infants, children, and adolescents treated with 15 mg/kg/dose and in adults treated with a 1000-mg dose [1].

A 20 mg/kg loading dose achieved a Cmax of 15 to 25 mg/L in 19 neonates (27 to 42 weeks gestational age) included in the PARANEO study. An effect compartment concentration of 10 mg/L was associated with a pain score reduction of 3.4 units [31]. A mean plasma concentration of 11 mg/L after acetaminophen IV 10 mg/kg every 6 hours (with or without a 20 mg/kg loading dose) was predicted from a pharmacokinetic analysis of 158 neonates (32 to 44 weeks postmenstrual age) [32].

Based on a population pharmacokinetic analysis of 220 patients varying from preterm infants through adults, the following table provides IV doses to achieve an acetaminophen concentration of 9 mg/L and pharmacokinetic parameters [33]:

Acetaminophen (population pharmacokinetics)

To Achieve Target Average Acetaminophen Concentration of 9 mg/L			Pharmacokinetic parameters		
Weight range (kg)	Loading Dose IV (mg/kg)	Maintenance Dose IV every 6 hours (mg/kg)	Cl (L/hr)	Vd (L)	half-life (hrs)
0.5 to 1	11.2	5.1	0.047	0.18	2.6
1 to 1.5	12.1	6	0.11	0.36	2.2
1.5 to 2	12.2	6.8	0.19	0.54	2
2 to 3	13.3	7.4	0.27	0.72	1.8
3 to 5	12.8	8.5	0.47	1.08	1.6
5 to 8	13.5	10.4	0.96	1.79	1.3
8 to 9	16.1	12.4	1.8	2.87	1.1
9 to 15	16.8	12.9	2.1	3.23	1

15 to 20 19.2 14.8 4.1 5.38 0.9
20 to 35 18.4 15.4 5.7 7.17 0.9
35 to 50 18.3 15.2 9.9 12.55 0.9
50 17.4 14.5 13.4 17.93 0.9

Oral/Rectal: Target concentrations above 10 mg/L are predicted in 50% of patients administered acetaminophen (30 mg/kg orally loading dose, 15 mg/kg/dose orally every 8 hours and 37.5 mg/kg rectally loading dose, 20 mg/kg/dose every 8 hours) in a population pharmacokinetic analysis (n=30, 1 to 90 days old, 31 to 40 weeks gestational age) [34].
ABOUT
Special Considerations/Preparation
Oral: Available orally in various liquid formulations containing 160 mg/5 mL (32 mg/mL), 80 mg/0.8 mL (100 mg/mL), and 500 mg/15 mL (33.33 mg/mL). Some formulations are alcohol, dye, and sugar free.
Rectal: Suppositories strengths are 80,120, 325, and 650 mg. Inaccurate dosing may occur with rectal administration because of unequal distribution of acetaminophen in the suppositories.
Injection: Intravenous formulation available in a 100-mL glass vial containing 1000 mg (10 mg/mL). Do not refrigerate or freeze. Vial is for single use only and should be used within 6 hours of opening. [20]. However, IV acetaminophen remained stable for up to 84 hours at room temperature when withdrawn into syringes (100 mg, 250 mg, and 500 mg) and in the original vial (250 mg and 900 mg). Sterility was not tested [35].
Treatment of Serious Acetaminophen Toxicity: N-acetylcysteine (NAC), 150 mg/kg in 5% dextrose or 1/2 NS given IV over 60 minutes (loading dose), followed by 50 mg/kg in 5% dextrose or 1/2 NS over 4 hours, then 100 mg/kg in 5% dextrose or 1/2 NS over 16 hours.
NAC should be continued until clinical and biochemical markers of hepatic injury improve, and acetaminophen concentration is below the limits of detection. NAC solution concentrations of 40 mg/mL have been used to avoid fluid overload and hyponatremia in the neonate.

AcetaZOLAMIDE
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
Posthemorrhagic Ventricular Dilation, Adjunct; Prevention of Shunt Placement:
Ineffective and associated with increased neurologic morbidity compared with standard of care [1].
Uses
Metabolic alkalosis, chronic: Serum bicarbonate was reduced in 89 infants and neonates with metabolic alkalosis associated with chronic respiratory insufficiency treated with 129 acetaZOLAMIDE courses in a retrospective review. The regimen was a single-course of 3 to 5 mg/kg/dose IV every 6 hours up to a maximum 4 doses/24-hour period. The mean measured serum bicarbonate was reduced from 29.5+/-3.7 mEq/L to 26.9+/-3.8 mEq/L, base excess was reduced from 10+/-3.4 mEq/L to 4.8+/-4 mEq/L, and serum chloride was increased from 98.9+/-5.3 mEq/L to 101.2+/-5.5mEq/L after 24 hours of acetaZOLAMIDE administration (p less than 0.001 for all measures). A significant reduction in pH (7.41 to 7.37) and pCo2 (58.5 to 55.6 mmHg) and an increase in serum creatinine (0.38 to 0.43 mg/dL) was observed. Uncompensated respiratory acidosis occurred in 4 patients. Neonatal outcome was not assessed [4].
Posthemorrhagic ventricular dilation (PHVD), adjunct; Prevention of shunt placement: Use of acetaZOLAMIDE and furosemide in preterm infants with PHVD was associated with a higher rate of shunt placement, death, and increased neurological morbidity as compared to standard therapy alone, in a multicenter, randomized, controlled trial (n=177). Infants less than 3 months beyond the expected date of delivery and with a ventricular width more than 4 mm above the 97th percentile after intraventricular hemorrhage received either standard therapy plus acetaZOLAMIDE 100 mg/kg daily and furosemide 1 mg/kg daily (n=88) or standard therapy alone (n=89). Mean gestation age was 28.5 weeks and median postnatal age was 23.5 days in the drug therapy group. Median treatment duration of acetaZOLAMIDE was 35 days. Assessments at 1 year showed that death or shunt placement had occurred in 56 infants (63.3%) in the drug therapy group and in 46 (52.2%) allocated to standard therapy (11.1% (CI, -3.2% to 25.2%; p=0.15). Adverse effects were reported in 38 infants, 23 of whom required permanent discontinuation of drug

therapy [1]. In a small cohort study, 9 of 10 preterm infants with raised intracranial hypertension secondary to PVHD treated with acetaZOLAMIDE and furosemide avoided placement of a ventriculoperitoneal shunt; in comparison, 3 of 6 patients who received serial lumbar puncture avoided shunt placement. acetaZOLAMIDE was started at 20 mg/kg/day and increased by 10 mg/kg up to 100 mg/kg/day in 3 divided doses administered orally or if necessary, IV; dose of furosemide was 1 mg/kg daily orally or IV. Mean gestational age was 28.4 weeks [5]. Limited use of acetaZOLAMIDE may be warranted in infants with PVHD and raised intracranial hypertension based on the findings of Kennedy et al, 2001 [1].

Pediatric FDA Approved Indications

Oral extended-release capsules:

Indicated in patients 12 years or older for the prevention or amelioration of symptoms associated with acute mountain sickness despite gradual ascent. Also indicated in patients 12 years or older as adjunctive treatment of open-angle glaucoma, secondary glaucoma, and preoperatively in acute closed-angle glaucoma when delay of surgery is indicated in order to lower intraocular pressure. Safety and efficacy of oral extended-release capsules not established in pediatric patients younger than 12 years [6].

IV and oral immediate-release:

Safety and efficacy of IV injection [2] and oral immediate-release tablets [7] not established in pediatric patients.

Administration

IV Injection: IV route preferred; IM use not recommended [2]. Recommended concentrations for intermittent IV are 50 mg/mL or 100 mg/mL [3].

MEDICATION SAFETY

Contraindications/Precautions

Contraindicated with depressed sodium and/or potassium blood serum levels, marked renal or hepatic disease or dysfunction (including cirrhosis), suprarenal gland failure, hyperchloremic acidosis, and long-term administration in patients with chronic noncongestive angle-closure glaucoma [7]. Sulfonamide derivative; cross sensitivity possible [6][2].

Increasing dose does not increase effect; it may decrease diuresis and increase risk of drowsiness and paresthesia. May precipitate or aggravate acidosis in patients with pulmonary

obstruction or emphysema where alveolar ventilation may be impaired [2]. Gradual ascent recommended when used for acute mountain sickness [6][7].
Long-term therapy in pediatric patients has resulted in growth retardation secondary to chronic acidosis. Blood glucose increases and decreases have been reported in patients with diabetes mellitus or impaired glucose tolerance. May cause electrolyte imbalances (eg, hyperkalemia, hyponatremia, and metabolic acidosis); caution recommended with current, or predisposition to, electrolyte and acid/base imbalances (eg, impaired renal function, diabetes mellitus, and impaired alveolar ventilation) [6].
Adverse Effects
Nephrocalcinosis, per renal ultrasound, occurred more frequently in the acetaZOLAMIDE/furosemide group than standard therapy group (24% vs 4% (difference 19%, CI 9% to 30%), in a randomized, controlled trial (n=177) of preterm infants (mean gestation age 28.5 weeks and median postnatal age was 23.5 days) with post-hemorrhagic ventricular dilation. Median treatment duration of acetaZOLAMIDE was 35 days. [1].

Hypercalciuria occurred in 7 of 12 infants exposed to furosemide and acetaZOLAMIDE; nephrocalcinosis developed in 5 of the 7 patients with hypercalciuria [5]. A transient increase in intracranial pressure was demonstrated in 6 of 8 infants (25 to 37 weeks gestation, 16 to 121 postnatal days) with post-hemorrhagic hydrocephalus administered IV acetaZOLAMIDE 50 mg/kg. No increase was observed with oral administration. In all 4 preterm infants with chronic lung disease, discontinuation of acetaZOLAMIDE (IV and oral) was necessary due to the inability to compensate for the rise in pCo2[9].
Black Box Warning
Severe reactions to sulfonamides (eg, Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias) have occurred, rarely resulting in fatality. Sensitizations may recur. Discontinue use if hypersensitivity or other serious reactions occur.
Anorexia, tachypnea, lethargy, coma, and death have been reported with concomitant high-dose aspirin and acetaZOLAMIDE [7].
Solution Compatibility
D5W; D10W; D5LR; D5NS; D50.45%NaCl; NS; 0.45%NaCl.
Terminal Injection Site Compatibility

acetaZOLAMIDE reconstituted to 100 mg/mL:
Pantoprazole (4 mg/mL).
Compatibility information refers to physical compatibility and is derived from Trissels 2 Clinical Pharmaceutics Database. The determination of compatibility is based on concentrations for administration recommended herein. Drug compatibility is dependent on multiple factors (eg, drug concentrations, diluents, storage conditions). This list should not be viewed as all-inclusive and should not replace sound clinical judgment. The user is referred to Trissels 2 for more complete details. Trissels 2 Clinical Pharmaceutics Database, version updated on 06/15/2013.
Monitoring
Obtain a CBC and platelet count at baseline and regularly during treatment. Monitor serum electrolytes periodically [6][2][7]. Consider monitoring urinary pH in patients on acetaZOLAMIDE concomitantly with other antiepileptic drugs, particularly valproate [8].
MECHANISM OF ACTION/PHARMACOKINETICS
Pharmacology

acetaZOLAMIDE, a nonbacteriostatic sulfonamide, inhibits carbonic anhydrase from catalyzing the reversible hydration of carbon dioxide and dehydration of carbonic acid. In the eye, carbonic anhydrase inhibition reduces aqueous humor production resulting in a decrease in intraocular pressure. It also delays abnormal, paroxysmal excessive discharge from CNS neurons and affects promotion of diuresis and urinary alkalinization [2][6][7].
ABOUT
Special Considerations/Preparation
IV Injection: Available as an IV lyophilized powder for solution containing acetaZOLAMIDE 500 mg/vial [2].
Prior to use, reconstitute each 500-mg vial with at least 5 mL of sterile water for injection. May refrigerate reconstituted solution at 2 to 8 degrees C (36 to 46 degrees F) for up to 3 days. If kept at room temperature, use within 12 hours. Contains no preservatives; discard unused solution [2].
Oral Extended-Release Capsule: Available as an oral extended-release capsule containing acetaZOLAMIDE 500 mg [6].
Oral Tablet: Available as an oral tablet containing acetaZOLAMIDE 125 mg or 250 mg; also contains lactose monohydrate [7].
Extemporaneous Compounding:

acetaZOLAMIDE 25 mg/mL in a 1:1 mixture of ora-sweet and ora-plus, in a 1:1 mixture of ora-sweet SF and ora-plus, and in cherry syrup (concentrated cherry syrup diluted 1:4 with simple syrup) was stable for up to 60 days at 5 and 25 degree C. The liquids were protected from light [10].
acetaZOLAMIDE 25 mg/L in 70% sorbitol solution with a suspension vehicle, sweeteners, flavoring agents, preservatives, humectants, and pH adjusters was stable for at least 79 days at 5, 22, and 30 degrees C. Maintain at a pH 4 to 5 and protected from light. The following are directions for compounding 300 mL of a 25 mg/mL acetaZOLAMIDE suspension (alexander, 1991)[11]:
Triturate 30 acetaZOLAMIDE 250-mg tablets in a glass mortar.
Slowly add approximately 30 mL of 70% sorbitol solution and levigate the powder.
Slowly add 1.5 g of sodium carboxymethylcellulose to 50 mL of warm purified water, USP, and allow the mixture to hydrate for 15 to 20 minutes.
Add 1.5 g of aluminum magnesium silicate to a separate 50 mL portion of purified water, USP.
Combine the hydrated sodium carboxymethylcellulose and dispersed aluminum magnesium silicate with the levigated powder in the glass mortar.
Geometrically incorporate 60 mL of syrup, USP, 7.5 mL of glycerin, USP, and 6 mL of paraben stock solution (2.5% methylparaben and 1% propylparaben in propylene glycol) with constant agitation until a homogeneous mixture forms.
Transfer contents of mortar to a 500-mL graduated cylinder.
Add 0.015 g of FD&C Red No. 40 and 0.3 mL of strawberry flavor.

Rinse the mortar with a 30-mL portion of purified water, USP, and transfer to a graduated cylinder. Repeat this step until the volume of the liquid reaches 300 mL.
Homogenize utilizing a suitable blender.
Adjust the pH to 5 using 36% w/w hydrochloric acid (usually 1 to 3 drops).
Transfer into an amber glass bottles with constant stirring. Add a "Shake well before using" auxiliary label.

Acetylcysteine
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
Acetaminophen Overdose, Acute
Loading Dose Protocol
If the time of acute acetaminophen ingestion is unknown, administer a loading dose immediately, and use acetaminophen concentration levels to determine need for continued treatment [1][2].
If acetaminophen concentrations cannot be obtained or are uninterpreted within 8 hours of acetaminophen ingestion or signs of acetaminophen toxicity are present, administer a loading dose immediately and continue treatment [1][2].
If the patient presents more than 8 hours after ingestion and the time of ingestion is known, administer a loading dose immediately and use acetaminophen concentration levels to determine the need for continued treatment [1][2].
If less than 8 hours have passed since ingestion, and the time of ingestion and acetaminophen concentration are known, use the Rumack-Matthew nomogram to determine if treatment is needed [1][2]:
If acetaminophen concentrations are at or above the possible toxicity line (dotted line in nomogram), administer a loading dose.
If acute overdose was from extended-release formulation and the acetaminophen level is below the possible toxicity line at 4 hours post ingestion, draw a second sample 8 to 10 hours after the acute ingestion. Then if the second value is at or above the possible toxicity line (dotted line in nomogram), administer a loading dose.
If acetaminophen concentrations are below the possible toxicity line, but time of ingestion is unknown or sample was taken less than 4 hours post ingestion, administer a loading dose.
If acetaminophen concentrations at below the possible toxicity line, time of ingestion is known, and the sample was taken more than 4 hours post ingestion, do not administer acetylcysteine as the probability of hepatotoxicity is minimal.
Maintenance Dose Protocol[1][2]
Determine the need for continued therapy after the loading dose, based on the acetaminophen concentration:

If the acetaminophen concentration is above the possible toxicity line according to the nomogram, or if the concentration was not obtained, continue treatment with the maintenance dose.
If the acetaminophen concentration is below the possible toxicity line, the time of ingestion is known, and the sample was taken more than 4 hours post ingestion, discontinue treatment.
If the acetaminophen concentration was in the non-toxic range, but time of ingestion is not known or less than 4 hours, obtain a second sample and consider clinical condition of patient in deciding whether to continue treatment. A complete treatment course if recommended if there is any uncertainty regarding the patient's risk for hepatotoxicity.
Continued Therapy Following Completion of Loading and Maintenance Doses Protocol [2]

Consider therapy beyond the loading and maintenance doses in cases of suspected massive overdose, with concomitant ingestion of other substances, or in patients with preexisting liver disease.
If acetaminophen levels are still detectable following the last maintenance dose, or if ALT/AST levels are still increasing or the INR remains elevated, continue maintenance doses and contact a United States regional poison center at 1-800-222-1222 or the special health professional assistance line for acetaminophen overdose at 1-800-525-6115.
Oral
Effervescent Tablets and Oral solution
Loading dose: 140 mg/kg orally [1][3]
Maintenance doses: 70 mg/kg orally every 4 hours for 17 doses starting 4 hours after loading dose [1][3].
IV
Loading dose: 150 mg/kg IV in 3 mL/kg for those weighing 5 kg or more administered over 1 hour. Adjust the total IV volume, as clinically necessary, to avoid fluid overload [4][5][6][2].
Second dose: 50 mg/kg IV in 7 mL/kg for those weighing 5 kg or more administered over 4 hours. Adjust the total IV volume, as clinically necessary, to avoid fluid overload [4][5][6][2].
Third dose: 100 mg/kg IV in 14 mL/kg for those weighing 5 kg or more administered over

16 hours. May continue beyond 21 hours if clinically indicated. Adjust the total IV volume, as clinically necessary, to avoid fluid overload [4][5][6][2].

Repeated Supra-therapeutic Acetaminophen Ingestion Effervescent Tablets: Rumack-Matthew nomogram does not apply. Contact regional poison center (1-800-222-1222) or a special health professional assistance line for specific dosage and administration information [1].

Uses

Acetaminophen Overdose: For specific treatment management call 1-800-222-1222 (regional poison center) or 1-800-525-6115 (special health professional assistance line) [7].

Management of acetaminophen overdose is based on adult and some pediatric data with most of pediatric management extrapolated from adult data. The Rumack-Matthew nomogram (based on adult data) stratifies the risk of hepatoxicity based on acetaminophen concentrations at a specified time after a single acute acetaminophen ingestion (4 to 24 hours post ingestion); however, the nomogram may not be appropriate to utilize in the neonate population. In adults, patients with acetaminophen concentrations within the possible or probable toxic range would warrant acetylcysteine treatment. The ideal time of acetylcysteine administration is within 8 to 10 hours postingestion. The nomograph can not be used with other types of ingestions (greater than 24 hours after presentation, an unknown time or duration of ingestion, extended-release preparation ingestion, or a repeated supra-therapeutic ingestion). Although weaker evidence exist, acetylcysteine can be administered to patients with hepatic failure presumably due to acetaminophen, to patients who have hepatotoxicity thought to be due to acetaminophen, and to patients who have a suspected or known acetaminophen overdose, including repeated supra-therapeutic ingestions [8]. The Rumack-Matthew nomogram, which was developed using data from oral overdoses, may not be appropriate when acetaminophen overdose is received by the IV route. Under these circumstances, acetylcysteine should be considered after a single IV dose

above 60 mg/kg [9].

Data in neonates treated with acetylcysteine are limited to case reports [10][11][4][5][6][12]

with ages ranging from 1 day of age (3.78 kg) [12] to 22 days of age (4.1 kg) [4], including preterm neonates as young as postmenstrual age 27.3 weeks (12 days of age; weight 940 grams) [11]. All neonates experienced full recovery with most experiencing no evidence of liver toxicity during and after the course of acetylcysteine treatment. Although neonates may not be as susceptible to liver injury compared to children or adults due to differences in hepatic development, acetylcysteine is the standard treatment.

Gastric Lactobezoar: A gastric lactobezoar was successfully treated after 4 doses of acetylcysteine 10 mg/kg/dose via nasogastric (NG) tube every 6 hours in a 1 month of age full-term infant. Each dose was diluted in 50 mL of normal saline and administered over 30 minutes, then the NG tube was clamped for 2 hours, followed by aspiration at 3 and 6 hours after the dose [13].

Lung Disease, Non-Cystic Fibrosis: Evidence is limited and does not support the use of oral or inhaled acetylcysteine for non-cystic fibrosis lung disease such as primary ciliary dyskinesia, chronic lung disease of infancy, pneumonia, asthma, atelectasis, inhalation injury, or lower respiratory tract infection in pediatric patients or neonates [14]. A 6-day course of IV acetylcysteine (16 to 32 mg/kg/day) started before the age of 36 hours did not improve mortality, the incidence of bronchopulmonary dysplasia, or lung function in a randomized, double-blind, placebo-control trial (n=391; weight range 500 to 999 g) [15][16].

Furthermore, harm was demonstrated in 10 ventilated premature infants with chronic lung disease and treated with intratracheally administered acetylcysteine for 7 days [17].

Pediatric FDA Approved Indications

Inhalation Solution:

Indicated as adjuvant therapy for patients with abnormal, viscid, or inspissated mucous secretions in several conditions, including [3]:

Acute bronchopulmonary disease
Atelectasis due to mucous obstruction
Chronic asthmatic bronchitis
Chronic respiratory disease
Diagnostic bronchial studies
Post-traumatic chest conditions
Pulmonary complications of cystic fibrosis
Respiratory complication of surgical procedure
Tracheostomy care
Use during anesthesia

Oral/IV Solution:

Indicated as an antidote to prevent or lessen hepatic injury that may occur following the

ingestion of a potentially hepatotoxic quantity of acetaminophen [3] in patients with acute ingestion or from repeated supratherapeutic ingestion [2].
Effervescent Tablets:
Indicated as an antidote to prevent or lessen hepatic injury that may occur following the ingestion of a potentially hepatotoxic quantity of acetaminophen in patients with acute ingestion or repeated supra-therapeutic ingestion (exposure to higher than recommended

dosages for extended periods of time) [1].
Administration
Effervescent Tablet: Dissolve two 2.5-gram tablets in 100 mL of water for a 50 mg/mL solution [1]
Administer immediately or within 2 hours of preparation once tablets are dissolved. If vomiting occurs within 1 hour of administration, repeat dose. May be administered by nasoduodenal tube [1].
Oral Solution: Dilute the 20% solution with diet cola or other diet soft drink to a final concentration of 5% (add 3 mL of diluent for each 1 mL of 20% solution; do not decrease the proportion of diluent). If administered via gastric tube or Miller-Abbott tube, water may be used as the diluent. Administer within 1 hour of dilution. Repeat dose if patient vomits within 1 hour of administration. Dilution may minimize vomiting. May be administered by duodenal intubation if persistent vomiting is present. Not for parenteral injection [3].
If activated charcoal has been administered, then gastric lavage must be performed before administration of oral acetylcysteine [3].
IV Solution: Acetadote is hyperosmolar (2600 milliosmoles/liter [mOsmol/L]) and the osmolarity of the solution is increased as the diluent volume is decreased; adjust osmolarity to physiologically safe level, generally not less than 150 mOsmol/L in children [7].
Examples of Acetadote(R) Concentration and Osmolarity in 3 Solutions

Acetylcysteine Concentration	Sterile Water for Injection	1/2 Normal Saline	D5W
7 mg/mL	91 mOsmol/L*	245 mOsmol/L	343 mOsmol/L
24 mg/mL	312 mOsmol/L	466 mOsmol/L	564 mOsmol/L

* Adjust osmolarity to a physiologically safe level (generally not less than 150 mOsmol/L for pediatric patients)
Acetylcysteine IV injection product information, 7/2016

Concentration of vial is 200 mg/mL. See Dose Section for rate and infusion concentration [7].
MEDICATION SAFETY
Contraindications/Precautions
Inhalation solution: Liquefied bronchial secretions may increase in volume, leading to airway obstruction if cough is inadequate; mechanical suction may be required.
Bronchospasm may occur in asthmatics. As increased concentration of drug may occur from solvent evaporation, dilution of nebulizing solution with appropriate amounts of sterile water for injection is recommended [3].
IV solution: Acute flushing and erythema may develop, usually within 30 to 60 minutes after initiating therapy and usually will spontaneously resolve. However, serious acute hypersensitivity reactions, including fatal cases, have been reported. Use with caution in patients with asthma due to risk of bronchospasm. In patients less than 40 kg and for those

requiring fluid restriction, fluid overload potentially leading to hyponatremia, seizure, and death may occur; therefore, diluent volume needs to be adjusted [2].
Oral solution: If encephalopathy due to hepatic failure occurs, discontinue treatment to avoid further exposure to nitrogenous substances. Evaluate risk versus benefit in patients at risk of gastric hemorrhage (eg, esophageal varices, peptic ulcer) due to increased vomiting with treatment [3].
Adverse Effects
IV infusion of acetylcysteine did not produce adverse effects in one study of preterm newborns (n=10; gestational age, 25 to 31 weeks; weight, 500 to 1380 g) when administered at a mean rate of 4.2 mg/kg/hr for 24 hours, or in a second study of newborns (n=6; gestational age, 26 to 30 weeks; weight, 520 to 1335 g) when administered at a rate of 0.1 to 1.3 mg/kg/hr for 6 days [7].
Hypernatremia developed in a preterm infant (30 weeks gestation) administered oral acetylcysteine solution (33.5 mmol/kg/day sodium from acetylcysteine) for meconium ileus. Sodium concentration returned to normal after acetylcysteine was discontinued [18].
Solution Compatibility
D5 W; 0.45%NaCl.
Terminal Injection Site Compatibility
Acetylcysteine 100 mg/mL
Vancomycin 10 mg/mL.

Terminal Injection Site Incompatibility
Cefepime, ceftazidime.
Compatibility information refers to physical compatibility and is derived from Trissels 2 Clinical Pharmaceutics Database. The determination of compatibility is based on concentrations for administration recommended herein. Drug compatibility is dependent on multiple factors (eg, drug concentrations, diluents, storage conditions). This list should not be viewed as all-inclusive and should not replace sound clinical judgment. The user is referred to Trissels 2 for more complete details.
Trissels 2 Clinical Pharmaceutics Database, version updated on 06/15/2013.
Monitoring

Inhalation Therapy: Monitor patients with asthma closely during inhalation therapy.
Monitor renal and hepatic function and electrolytes throughout therapy [3].
IV/Oral Therapy for Overdose:
Obtain plasma or serum acetaminophen levels prior to detoxification. For acute ingestion, obtain as early as possible but no sooner than 4 hours postingestion [1][2].
If extended-release acetaminophen was ingested and the acetaminophen concentration at 4 hours post ingestion was below the possible toxicity line, draw a second sample at 8 to 10 hours post ingestion [1][2].
Assess hepatic function (AST, ALT, bilirubin, INR, prothrombin time), renal function (creatinine and BUN), blood glucose, and electrolytes prior to detoxification, and throughout treatment [1][2].
Assess acetaminophen levels as needed during treatment to determine need for continued therapy [1][2].
Assess acetaminophen levels, ALT/AST, and INR after the last maintenance dose [1][2].
Carefully monitor patients with asthma or with a history of bronchospasm during initiation and throughout therapy [1][2].
MECHANISM OF ACTION/PHARMACOKINETICS
Pharmacology
Systemic: Acetylcysteine may protect against acetaminophen overdose-induced hepatotoxicity by maintaining or restoring hepatic concentrations of glutathione, or by acting as an alternate substrate for conjugation with reactive acetaminophen metabolites [1][2].
Glutathione is required to inactivate an intermediate metabolite of acetaminophen that is

thought to be hepatotoxic. In acetaminophen overdose, excessive quantities of this
metabolite are formed because the primary metabolic pathways (glucuronide and sulfate
conjugation) become saturated. CYP2E1 then metabolizes a larger fraction of the ingested
dose to form an increased amount of the toxic metabolite [3].
Metabolism of acetylcysteine is believed to form cysteine and disulfides (N,N-diacetylcysteine
and N-acetylcysteine), with further metabolism of cysteine to form glutathione and other
metabolites. Acetylcysteine steady-state Vd and protein binding were 0.47 L/kg and 66% to
87%, respectively. Urinary recovery was 13% to 38% within 24 hours of a single oral dose.
Mean total body clearance was 0.11 L/hr/kg with an estimated renal clearance of 30% of the
total. Mean half-life was 5.6 hours [1][2].
Mean elimination half-life was longer in premature newborns (11 hours) compared with
adults (terminal half-life, 5.6 hours) [19]. Clearance (32 to 62 mL/kg/hr) and Vd (167 to
1010 mL/kg) were correlated with weight and gestational age in 10 neonates (mean 27.7
weeks gestation; mean 863 grams) started on 4.2 mg/kg/hr IV acetylcysteine soon after
birth; half-life did not correlate with either parameter. A mean steady-state concentration of
161 micromole/L was attained within 2 to 3 days in 5 of 6 neonates (mean 27.6 weeks
gestation; mean 894 grams) started on 0.3 to 1.3 mg/kg/hr IV acetylcysteine at the age of
24 hours and continued for a duration of 6 days [19].
]Inhalation: Acetylcysteine exerts its mucolytic action through its free sulfhydryl group,
which opens the disulfide linkage in mucus and lowers its viscosity. This action increases with
increasing pH and is most significant at pH 7 to 9. The mucolytic action of acetylcysteine is
not affected by the presence of DNA [3].

ABOUT
Special Considerations/Preparation
Effervescent Tablets:
Supplied as 500 mg or 2.5 g effervescent tablets for oral solution. Dissolve effervescent
tablets and use within 2 hours [1].
Store at a controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F),
with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F). Store in
original packaging until ready for use and protect from moisture [1].

IV Injection: Available as a 20% IV solution containing acetylcysteine 200 mg/mL in 30-mL single-dose vials [7].
A color change of the solution to slight pink or purple may occur once the vial is punctured, but product quality is not affected. Contains no preservatives. Discard unused solution left in vial after opening. Diluted solution may be stored at room temperature for up to 24 hours [7].
Oral/Inhalation Solution: Available in 10-mL and 30-mL vials of a 10% (100 mg/mL) or 20% (200 mg/mL) acetylcysteine sodium sterile, unpreserved solution for oral or inhalation use (not for injection). Do not mix with antibiotics such as tetracycline, oxytetracycline, or erythromycin lactobionate. Opened vial may be refrigerated for up to 96 hours [3].
Acetylcysteine inhalation therapy was chemically unstable with dornase alfa. Although chemically stable together, aerosol characteristics have not been studied when the following were combined with acetylcysteine cromolyn, salbutamol, ipratropium, or colistimethate sodium [20].

Acyclovir
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
Herpes Simplex Virus Infection, Treatment and Preemptive Therapy
Infections of the CNS, Skin, Eye, Mouth, or Disseminated
Population based pharmacokinetic/pharmacodynamic data supports alternative frequency of administration. See USES section for details.[1]
Less than 30 weeks postmenstrual age: 20 mg/kg IV every 8 [2][3][4] to 12 hours [1].
30 weeks or more postmenstrual age: 20 mg/kg IV every 8 hours [2][3][1][4].
Treat localized herpes simplex disease for 14 days and disseminated or CNS disease for 21 days [2][3][4]. For CNS disease, continue IV therapy for another 7 days, when repeat DNA polymerase chain reaction (cerebrospinal fluid herpes simplex virus) is positive after 19 to 21 days of acyclovir therapy. Continue IV therapy until PCR is negative [2]. The duration for preemptive therapy without proven disease is 10 days [4].
Herpes Simplex Virus Infection (CNS, Disseminated Disease, Skin, Eye, or Mouth),

Chronic suppression: 300 mg/m2/dose orally 3 times a day when disease is severe and recurrent. Begin suppressive therapy immediately after completion of IV treatment and continue for 6 months [2][5][6].
Varicella-Zoster Virus Infection: 10 to 15 mg/kg/dose IV every 8 hours for 5 to 10 days [7][8][9][10].
Dose Adjustments
Preterm infant less than 33 weeks gestational age: give usual IV dose every 12 hours [11].
Renal
CrCl 25 to 50 mL/min/1.73 m(2) or serum creatinine (SCr) 0.8 to 1.1 mg/dL: give usual IV dose every 12 hours [11].
CrCl 10 to 25 mL/min/1.73 m(2) or SCr 1.2 to 1.5 mg/dL with decreasing urine output: give usual IV dose every 24 hours [11].
CrCl less than 10 mL/min/1.73 m(2) or SCr greater than 1.5 mg/dL or urine output less than 1 mL/kg/hour: decrease IV dose by 50% and give every 24 hours [11].
Uses
Neonatal herpes simplex virus (HSV) infections, known or suspected : Acyclovir treatment should be initiated in all infants, including HIV-positive, with herpes disease. In asymptomatic neonates born to women with active herpes lesions, initiation of acyclovir is dependent on risk of transmission to the neonate [2][3][4]. Adverse effects (AE) were common, but severe AEs were rare with a median dose of acyclovir 60 mg/kg/day IV in a retrospective review of Pediatrix Medical Group data (n=89 newborn infants) [16].
Dose Regimen

Based on results from a clinical trial, the standard dose and dosing interval is 20 mg/kg IV every 8 hours (60 mg/kg/day). Although mortality rate was reduced when compared with the 30 mg/kg/day (10 mg/kg/dose every 8 hours) regimen, the 60 mg/kg/day regimen still demonstrated a 24-month mortality rate of 31% among infants with disseminated HSV disease and 6% among infants with CNS HSV disease. Furthermore, the dose did not improve the rates of normal infant development [4][17]. Investigators of a small population pharmacokinetic study proposed the following frequencies for a 20 mg/kg dose: every 12 hours for infants less than 30 weeks postmenstrual age (PMA) (n=13), every 8 hours for

infants 30 to less than 36 weeks PMA (n=9), and every 6 hours for infants 36 to 41 weeks PMA (n=6) to achieve a surrogate pharmacodynamic acyclovir target concentration of 3 mg/L or more. This target concentration theoretically would achieve CSF concentrations of 1 mg/L or more. Safety and efficacy were not evaluated with these regimens. One infant experienced an elevated serum creatinine, which was considered related to acyclovir. Doses greater than 80 mg/kg/day (range 87 to 158 mg/kg/day) were administered to 47% of neonates (15 out of 32 infants) [1].

Neonatal HSV infection, Chronic suppressive therapy

Based on data reported from 2 parallel, phase III, double-blind, placebo-controlled studies (n=45 with CNS disease; n=29 with skin, eye, mouth (SEM) disease), 6 months of suppressive oral acyclovir therapy (300 mg/m2/dose 3 times a day) started immediately after IV treatment for CNS HSV disease was associated with better neurological outcomes when compared with placebo. Of the 28 infants with CNS disease assessed at 12 months (acyclovir=16; placebo=12), Bayley Scales of Infant Development (2nd Edition) Mental Scores were significantly higher in patients receiving acyclovir compared with patients receiving placebo (88.24 vs 68.12; p=0.046). In patients with SEM disease receiving 6 months of suppressive oral acyclovir therapy started immediately after IV treatment, the time to 2 recurrences of skin lesions was 1.7 months longer in the treatment group compared with placebo. Of the 15 infants with SEM disease assessed at 12 months, there were no differences in Bayley scores between acyclovir and placebo. An absolute neutrophil count of 500 cells/mm3 or less was reported in 20% to 25% of patients receiving acyclovir compared with 5% to 7% receiving placebo; no patient had complications associated with neutropenia [5].

Varicella-zoster virus infections with CNS and pulmonary involvement. Acyclovir treatment is recommended in infants with varicella-zoster infection having CNS or pulmonary involvement [7][8][9][10].

Administration

Intravenous route: Administer as IV infusion over 1 hour at a concentration of 7 mg/mL or less in D5W or NS [12].

Oral route: take with or without food; for suspension, shake well before measuring each dose [13].

Extravasation ManagementNeonatal data are limited to pooled data from 10 case

reports/case series (n=237) and are not specific to acyclovir extravasation; subcutaneous saline irrigation with or without hyaluronidase infiltration was commonly used. No standardized management was established. An option for more severe injuries (stages 3 and 4) is subcutaneous irrigation with saline, but this is not advocated as standard treatment. Conservative management is appropriate for mild extravasation (stages 1 and 2) [14].

Although not neonatal-specific, the following are recommendations for extravasation of acidic or alkaline agents (acyclovir is alkaline with a pH of 11) [15]

General:
Stop and disconnect infusion; do not remove the cannula or needle
Attempt to gently aspirate as much extravasated agent as possible; avoid manual pressure
Remove cannula or needle
Dry heat and elevation
Closely monitor for signs of coagulation and ischemia
Avoid attempt at pH neutralization (acyclovir - pH 11)
Monitor and consider the need for surgical management such as surgical flushing with normal saline or debridement and excision of necrotic tissue (especially if pain persists for 1 to 2 weeks). In cases of compartment syndrome, surgical decompression may be required

Refractory Events:
Hyaluronidase 15 units intradermally along injection site and edematous area. Give as five, 0.2-mL intradermal injections along extravasation site and edematous tissue.

Inadvertent Intraarterial Administration:
Leave inadvertent intraarterial line in place for diagnostics
Systemic heparin titrated to therapeutic anticoagulant effect.
Stellate ganglion block

MEDICATION SAFETY

Contraindications/Precautions

Precautions
Administration: Rapid rate of infusion may lead to renal tubular damage [18]
Hematologic: Thrombotic thrombocytopenic purpura and hemolytic uremic syndrome, including fatal cases, has been reported in immunocompromised patients [18].
Neurologic: Encephalopathic changes (eg, lethargy, obtundation, tremors, confusion,

hallucinations, agitation, seizures, or coma) have been reported; use with caution in patients with underlying neurologic abnormalities, significant hypoxia, or serious renal, hepatic, or electrolyte abnormalities [18].
Renal: Impaired renal function may occur and is dependent upon rate of administration; risk is increased in patients with preexisting renal disease and dehydration, and with concomitant use of other nephrotoxic drugs [18].
Renal: Precipitation of acyclovir crystals in renal tubules may occur and can result in acute renal failure; accompany administration with adequate hydration [18].
Renal: Renal failure, including fatal cases, has been reported [18].
Adverse Effects

Common Adverse Effects: Common adverse events include nausea, vomiting, and rash [12].
Cardiovascular: Hypotension requiring inotropes (9%) occurred in a retrospective review of Pediatrix Medical Group data (n=89 newborn infants treated for herpes simplex virus disease) [16]
Hepatic: Elevations of hepatic transaminases (1% to 2%) [18].
Hematologic:
Leukopenia (16%) and thrombocytopenia (25%), which occurred within a median of 1 to 2 days, were common in a retrospective review of Pediatrix Medical Group data (n=89 newborn infants treated with high-dose acyclovir for herpes simplex virus disease).
Neutropenia occurred in 6% of infants, most of whom were treated with granulocyte colonystimulating factor. Severe hematologic events were rare (0% to 3%) [16].
Among infants receiving high-dose acyclovir for neonatal HSV disease, the major toxicity was neutropenia (absolute neutrophil count less than 1000/mm3), which was observed in 20% of neonates [2]. Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome, resulting in death, have been reported in some immunocompromised patients receiving acyclovir.
Overall, hematologic abnormalities occurred in less than 1% [18][12].
Immunologic: Development of certain acyclovir-resistant viruses may cause severe disease in infants [18].
Neurological: Seizures (9%) occurred in a retrospective review of Pediatrix Medical Group

data (n=89 newborn infants treated with high-dose acyclovir for herpes simplex virus disease) [16]
Renal: Mild elevations of creatinine concentrations (2%) were reported in a retrospective review of Pediatrix Medical Group data (n=89 newborn infants treated with high-dose acyclovir for herpes simplex virus disease) [16]
Renal failure, in some cases fatal, has been reported [18]..
Vascular: Phlebitis at the injection site occurred in 9% of patients [18].
Solution Compatibility
D5W and NS.
Terminal Injection Site Compatibility
Amikacin, ampicillin, aminophylline, cefazolin, cefotaxime, cefoxitin, ceftazidime, ceftriaxone, chloramphenicol, cimetidine, clindamycin, dexamethasone, erythromycin lactobionate, famotidine, fluconazole, gentamicin, heparin, hydrocortisone succinate, imipenem/cilastatin, linezolid, lorazepam, magnesium sulfate, metoclopramide, metronidazole, milrinone, morphine, nafcillin, oxacillin, penicillin G, pentobarbital, piperacillin, potassium chloride, propofol, ranitidine, remifentanil, sodium bicarbonate, theophylline, ticarcillin, tobramycin, trimethoprim/sulfamethoxazole, vancomycin, and zidovudine.
Terminal Injection Site Incompatibility

Fat emulsion. Aztreonam, caffeine citrate, caspofungin, cefepime, dobutamine, dopamine, meropenem, and piperacillin-tazobactam.
Monitoring
Laboratory
Monitor renal function at baseline and at least once weekly, particularly in patients with preexisting renal dysfunction on prolonged therapy [2].
MECHANISM OF ACTION/PHARMACOKINETICS
Pharmacology
Antiviral drug that is preferentially taken up by infected cells; inhibits viral DNA synthesis. CSF concentrations are 30% to 50% of serum concentrations. Oral absorption is 15% to 30%. Most of administered dose is excreted unchanged in urine, primarily via glomerular filtration. Protein binding and metabolism are minimal. Serum half-life is 3 to 4 hours in patients with normal renal and hepatic function. The clearance increased with time in the premature neonate from 0.211 L/hr/kg for those

less than 30 weeks postmenstrual age (PMA), 0.449 L/hr/kg for those 30 to less than 36 PMA, and 0.589 L/hr/kg for those 36 to 41 PMA in a population pharmacokinetic study (n=28). The corresponding half-lives were 10.2 hours, 6.55 hours, and 3 hours. For 20 mg/kg doses, the IV frequency suggested was every 12 hours for infants less than 30 weeks PMA, every 8 hours for infants 30 to less than 36 weeks PMA, and every 6 hours for infants 36 to 41 weeks PMA. These regimens were then assessed using a data set of 1000 infants to simulate acyclovir exposure. The proposed dosing regimens predict that the steady state plasma concentration at 50% of the dosing interval would be greater than or equal to 3 mg/L in greater than 90% of infants. Although, toxic levels are unknown, concentrations associated with neurotoxicity in a small amount of patients have been identified as 50 to 70 mg/L. These predicted neurotoxic concentrations were exceeded in 0.9% and 0.3% of infants, respectively [1].

Dosing simulations of the proposed and standard dose regimens using a database of 1000 infants provide the following percentages of infants who would be expected to achieve a target concentration of 3 mg/L or more [1].

Regimens and Target Concentrations

Postmenstrual Age	IV Dose	N	Percent of Infants with Concentrations of 3 mg/L or more		
			Cmax at steady state	C50 at steady state	Cmin at steady state
Proposed Regimen (Sampson, 2014)					
Less than 30 weeks	20 mg/kg/dose every 12 hours	218	100%	97%	89%
30 to less than 36 weeks	20 mg/kg/dose every 8 hours	373	98%	94%	75%
36 to 41 weeks	20 mg/kg/dose every 6 hours	409	96%	86%	56%

Standard Dose Regimen (Kimberlin, 2001)

Less than 30 weeks	20 mg/kg/dose every 8 hours	218	100%	100%	100%

30 to less than 36
weeks
20 mg/kg/dose every 8
hours
373 98% 94% 74%
36 to 41 weeks 20 mg/kg/dose every 8
hours 409 94% 70% 10%
KEY: C50 at steady state = steady state plasma
concentrations at 50% of the dosing interval
Sampson, 2014
ABOUT
Special Considerations/Preparation
Injection
Availability: Solution (50 mg/mL) or as powder for
solution in 500-mg and 1-g vials.
Prepare powder for solution by dissolving contents of
500-mg vial in 10 mL sterile water for
injection. Reconstituted solution is stable at room
temperature for 12 hours. Do not
refrigerate[12].
Infusion solution concentration should be no greater
than 7 mg/mL[12].
A 5-mg/mL dilution may be made by adding 1 mL of 50
mg/mL concentration to 9 mL of
preservative-free normal saline. Dilution should be
used within 24 hours.
Oral
Oral suspension available in 200-mg/5 mL
concentration. Store at room temperature. Shake
well before administration [13].

Adenosine
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
Starting dose: 50 mcg/kg rapid IV push or intraosseous
(1 to 2 seconds).
Increase dose in 50 mcg/kg increments every 2 minutes
until return of sinus rhythm. Usual
maximum dose: 250 mcg/kg.
Uses
Acute treatment of sustained paroxysmal
supraventricular tachycardia.
It may also be useful in establishing the cause of the
SVT.
Administration
Administer as a rapid IV bolus over 1 to 2 seconds.
Infuse directly into a vein or as close to
the patient as possible. Follow with a rapid saline
flush of 5 to 10 mL after each bolus [1][2]
[3].
Concentration: Dilutions of a 3 mg/mL vial can be made
with NS for doses less than 0.2 mL

(600 mcg). Use 1 mL (3000 mcg) with 9 mL NS to make a solution with a final concentration of 300 mcg/mL [3].

MEDICATION SAFETY

Contraindications/Precautions

Contraindicated in patients with second- or third-degree AV block and patients with sinus node disease, such as sick sinus syndrome or symptomatic bradycardia (except patients with functioning pacemaker) [3].

Cardiac arrest, in some cases fatal, sustained ventricular tachycardia (requiring resuscitation), and myocardial infarction have been reported following adenosine infusion.

Patients with signs or symptoms of acute myocardial ischemia (eg, unstable angina or cardiovascular instability) have an increased risk for serious cardiovascular reactions with adenosine administration; therefore, avoid use in these patients. Cardiac resuscitative measures should be available prior to infusion [4].

Hemorrhagic and ischemic cerebrovascular accidents have been reported. Seizures (new or recurrent) have been reported and may require emergent management. Concomitant use of aminophylline increases the risk of seizures [5].

Hypersensitivity reactions, including dyspnea, tightening of the throat, flushing, erythema,

rash, and chest discomfort, have been reported and may require symptomatic treatment or resuscitative measures [6].

Adverse Effects

Flushing, dyspnea, and irritability occur frequently, but usually resolve within 1 minute.

Transient (duration less than 1 minute) arrhythmias may occur between termination of SVT and onset of normal sinus rhythm. Apnea has been reported in one preterm infant.

Recurrence of SVT occurs in approximately 30% of treated patients.

Aminophylline/Theophylline and caffeine diminish adenosine's effect by competitive antagonism.

Solution Compatibility

D5W and NS.

Monitoring

Continuous EKG and blood pressure monitoring.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Adenosine is the pharmacologically active metabolite of ATP. It acts by depressing sinus node automaticity and AV node conduction. It does not have negative inotropic effects. Response

should occur within 2 minutes of the dose. Estimated serum half-life is 10 seconds.
ABOUT
Special Considerations/Preparation
Supplied in 2-mL vials containing 6 mg adenosine dissolved in NS. Contains no preservative.
Store at room temperature. Do not refrigerate; crystallization will occur. Solution must be clear at the time of use.
Dilutions can be made with NS for doses less than 0.2 mL (600 mcg). Use 1 mL (3000 mcg) with 9-mL NS to make a solution with a final concentration of 300 mcg/mL.

Albumin (Human)
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
Hemolytic disease of the newborn:
1 g/kg of 25% albumin IV administered approximately 1 hour prior to exchange transfusion [1][2].
Hypotension: 0.5 g/kg (10 mL/kg) of 5% albumin IV over 20 to 30 minutes; may be repeated [3][4][5][6] up to maximum of 3 doses[6].
Septic shock: 0.5 g/kg (10 mL/kg) of 5% albumin IV over 5 to 10 minutes with repeat doses as needed up to maximum 3 g/kg (60 mL/kg) in the first hour until perfusion improves or hepatomegaly develop [7].
Uses
Cardiopulmonary bypass, adjunct to priming fluids: The agents of choice for the priming solution for cardiopulmonary bypass pumps are crystalloid solutions (for example, lactated Ringer's solution and NS). Nonprotein colloids in addition to crystalloids may be preferred when pulmonary shunting is a concern. For postoperative volume expansion, the preferred order of choice is crystalloids, nonprotein colloids (for example hetastarch, dextran, and synthetic colloids), and lastly albumin [15].
In cardiopulmonary bypass performed in neonates, human albumin has been added to the priming solution [16][17][18].
In addition to other components, 5% albumin 200 mL replaced fresh frozen plasma [17] or

20% albumin 100 mL replaced a portion of the fresh frozen plasma in the priming solution [16].

Hemolytic disease of the newborn: Albumin may be used to bind free serum bilirubin in infants with severe hemolytic disease prior to exchange transfusion [1]; it should not be administered in conjunction with phototherapy [2]. Immunoglobulin, not albumin, is recommended in infants with isoimmune hemolytic disease and an increasing total serum bilirubin despite intensive phototherapy or when bilirubin is within 2-3 mg/dL of exchange level [19].

Hyperbilirubinemia, adjunct to exchange transfusion: Adjunctive albumin is not included in the American Academy of Pediatrics recommendations for management of hyperbilirubinemia, [19]. however, guidelines from the University HealthSystem Consortium state albumin may be considered as an adjunct to exchange transfusion if administered concurrently, and not before, transfusion [15]. At one institution, albumin is considered before exchange transfusion, especially if serum albumin is less than 3.4 mg/dL [20]. Two studies of infants with intensive phototherapy failure (n=92; 32 weeks or more gestation; weighing more than 1000 g) demonstrated lower bilirubin levels at 6 and 12 hours post-exchange, shorter duration of phototherapy after exchange, and need for second exchange transfusion in albumin-treated neonates compared

with the control group [21][22]. The dosing regimen was 1 g/kg IV of 5% [22] or 20% albumin [21] administered 1 to 2 hours prior to exchange.

Hyperbilirubinemia, adjunct to phototherapy: Adjunctive albumin is not included in the American Academy of Pediatrics recommendations for management of hyperbilirubinemia [19]. In addition, the University HealthSystem Consortium states that albumin should not be administered as an adjunct to phototherapy [15]. Human 25% albumin 1 g/kg IV during the first 2 hours of intensive phototherapy rapidly reduced (by 2 hours) unbound bilirubin values compared with no albumin in a retrospective study (n=58; gestational age 39.4 weeks; birthweight 3245 g) of Japanese infants with hyperbilirubinemia. However, there was no difference in total bilirubin values [23]. A followup

study identified abnormalities of auditory brainstem responses at 6 months in 3 of 38 albumin-treated infants and 6 of 20 infants in the control group. At 2 years of age, abnormal development, including hearing loss, was not identified in either group [24].

Hypoalbuminemia: Albumin is not considered appropriate for treatment of hypoalbuminemia according to the University HealthSystem Consortium [15]. There is not enough evidence from randomized trials to determine if routine use of albumin (1 g/kg/day) in preterm neonates with hypoalbuminemia (less than 3 g/dL) is beneficial or harmful [25].

Hypotension: Albumin may be considered for volume expansion in neonates if 10 mL/kg of crystalloid solution is unsuccessful [15], however, the majority of very low birth weight (VLBW) premature infants (weighing 1500 grams or less and younger than 3 postnatal days) with hypotension are not hypovolemic [26][27]. When hypovolemia is present, albumin is generally not recommended for use; isotonic saline is preferred when a volume expander is needed [26].

Dopamine increased blood pressure better than albumin in preterm hypotensive neonates (weighing 1500 grams or less) younger than 24 hours (n=39) [28]. Albumin was superior to normal saline in neonates with hypotension in the first 24 hours of life in a randomized, double-blind study (n=101; mean birthweight 1528 to 1617 g; mean gestational age 30.1 to 30.8 weeks). Over 70% of neonates weighing less than 1500 g failed bolus therapy with either albumin or normal saline and required dopamine infusion. The rate for intraventricular hemorrhage was higher than the norm for both treatments; however, these hemorrhages were less common and less severe in the albumin treated group [3]. In contrast, 2 studies (n=104) did not demonstrate a difference between albumin and isotonic saline in normalizing mean arterial pressure [29][6].

Nephrotic syndrome, adjunct for edema: Diuretics alone are first line therapy, however, short-term use of 25% albumin may be considered in conjunction with a diuretic in patients with acute several peripheral or pulmonary edema having failure with diuretic therapy alone [15][30][15]. In pediatric patients with severe edema secondary to nephrotic syndrome, diuretics (eg, loop and thiazide) and 25% albumin infusions may be required in addition to a low-sodium diet and fluid restriction [31][15]. The benefit of albumin and a diuretic is transient and furthermore, albumin may lead to hypertension, pulmonary edema, and

congestive heart failure [31].
Studies are lacking in neonates. In one case-series (n=7) of full-term infants diagnosed with congenital nephrotic syndrome, the regimen was 20% albumin 1 g/kg IV (based upon ideal body weight) over 4 hours followed by IV furosemide (0.5 to 1 mg/kg) when needed [32].
Perioperative hemodynamic support: No differences in hemodynamics, fluid input, or fluid output were observed between perioperatively administered human 5% albumin and 6% hydroxyethyl starch 130/0.4 (Voluven) in newborns (at 30 weeks gestation) and infants younger than 24 months of age undergoing non-cardiac surgery in a randomized,

open-label trial (n=82). Infusion volume and rate were adjusted to maintain stable hemodynamics [33].
Polycythemia, adjunct to dilutional exchange transfusion: Crystalloid solutions, such as normal saline or Ringers solution, are considered the solutions of choice for exchange transfusion in neonates with polycythemia. Albumin is more expensive, frequently in short supply, and has a potential risk of infection. [34][35].
Resuscitation: Albumin is not used during neonatal resuscitation. Isotonic crystalloid solution or blood is recommended for volume expansion during resuscitation [36].
Severe Sepsis and Septic Shock:[7][37]
Hemodynamic Support - First 60 Minutes
Time Management- Proceed to next step if shock persists
0
minutes
Maintain airway and establish access
5
minutes
Push 10 mL/kg isotonic crystalloid or colloid boluses up to 40 mL/kg until improved perfusion or unless hepatomegaly.
Begin prostaglandin infusion until rule out ductal-dependent lesion.
15
minutes
DOPamine less than 10 mcg/kg/min +/- DOBUTamine for fluid-refractory shock
EPINEPHrine 0.05 to 0.3 mcg/kg/min for fluid-refractory DOPamine-resistant shock
60 min
Cold shock-Poor LV function
Normal blood pressure

ScvO(2) less than 70%*/Hgb greater than
12 g/dL
SVC flow less than 40 mL/kg/min or CI less
than 3.3 L/min/m(2)
Add nitrovasodilator milrinone or inamrinone
with volume loading
Cold shock- Poor RV function
PPHN
ScvO(2) less than 70%*
SVC flow less than 40 mL/kg/min or CI less
than 3.3 L/min/m(2)
Inhaled nitric oxide
Inhaled iloprost or IV adenosine
IV milrinone or inamrinone
Warm shock- Low blood pressure
Titrate volume
Add norepinephrine
Vasopressin or terlipressin or angiotensin
Refractory shock
Hydrocortisone if absolute adrenal
insufficiency.
Triiodothyronine if hypothyroid.
Begin pentoxifylline if VLBW newborn.
Consider closing PDA if hemodynamically
significant.
ECMO
Goals
First Hour: restore and maintain heart rate
thresholds, capillary refill of 2 seconds or less, and
normal blood pressure.
NICU: normal MAP-CVP, preductal and postductal oxygen
saturation difference less than 5%,
*ScvO(2) greater than 70% (except congenital heart
patients with mixing lesions), SVC flow greater
than 40 mL/kg/min, or cardiac index greater than 3.3
L/min/m(2)
KEY: CI = cardiac index, Hgb = hemoglobin, LV function
= left ventricle function, MAP-CVP = mean
arterial pressure-central venous pressure, PDA =
patent ductus arteriosus, PPHN = persistent
pulmonary hypertension of the newborn, ScvO(2) =
continuous central venous oxygen saturation,
SVC = superior vena cava, VLBW = very low birth weight
Davis et al: Crit Care Med 2017;45(6)

Pediatric FDA Approved Indications
AlbuRx-25 and Flexbumin 25%: Indicated for hemolytic
disease of the newborn to
attempt to bind and detoxify unconjugated bilirubin in
infants with severe hemolytic disease
prior to exchange transfusion [1][2].
Kedbumin: In patients 12 to 16 years of age, indicated
for hypovolemia,

hypoalbuminemia, burns (after 24 hours post burn in patients experiencing severe albumin depletion in order to favor edema reabsorption), ovarian hyperstimulation syndrome, and adult respiratory distress syndrome, and in cardiopulmonary bypass (as part of the priming fluids), hemodialysis, and to prevent central volume depletion after paracentesis due to cirrhotic ascites [14].

Safety of albumin solutions has been demonstrated in children provided the dose is appropriate for body weight; however, the safety of Flexbumin 25% has not been evaluated in sponsor conducted pediatric studies[1].

No clinical studies using Albuminar-5 have been conducted in pediatric patients. Safety and effectiveness in pediatric patients have not been established. However, extensive experience in patients suggests that children respond to Albuminar-5 in the same manner as adults [8]

Administration

Administer slow enough to avoid too-rapid plasma volume expansion. The 5% and 25% may be administered without dilution or diluted with normal saline or D5W [1][8].

Adequately hydrate patients during or after infusion of albumin 25% solutions [9][10].

In patients with normal blood volume, avoid circulatory overload and pulmonary edema by administering albumin no faster than 1 mL/min [1][11][12].

In the presence of hypertension, infuse at a slower rate [13][8].

Do not administer more than 4 hours after vial has been entered. Ensure substitution of other blood constituents (coagulation factors, electrolytes, platelets, and erythrocytes) is adequate when replacing comparatively large volumes of albumin or if blood loss is severe [1][9][14][2].

Warm to room temperature if infusing large volumes. In plasma exchange, adjust infusion rate to the rate of removal [14].

MEDICATION SAFETY

Contraindications/Precautions

Contraindicated :

Severe anemia or cardiac failure [14][38][9][10] with normal or increased intravascular volume

History of hypersensitivity reaction to albumin preparations or to any component of the product (eg, N-acetyltryptophan, sodium caprylate) [11][1]

Precaution

Administration: Conditions where hypervolemia and/or hemodilution may occur may

require dose and infusion rate adjustment; increased risk with heart failure, hypertension, esophageal varices, pulmonary edema, hemorrhagic diathesis, severe anemia, and renal

failure; monitoring recommended [11][1]
Administration: Circulatory overload or cardiac overload (eg, headache, dyspnea, jugular venous distention, rales and abnormal elevations in systemic or central venous blood pressure) may occur; monitoring recommended [11][1][39][40][41]; discontinue use at first clinical signs of cardiovascular overload [11][1]
Administration: Rapid rise in blood pressure may occur; monitoring recommended [39][40][41]
Administration: Do not dilute product with Sterile Water for Injection as there is risk of hemolysis, including potentially fatal cases, and acute renal failure in recipients [11][1]
Hematologic: Re-bleeding secondary to clot disruption can occur in trama and postoperative surgery patients; monitoring recommended [11][1]
Immunologic: Hypersensitivity reactions, including anaphylactic reactions, have been observed; discontinue use for suspected hypersensitivity reaction; implement standard treatment for anaphylactic shock [11][1]
Immunologic: Infectious agent transmission may occur, including a risk of exposure to viruses, Creutzfeldt-Jakob disease or variant Creutzfeldt-Jakob disease, and other pathogens [11][1][39][40][41].

Adverse Effects

Common: flushing, urticaria, fever, chills, nausea, vomiting, tachycardia, and hypotension.
These reactions usually subside when the infusion rate is slowed or stopped [14].
Lid edema occurred in 19.5% and 29.3% of newborns (at 30 weeks gestation) and infants younger than 24 months of age undergoing non-cardiac surgery receiving albumin 5% and hydroxyethyl starch 130/0.4, respectively [33].

Solution Compatibility

D5W, D10W, D5LR, D5NS, D50.45%NaCl, NS, 0.45%NaCl.

Solution Incompatibility

Protein hydrolysates, amino acid mixtures, or alcohol-containing solutions [2][14].

Terminal Injection Site Compatibility

Albumin, Human, 20%
Lorazepam 0.33 mg/mL.
Albumin, Human, 25%
Diltiazem 5 mg/mL, ketamine 50 mg/mL.

Terminal Injection Site Incompatibility
Fat emulsion, micafungin, midazolam, vancomycin, verapamil.
Monitoring
Closely monitor infusion rates and the patient's clinical state during infusion. Observe injured patients after restoration of blood pressure for bleeding points that may have failed to bleed at lower blood pressure [38][9][10].
Closely monitor for circulatory overload during administration. Regularly monitor hemodynamic performance, including arterial blood pressure and pulse rate, central venous pressure, pulmonary artery occlusion pressure, urine output, electrolyte levels, and HCT/Hb [14].
Closely monitor hemodynamic parameters after administering for evidence of cardiac or respiratory failure, renal failure or increasing intracranial pressure [11][1]
For a full-term newborn, the target heart rate and perfusion pressure (mean arterial pressure minus central venous pressure) are 110 to 160 beats/min and 55 mmHg, respectively [7].
MECHANISM OF ACTION/PHARMACOKINETICS
Pharmacology
Albumin products of various concentration are an aqueous solution of albumin obtained from large pools of human plasma. The colloid osmotic or oncotic properties of albumin are utilized for plasma or blood volume deficit and for oncotic deficit from hypoproteinemia [10] [38][9][2].[14]. Albumin's ability to bind and transport various molecules allows for use to bind free albumin in infants having severe hemolytic disease of the newborn [2].
The total exchangeable albumin pool is 4 to 5 g/kg (intravascular, 40% to 45%; extravascular, 55% to 60%) and the half-life of albumin is approximately 19 days.
Metabolism is achieved by feedback regulation; elimination is primarily intracellular (lysosomal proteases). During the first 2 hours following albumin infusion in healthy subjects, less than 10% leaves the intravascular compartment [14].
ABOUT
Special Considerations/Preparation
Albuminar-5: Preservative-free IV solution containing serum albumin 5% and supplied as 2.5 g/50 mL, 12.5 g/250 mL, and 25 g/500 mL in single-dose vials. May be administered undiluted [10].

Albuminar-20: Preservative-free IV solution containing serum albumin 20% and supplied

as 10 g/50 mL and 20 g/100 mL in single-dose vials [38].
Albuminar-25: Preservative-free IV solution containing serum albumin 25% and supplied
as 5 g/20 mL, 12.5 g/50 mL, and 25 g/100 mL in single-dose vials [9].
AlbuRx-25: Preservative-free IV solution containing serum albumin 25% and supplied as
12.5 g/50 mL and 25 g/100 mL in single-dose vials. Do not store at temperatures above 30
degrees C (86 degrees F) [2].
Flexbumin 5%: Preservative-free IV solution containing serum albumin 25% and
supplied as 12.5 g/250 mL in a single-dose plastic container. Do not store above 30 degrees
C and protect from freezing [1]
Flexbumin 25%: Preservative-free IV solution containing serum albumin 25% and
supplied as 12.5 g/50 mL and 25 g/100 mL in single-dose plastic containers. Do not store
above 30 degrees C and protect from freezing [1]
Kedbumin: Preservative-free IV solution containing serum albumin 25% (0.25 g/mL) and
supplied in 50-mL and 100-mL single-dose vials. Do not freeze or store above 30 degrees C.
Protect from light [14].
Albumin 25% solutions should only be diluted in suitable infusion solutions, such as D5W or
NS. Dilution of albumin 25% with sterile water for injection produces a hypotonic solution
that may result in life-threatening hemolysis and acute renal failure [1][9][14][2].

Albuterol
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
Bronchodilation: 0.1 to 0.5 mg/kg/dose every 2 to 6 hours via nebulizer.
1 Metered-dose inhaler (MDI) actuation per dose (approximately 0.1 mg or 100 mcg) every 2
to 6 hours via MDI with spacer device placed in the inspiratory limb of the ventilator circuit.
Simulated neonatal lung models suggest greater delivery when using a spacer with the MDI.

Use chlorofluorocarbon free preparations when administering to neonates.
For nebulizations, use preservative-free solutions; benzalkonium chloride in the 20-mL multidose bottles may cause bronchoconstriction, particularly with frequent or continuous administration [1].
Oral: 0.1 to 0.3 mg/kg/dose orally every 6 to 8 hours.
Treatment of hyperkalemia
Preterm neonates: 0.4 mg/dose every 2 hours via nebulization until serum potassium decreases to desired safe level (eg, less than 5 mmol/L) [2]. Consider alternative potassiumlowering therapies for potassium levels greater than 7.5 mmol/L.
Uses
Bronchodilator
Hyperkalemia in preterm neonates: Published data using the nebulized formulation of albuterol for the treatment of hyperkalemia in preterm neonates are limited to one randomized, placebo-controlled trial (n=19). Following administration every 2 hours until serum potassium dropped below 5 mmol/L (or a maximum of 12 doses), nebulized albuterol (n=8) was effective in lowering potassium levels at 4 and 8 hours when compared with placebo (saline via nebulization; n=11) [2].
Bronchiolitis: Albuterol is not recommended for the routine treatment of bronchiolitis in infants and children. Consistent benefits have not been demonstrated. There are a lack of data in those with severe disease or with respiratory failure [12].
Administration
Inhalation
ProAir HFA, Proventil HFA, Ventolin HFA
Metered-dose inhaler: Shake well before each spray; canister should be at room temperature before use. Prime before using for the first time, or if the inhaler has not been used for more than 2 weeks, or when the inhaler has been dropped; prime the inhaler by spraying it 4 times for Proventil HFA or Ventolin HFA or 3 times for ProAir HFA into the air, away from the face [3][4][5]. Use a spacer or a valve holding chamber in younger

patients (less than 5 years of age) or patients with poor inhaler technique. A mask should be added for children less than 4 years of age [6].
Proair Respiclick, Proair Digihaler
Metered-dose inhaler: Does not require priming [7][8]

Do not use with spacer or volume holding chamber [7][8]
Keep inhaler clean and dry by wiping with dry cloth or tissue as needed; never wash or put any part of inhaler in water [7][8]
Nebulization
Solution for inhalation: Use the entire contents of pre-diluted vials for inhalation via nebulizer immediately after opening [9]. The dose withdrawn from the 0.5% 20-mL multidose bottle must be further diluted with sterile normal saline to a total volume of 3 mL prior to administration [10]. Preservative-free solutions are recommended, particularly with continuous nebulization; benzalkonium chloride in 20-mL multidose bottles may cause bronchoconstriction [1]. There are no data in neonates, however, no significant differences in response were observed between albuterol solutions with and without benzalkonium chloride in a retrospective study of 128 hospitalized pediatric patients (4 to 17 years of age) administered continuous nebulized albuterol [11].
Administer via nebulizer over 5 to 15 minutes at a gas flow of 6 to 8 L/minute [10][6][9]. A tight-fitting face mask should be used in patients who cannot use a mouthpiece [6].
MEDICATION SAFETY
Contraindications/Precautions
Contraindications
Proair Respiclick and Proair Digihaler are contraindicated in patients with history of hypersensitivity to albuterol and/or severe hypersensitivity to milk proteins [7][8].
Precautions
Cardiovascular:Use sympathomimetic amines with caution in patients with preexisting cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; possibility for cardiovascular events seen in heart rate, blood pressure and ECG changes [7][8][5][13][14][15][16][17]. Discontinuation may be required [7][8]
Endocrine and metabolic: Use caution in patients with preexisting diabetes mellitus [7][8] [5][14][13][15][16][17] as large doses of IV albuterol have been reported to aggravate condition [7][8]
Endocrine and metabolic: Use caution in patients with preexisting ketoacidosis [7][5][14] [13] as large doses of IV albuterol have been reported to aggravate condition [7][8]
Endocrine and metabolic: Use caution in patients with preexisting hyperthyroidism [7][8] [5][13][14][15][16][17]
Endocrine and metabolic: Hypokalemia has occurred but considered transient and not

requiring supplementation, but has potential to lead to other cardiovascular side effects [7][8][5][13][14][15][16][17]
Higher doses: Fatalities have been reported upon exceeding recommended doses or excessive use. The cause of death is unknown, but severe acute asthmatic crisis and subsequent hypoxia suspected [7][8][5][14][13]
Immunologic: Rare immediate hypersensitivity can occur and manifest as symptoms of urticaria, angioedema, rash, bronchospasm, anaphylaxis, and oropharyngeal edema [7][8]. Consider not reinitiating if immediate hypersensitivity occurs [7][5][14][13]

Immunologic: Lactose, used as an inactive ingredient in some inhalers, could lead to immediate hypersensitivity reactions to milk proteins, including anaphylaxis, angioedema, pruritus, and rash [7][8]
Neurologic: Use caution in patients with preexisting convulsive disorders [7][8][5][14][13][15][16][17]
Respiratory: Beta adrenergic agonist therapy alone may be insufficient to control asthma in many patients; consider adding anti-inflammatory agents (eg, corticosteroids) to therapeutic regimen [7]
Respiratory: Benzalkonium chloride preservative, in the multi-dose bottle for nebulization, may induce bronchoconstriction; use only single-use preservative-free, albuterol, particularly when using continuous nebulized albuterol (off-label use) [1].
Respiratory: Asthma deterioration may occur suddenly over a few hours or chronically over a few days; use of more albuterol than usual may indicate asthma deterioration [8], consider alternative therapy [5][14][13] and reevaluation of treatment regimen, giving special consideration to possible need for anti-inflammatory treatment [7]
Respiratory: Potentially life-threatening paradoxical bronchospasm has been reported and often occurs with first use of new canister. Discontinue immediately if this occurs and consider alternative treatments [7][8][5][14][13]
Adverse Effects
Tachycardia, arrhythmias, tremor, hypokalemia, and irritable behavior.
Monitoring
Assess degree of bronchospasm. Continuous EKG monitoring. Consider not administering

when heart rate is greater than 180 beats per minute. Serum potassium [2].
MECHANISM OF ACTION/PHARMACOKINETICS
Pharmacology
Specific ?2-adrenergic agonist. Minimal cardiovascular effects unless used concurrently with aminophylline. Stimulates production of intracellular cyclic AMP, enhancing the binding of intracellular calcium to the cell membrane and endoplasmic reticulum, resulting in bronchodilation. Enhances mucociliary clearance. Drives potassium intracellular. Studies in vitro indicate that approximately 5% of a MDI dose administered using an in-line holding chamber/spacer device, versus less than 1% of a nebulizer dose, is delivered to the lung. Optimal aerosol dose in neonates is uncertain due to differences in aerosol drug delivery techniques. The therapeutic margin appears to be wide. Well absorbed when administered orally. Onset of action is 30 minutes; duration is 4 to 8 hours. Serum half-life is approximately 6 hours (adults). Time to peak serum concentration is 3 to 4 hours. Tolerance may develop.

ABOUT
Special Considerations/Preparation
Oral dosage form: Syrup, 2 mg/5 mL.
Solution for inhalation: Pre-diluted 0.63 mg/3 mL (0.021%), 1.25 mg/3 mL (0.042%), and 2.5 mg/3 mL (0.083%) unit dosed vials. Albuterol 0.5% multidose 20-mL bottle contains benzalkonium chloride 0.01%. After the dose is withdrawn from the concentrated 0.5% solution, dilute with sterile normal saline to a total volume of 3 mL per dose prior to nebulization [10].
Store unit dose vial in protective foil pouch at all times to protect it from light; use within 1 week once removed from the foil pouch. Do not use if the solution in the vial changes color or becomes cloudy. Store at controlled room temperature between 20 to 25 degrees C [18] [9].
Stability and Sterility
Preservative-free (PF) Albuterol Solution (0.67 mg/mL and 0.17 mg/mL): Albuterol single-use mini nebs (2.5 mg/0.5 mL, PF, Nephron Pharmaceuticals, West Colombia, SC) diluted with normal saline for irrigation to a concentration of 0.67 mg/mL and 0.17 mg/mL was stable through 168 hours when stored at room temperature (20 to 25C) and at

refrigeration (2 to 8C). There was no bacterial growth detected throughout 10 days of incubation. [19].
Stability and Sterility
Benzalkonium Chloride (BAC)-Albuterol Solution (0.67 mg/mL and 0.17 mg/mL):
Albuterol BAC (5 mg/mL, Hi-Tech Pharmaceuticals, Amityville, NY) diluted with normal saline for irrigation to a concentration of 0.67 mg/mL and 0.17 mg/mL was stable through 168 hours when stored at room temperature (20 to 25C) and at refrigeration (2 to 8C). There was no bacterial growth detected throughout 10 days of incubation. [19].
Metered-Dose Inhaler: Pressurized hydrofluoroalkane metered dose inhaler (contains no chlorofluorocarbons (CFC)). Proventil HFA and Ventolin HFA 90 mcg albuterol base per actuation.

Alprostadil
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
Initial dose: 0.05 to 0.1 mcg/kg per minute by continuous IV infusion.
Titrate to infant's response--oxygenation versus adverse effects.
Maintenance dose: May be as low as 0.01 mcg/kg per minute.
Higher initial doses are usually no more effective and have a high incidence of adverse effects.
May also be given via UAC positioned near ductus arteriosus.
Uses
To promote dilation of ductus arteriosus in infants with congenital heart disease dependent on ductal shunting for oxygenation/perfusion.
Pediatric FDA Approved Indications
To promote dilation of ductus arteriosus in infants with congenital heart disease (ie, pulmonary atresia, pulmonary stenosis, tricuspid atresia, tetralogy of Fallot, interruption of the aortic arch, coarctation of the aorta, or transposition of the great vessels with or without other defects) dependent on ductal shunting for oxygenation/perfusion [1][3][4][5]. Low success rates for prostaglandin E1 are usually due to an irreversibly closed ductus and severe acidemia and collapse. Functional closure of the ductus occurs within a few hours of birth,

and anatomical closure occurs in 21 days (normal term infant) [4].
Administration
Continuous infusion via a large vein is the preferred route of administration. May also be given via UAC positioned near the ductus arteriosus. For continuous infusion, dilute in compatible solution to a concentration of 2 to 20 mcg/mL [1]. The recommended standard concentrations are 1, 2.5, 5, 10, and 20 mcg/mL for continuous infusions [2].
MEDICATION SAFETY
Contraindications/Precautions
CONTRAINDICATIONS: None
PRECAUTIONS:

Cardiovascular: Structural alterations (intimal lacerations, decreased medial muscularity, and disruption of the medial and internal elastic lamina) of the ductus and pulmonary arteries have been observed [6].
Gastrointestinal: Gastric outlet obstruction due to antral hyperplasia may occur; dose- and duration-related [6].
Hematological: Use with caution in neonates with bleeding tendencies [6].
Musculoskeletal: Cortical proliferation of the long bones has been observed with long-term infusions; resolution with discontinuation of alprostadil [6].
Respiratory: Do not use in neonates with respiratory distress syndrome [6].
Adverse Effects
Common (6% to 15%): Apnea (consider treating with aminophylline), hypotension, fever, leukocytosis, cutaneous flushing, and bradycardia. Hypokalemia reported with long-term therapy (greater than 20 days), especially with doses greater than 0.05 mcg/kg/minute.
Gastric outlet obstruction and reversible cortical proliferation of the long bones after prolonged treatment (greater than 120 hours).
Uncommon (1% to 5%): Seizures, hypoventilation, tachycardia, cardiac arrest, edema, sepsis, diarrhea, and disseminated intravascular coagulation.
Rare (less than 1%): Urticaria, bronchospasm, hemorrhage, hypoglycemia, and hypocalcemia.
Musculoskeletal changes: Widened fontanels, pretibial and soft tissue swelling, and swelling of the extremities may occur after 9 days of therapy. Cortical hyperostosis and

periostitis may occur with long-term (greater than 3 months) therapy. These changes resolve over weeks after discontinuation of therapy.
Black Box Warning
Apnea has been reported in 10% to 12% of neonates with congenital heart defects treated with alprostadil. Apnea is seen most often in neonates weighing less than 2 kg at birth, and usually appears during the first hour of drug infusion. Monitor respiratory status throughout treatment and be prepared to intubate/resuscitate.
Solution Compatibility
D5W and NS.
Terminal Injection Site Compatibility
Aminophylline, ampicillin, caffeine citrate, calcium chloride, cefazolin, cefotaxime, cimetidine, clindamycin, dobutamine, dopamine, fentanyl, furosemide, gentamicin, glycopyrrolate,

metoclopramide, metronidazole, nitroglycerin, nitroprusside, potassium chloride, penicillin G, tobramycin, vancomycin, and vecuronium.
Monitoring
Therapeutic
Restricted pulmonary blood flow: Improvement in blood oxygenation demonstrates efficacy [6]
Restricted systemic blood flow: Improvement of systemic blood pressure and blood pH demonstrates efficacy [6]
Toxic
Cardiovascular: Measure arterial pressure intermittently by umbilical artery catheter, auscultation, or with a Doppler transducer [6].
Gastrointestinal: Monitor for signs and symptoms of antral hyperplasia and gastric outlet obstruction in neonates administered alprostadil for more than 120 hours [6].
MECHANISM OF ACTION/PHARMACOKINETICS
Pharmacology
Alprostadil causes vasodilation of all arterioles. Inhibition of platelet aggregation. Stimulation of uterine and intestinal smooth muscle. Maximal drug effect usually seen within 30 minutes in cyanotic lesion; may take several hours in acyanotic lesions.
ABOUT
Special Considerations/Preparation
Supplied: 500 mcg in 1 mL of dehydrated alcohol ampules that must be refrigerated. Dilute before administration to a concentration of 20 mcg/mL or less. Prepare fresh infusion solutions every 24 hours.
Dilutions and Stability

Alprostadil 11 mcg/mL in 250 mL of 0.9% sodium chloride stored in polyvinyl chloride (Viaflex) containers at refrigerated temperature and protected from light was stable for 10 days. Prostin VR Pediatric was used for this stability study [7].
Alprostadil 20 mcg/mL in 0.9% sodium chloride stored in glass ampules or plastic syringes was stable (degrades to 90%) for 106.5 days at 4C and 9.8 days at 25C and stable (degrades to 95%) for 51.8 days at 4C and 4.8 days at 25C. Storage in plastic syringes led to components leaching from the plastic and silicone piston head seals. Prostin VR Pediatric was used for this stability study [8].
When mixing in a volumetric infusion chamber, undiluted alprostadil should not come in

contact with the walls of the chamber. Add the appropriate amount of IV solution to chamber, then add the undiluted alprostadil solution. Replace volumetric infusion chamber if the appearance of the chamber changes and the solution becomes hazy[6].
Sample Dilution and Infusion Rate: Mix 1 ampule (500 mcg) in 50 mL of compatible solution (eg, D5W) yielding an approximate concentration of 10 mcg/mL. Infuse at a rate of 0.01 mL/kg/min to provide a dose of 0.1 mcg/kg/minute [6]

Alteplase

DOSING/ADMINISTRATION
Dose
Restoration of function to central venous catheter: Instill into dysfunctional catheter at a concentration of 1 mg/mL. Use 110% of the internal lumen volume of the catheter, not to exceed 2 mg in 2 mL. If catheter function is not restored in 120 minutes after 1 dose, a second dose may be instilled.
An alternative dosing regimen using a smaller dose (0.5 mg diluted in NS to volume required to fill the central venous catheter) was used in children 10 kg or less in 1 study (n=25; infants as young as 7 weeks included).
Dissolution of intravascular thrombi: 200 mcg/kg per hour (0.2 mg/kg per hour).

Duration of therapy is 6 to 48 hours. If administering directly into the thrombus, dose may be increased after 6 hours to a maximum of 500 mcg/kg per hour. If localized bleeding occurs, stop infusion for 1 hour and restart using 100 mcg/kg per hour. Discontinue heparin several hours prior to initiation of therapy.
Note: Reports in the literature are a collection of cases gathered over several years. Some authors used loading doses, others did not. Infused doses ranged from 20 to 500 mcg/kg per hour. Complications were most often linked with higher doses and longer duration of therapy.
Call 1-800-NOCLOTS for case reporting and treatment guidance.
Uses
Dissolution of intravascular thrombi of recent onset that are either intraarterial or lifethreatening.
Adjuvant treatment of infective endocarditis vegetations.
Restoration of function to central venous access devices as assessed by the ability to withdraw blood.
Administration
Restoration of function to central venous catheter: Concentration of 1 mg/mL. Use 110% of the internal lumen volume of the catheter, not to exceed 2 mg in 2 mL [1][2][3][4].
Alternatively, use a smaller dose (0.5 mg diluted in NS to volume required to fill the central venous catheter) [5].
Dissolution of intravascular thrombi: May be administered as reconstituted at 1 mg/mL or further diluted in compatible diluent (in PVC bags or glass vials) to a concentration of 0.5 mg/mL [6].

Call 1-800-NOCLOTS for case reporting and treatment guidance.
MEDICATION SAFETY
Contraindications/Precautions
Use is contraindicated in patients with acute ischemic stroke under the following conditions [7]:
Active internal bleeding
Bleeding diathesis
Current intracranial hemorrhage
Hypertension that is current, severe, and uncontrolled
Intracranial or intraspinal surgery within the last 3 months
Intracranial conditions that may increase the risk of bleeding (ie, neoplasm, aneurysm, arteriovenous malformation)

Serious head trauma within the last 3 months
Subarachnoid hemorrhage
Use is contraindicated for the treatment of acute myocardial infarction or pulmonary embolism under the following conditions [7]:
Active internal bleeding
Bleeding diathesis
Hypertension that is current, severe, and uncontrolled
Intracranial or intraspinal surgery within the last 3 months
Intracranial conditions that may increase the risk of bleeding (ie, neoplasm, aneurysm, arteriovenous malformation)
Recent history of stroke
Serious head trauma within the last 3 months
Precautions
Administration: Avoid noncompressible arterial, internal jugular, or subclavian punctures or IM injection [7]
Angioedema: Angioedema has been reported during and up to 2 hours after administration in patients with ischemic stroke or myocardial infarction; risk may have been increased with use of concomitant ACE inhibitors. Discontinue and institute appropriate therapy if condition occurs [8]
Cardiovascular: Acute pericarditis or subacute bacterial endocarditis increase the risk of adverse effects [7]
Cardiovascular: Increased risk of thromboembolic events in patients with high likelihood of left-heart thrombus (eg, mitral stenosis or atrial fibrillation) [8]
Cardiovascular: Hypertensive patients (systolic, 175 mmHg or greater; diastolic, 110 mmHg or greater) are at an increased risk of adverse effects [7]
Cardiovascular: Stroke risk may outweigh treatment benefit in myocardial infarction

patients at low risk of cardiac death [7]
Endocrine and metabolic: Cholesterol embolism has been reported with thrombolytic agents [7]
Gastrointestinal: Recent gastrointestinal bleeding increases the risk of alteplase adverse effects [7]
Hematologic: Fatal hemorrhage associated with traumatic intubation has occurred [7]
Hematologic: If treatment is initiated before coagulation test results are available, discontinue if baseline INR or aPTT elevations are seen [7]

Hematologic: Bleeding may occur with concurrent anticoagulant therapy, especially at arterial puncture sites. If serious bleeding develops, discontinue and treat appropriately [8]
Hematologic: Active internal bleeding or embolic complications may occur with venous catheter occlusion [2]
Hematologic: Significant or fatal internal (ie, intracranial, retroperitoneal, gastrointestinal, genitourinary, respiratory) or external bleeding have been reported; discontinue use if serious bleeding occurs [9]
Hematologic: Serious bleeding at critical location can occur; discontinue use [2]
Hematologic: Septic thrombophlebitis increases the risk of adverse effects [7]
Hematologic: An occluded AV cannula at a seriously infected site increases the risk of adverse effects [7]
Hematologic: Hemostatic defects, including defects secondary to severe renal or hepatic disease, increase the risk of adverse effects [7]
Hematologic: Underlying DVT may not be adequately treated in pulmonary embolism patients [8]
Hematologic: Increased risk of re-embolization due to lysis of underlying DVT in pulmonary embolism patients [8]
Hematologic: Minimize arterial and venous punctures due to an increased risk of bleeding; discontinue use if serious bleeding occurs [7]
Hematologic: Thrombocytopenia [2]
Hepatic: Significant hepatic dysfunction increases the risk of adverse effects [7]
Immunologic: Hypersensitivity, including urticarial and anaphylactic reactions (eg, laryngeal edema, rash, and shock) with rare fatal outcome, have been reported [8][10]; if hypersensitivity occurs, discontinue use and institute appropriate therapy [8]
Immunologic: Catheter infection may occur with venous catheter occlusion [2]
Neurologic: Cerebrovascular disease increases the risk of adverse effects [7]
Ophthalmic: Hemorrhagic ophthalmic conditions, including diabetic hemorrhagic retinopathy, increase the risk of adverse effects [7]
Renal: Recent genitourinary bleeding increases the risk of adverse effects [7]
Reproductive: Pregnancy may increase the risk of adverse effects [7]
Reproductive: Recent genitourinary bleeding may increase the risk of adverse effects [7]
Surgery: Recent major surgery increases the risk of adverse effects [7][2]
Special populations: Recent trauma increases the risk of adverse effects [7]

Adverse Effects

Intracranial hemorrhage may occur, especially in premature infants treated for prolonged periods. Bleeding from venipuncture sites occurs in approximately half of treated patients.
The risk of complications increases at doses above 450 mcg/kg per hour.
Solution Compatibility

NS and D5W.
Terminal Injection Site Compatibility
Lidocaine, morphine, nitroglycerin, and propranolol.
Terminal Injection Site Incompatibility
Dobutamine, dopamine, and heparin.
Monitoring
Follow coagulation studies (PT, aPTT, fibrinogen, fibrin split products) prior to therapy and at least daily during treatment. Maintain fibrinogen levels greater than 100 mg/dL and platelets greater than 50,000/mm3. Echocardiography to assess clot lysis at least every 12 hours (every 6 hours optimal). Cranial ultrasound to assess for hemorrhage prior to therapy.
MECHANISM OF ACTION/PHARMACOKINETICS
Pharmacology
Alteplase binds strongly and specifically to fibrin in a thrombus and converts the entrapped plasminogen to plasmin. This initiates local fibrinolysis with limited systemic proteolysis. Alteplase has a shorter half-life than streptokinase and does not cause anaphylactic reactions. It is cleared rapidly from the plasma, primarily via the liver.
ABOUT
Special Considerations/Preparation
Activase is supplied as lyophilized powder in 50 mg and 100 mg vials. Reconstitute 50- or 100-mg vial by adding 50 or 100 mL of sterile water for injection (do not use bacteriostatic water for injection) respectively, for a concentration of 1 mg/mL. Can be further diluted with NS or D5W to a concentration of 0.5 mg/mL if necessary. Use reconstituted solution within 8 hours of mixing when stored refrigerated or at room temperature.
Cathflo Activase is supplied as lyophilized powder in 2-mg vials. Reconstitute by adding

2.2 mL sterile water for injection to a final concentration of 1 mg/mL. Do not use

bacteriostatic water for injection. Mix by gently swirling until the contents are completely dissolved. DO NOT SHAKE. Use reconstituted solution within 8 hours of mixing. Reconstituted solution may be stored refrigerated or at room temperature.

Amikacin

NeoFax Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Postnatal Age - Weight Dosing

These regimens were developed based on population pharmacokinetics, simulations, and subsequent prospective validations. Target concentrations: peak (1 hour after completion of 20 minute infusion) greater than 24 mg/L, trough (just before dose) less than 3 mg/L[1][2][3].

Weight	Postnatal Age	
	Younger than 14 days	14 days or older
800 g or less	16 mg/kg/dose every 48 hours	20 mg/kg/dose every 42 hours
801 to 1200 g	16 mg/kg/dose every 42 hours	20 mg/kg/dose every 36 hours
1201 to 2000 g	15 mg/kg/dose every 36 hours	18 mg/kg/dose every 30 hours
2001 to 2800 g	15 mg/kg/dose every 36 hours	18 mg/kg/dose every 24 hours
2800 g or greater	15 mg/kg/dose every 30 hours	18 mg/kg/dose every 20 hours

Smits et al, 2017; Rivera-Chaparro et al, 2017; Smits et al, 2015

Postnatal Age - Postmenstrual Age Dosing

These regimens were developed by a retrospective pharmacokinetic study (n=278). Target peak concentrations were attained in 84% of neonates (median (interquartile range): gestational age 36.9 weeks (30.1 to 38.9), postnatal age 1 day (0 to 2), and postmenstrual age 37 weeks (33 to 39)). Mean peak and trough concentrations were 28.5+/-5.8 mg/mL and 2+/-1.7 mg/L, respectively. Target concentrations: Peak of (30 minutes after completion of the infusion) 20 to 35 mg/L and trough (30 to 60 minutes before dose) less than 8 mg/L[4].

Postmenstrual Age	Postnatal Age	Dosage
29 weeks or less		
	0 to 7 days	14 mg/kg/dose every 48 hours
	8 to 28 days	12 mg/kg/dose every 36 hours
	29 days or older	12 mg/kg/dose every 24 hours

30 to 34 weeks
0 to 7 days 12 mg/kg/dose every 36 hours
8 days or older 12 mg/kg/dose every 24 hours
35 weeks or more All 12 mg/kg/dose every 24 hours
Hughes, 2017
Dosage Adjustment
Coadministration with ibuprofen: Prolong the dosing interval by 10 hours when
ibuprofen is administered [3].
Hypothermia/Asphyxia: Dose interval was prolonged by 10 hours in neonates with
asphyxia in a pharmacokinetic study [3].
Alternatively, dose adjustment was suggested based on a population pharmacokinetic modeling and simulation of retrospectively collected data for near term neonates with perinatal asphyxia treated with therapeutic hypothermia (n=56) [5]
combined with published data of preterm and term neonates (n=874) [3][6]. Proposed
regimen: 15 mg/kg/dose every 48 h for children between 1,200 g and 2,800 g and 15-
48

mg/kg/ dose every 42 h for neonate above 2,800 g for the first 2 consecutive doses during
hypothermia (33.5 degrees C) for target concentrations greater than 24 mg/L for peak and
less than 5 mg/L for trough. Less than 17% of dose simulations had trough concentrations
more than 5 mg/L [5]
Renal Impairment: Either prolong intervals or reduce dose [7].
Uses
Amikacin was effective for infections caused by gram-negative bacilli that are resistant to
other aminoglycosides. Usually used in combination with a ?-lactam antibiotic for neonatal
sepsis and other severe infections because of the possibility of infections due to grampositive
organisms such as streptococci or pneumococci [7].
Infective endocarditis: The following recommendations are based on a consensus of
experts [13]. The full pediatric guidelines can be found here:
https://doi.org/10.1161/CIR.0000000000000298
Organism Directed Therapy
Organism First-Choice Alternative Choice
Streptococci
Highly susceptible to penicillin G (MBC 0.1 mcg/mL or less); includes most viridans streptococci, groups A, B, C, G nonenterococcal, group D streptococci (S bovis, S equinus)
Penicillin G or
CefTRIAXone
Vancomycin or

First-generation
cephalosporin or
CefTRIAXone
Relatively resistant to penicillin (MBC 0.2 mcg/mL
or more); less-susceptible viridans streptococci
or
enterococci
Penicillin G or
Ampicillin +
Gentamicin (for first
2 weeks, or entire
course for
enterococci)
Vancomycin +
Gentamicin for
enterococci
Ampicillin +
CefTRIAXone (for
aminoglycoside (AMG)-
resistant enterococci or
AMG-intolerant patient)
CefTRIAXone +
gentamicin (not for
enterococcal endocarditis)
Resistant to penicillin Consult an infectious
disease specialist.

Staphylococci (S aureus or coagulase-negative
staphylococci)
Penicillin G susceptible (1 mcg/mL or less) (rare)
Penicillin G Oxacillin or
Nafcillin or
First-generation
cephalosporin or
Vancomycin
Penicillin G resistant (0.1 mcg/mL)
Oxacillin or
Nafcillin
with or without
Gentamicin
Vancomycin (for those
highly allergic to betalactam
antibiotics) or
First-generation
cephalosporin
Oxacillin (MRSA) resistant (4 mcg/mL) Vancomycin
Daptomycin for rightsided
endocarditis, maybe

for left-sided
Vancomycin resistant or intolerant Daptomycin Unknown
When prosthetic material present add riFAMpin
+ gentamicin (for first 2 weeks) for all
staphylococci

Gram-negative enteric bacilli
CefTAZidime or
Cefepime or
Cefotaxime or
CefTRIAXone
Plus gentamicin (or
tobramycin or
amikacin, depending
on susceptibility)
Broad-spectrum penicillin
Plus gentamicin (or
tobramycin or amikacin)
HACEK group
CefTRIAXone or
Cefotaxime or
Ampicillin-sulbactam
Ampicillin (when
susceptible)
Plus aminoglycoside
KEY: AMG = aminoglycosides; HACEK = Haemophilus species, Aggregatibacter species, Cardiobacterium hominis, Eikenella corrodens, and Kingella species; MBC = minimum bactericidal concentration, MRSA = methicillin-resistant Staphylococcus aureus (includes resistance to oxacillin, nafcillin, and cephalosporins)
Baltimore, 2015
Sepsis
Optimal treatment for suspected, early-onset sepsis is broad-spectrum antimicrobial coverage using a combination of ampicillin and an aminoglycoside (usually gentamicin); once a pathogen is identified, therapy should be narrowed unless synergism is required. Therapy should be discontinued at 48 hours if the probability of sepsis is low. Duration of treatment is usually 10 days for bacteremia without an identifiable focus [14].
There was no difference in failure rate between a 7-day vs 10-day duration of empiric treatment with IV cefTRIAXone and amikacin for culture-proven sepsis in 132 neonates, 1.5 kg or more and gestational age 32 weeks or more, who remitted clinically by day 5 in a randomized study. The follow-up period was 28 days. The median age at presentation was 3 days (2 to 4 days) and 56.8% had early-onset sepsis. The majority of organisms in blood cultures were Klebsiella spp. (40.9%), Staphylococcus aureus (22.7%), Enterobacter spp. (16.7%), and MRSA (7.6%) [15].
Pediatric FDA-Approved Indications
Short-term treatment of serious infections caused by susceptible strains of Gram-negative bacteria, including Pseudomonas species, E. coli, species of indole-positive and indolenegative

Proteus, Providencia species, Klebsiella-Enterobacter-Serratia species, and Acinetobacter (Mima-Herellea) species [7].

Administration

Dilute to a final concentration of 2.5 to 10 mg/mL [8][9][10][11] and administer as IV infusion by syringe pump over 60 to 120 minutes [12]; in neonatal studies amikacin was infused over 20 minutes [3] and in neonatal pharmacokinetic modeling studies infusion rates of 20 to 30 minutes were applied [6].

Administer as a separate infusion from penicillin-containing compounds. IM injection is

associated with variable absorption, especially in the very small infant.

MEDICATION SAFETY

Contraindications/Precautions

Precautions

Administration: In vitro mixing of aminoglycosides with beta-lactam antibiotics (penicillin or cephalosporins) may result in a significant mutual inactivation. A reduction in serum halflife or serum level may occur when an aminoglycoside or penicillin-type drug is administered by separate routes. Inactivation of the aminoglycoside is clinically significant only in patients with severely impaired renal function. Inactivation may continue in specimens of body fluids collected for assay, resulting in inaccurate aminoglycoside readings. Such specimens should be properly handled (assayed promptly, frozen or treated with betalactamase) [7]

Gastrointestinal: Clostridium difficile associated diarrhea has been reported and ranged from mild diarrhea to fatal colitis; discontinue use if suspected [7].

Immunologic: Allergic-type reactions, including anaphylaxis and life-threatening or less severe asthmatic reactions, may occur in patients with sulfite sensitivity as preparation contains sodium metabisulfite [7].

Neurologic: Use caution in patients with myasthenia gravis or parkinsonism; muscle weakness may be aggravated [7].

Topical irrigation: Irreversible deafness, renal failure, and death due to neuromuscular blockade have been reported following irrigation of both small and large surgical fields with aminoglycoside preparations [7].

Adverse Effects

Transient and reversible renal tubular dysfunction may occur, resulting in increased urinary

losses of sodium, calcium, and magnesium. Vestibular and auditory ototoxicity may occur.
The addition of other nephrotoxic and/or ototoxic medications (eg, furosemide, vancomycin) may increase these adverse effects. Increased neuromuscular blockade (ie, neuromuscular weakness and respiratory failure) may occur when used with pancuronium or other neuromuscular blocking agents and in patients with hypermagnesemia.
Black Box Warning
Patients treated with parenteral aminoglycosides should be under close clinical observation because of the potential ototoxicity and nephrotoxicity associated with their use. Safety for treatment periods which are longer than 14 days has not been established.
Neurotoxicity, manifested as vestibular and permanent bilateral auditory ototoxicity, can occur in patients with preexisting renal damage and in patients with normal renal function treated at higher doses and/or for periods longer than those recommended. The risk of aminoglycoside-induced ototoxicity is greater in patients with renal damage. High frequency deafness usually occurs first and can be detected only by audiometric testing. Vertigo may occur and may be evidence of vestibular injury. Other manifestations of neurotoxicity may

include numbness, skin tingling, muscle twitching and convulsions . The risk of hearing loss due to aminoglycosides increases with the degree of exposure to either high peak or high trough serum concentrations . Patients developing cochlear damage may not have symptoms during therapy to warn them of developing eighth-nerve toxicity, and total or partial irreversible bilateral deafness may occur after the drug has been discontinued.
Aminoglycoside-induced ototoxicity is usually irreversible.
Aminoglycosides are potentially nephrotoxic. The risk of nephrotoxicity is greater in patients with impaired renal function and in those who receive high doses or prolonged therapy.
Neuromuscular blockade and respiratory paralysis have been reported following parenteral injection, topical instillation (as in orthopedic and abdominal irrigation or in local treatment of empyema), and following oral use of aminoglycosides. The possibility of these phenomena should be considered if aminoglycosides are administered by any route, especially in patients

receiving anesthetics; neuromuscular blocking agents such as tubocurarine, succinylcholine, decamethonium; or in patients receiving massive transfusions of citrate-anticoagulated blood. If blockage occurs, calcium salts may reverse these phenomena, but mechanical respiratory assistance may be necessary.

Renal and eighth-nerve function should be closely monitored especially in patients with known or suspected renal impairment at the onset of therapy and also in those whose renal function is initially normal but who develop signs of renal dysfunction during therapy. Serum concentrations of amikacin should be monitored when feasible to assure adequate levels and to avoid potentially toxic levels and prolonged peak concentrations above 35 micrograms per mL. Urine should be examined for decreased specific gravity, increased excretion of proteins and the presence of cells or casts . Blood urea nitrogen, serum creatinine or creatinine clearance should be measured periodically. Serial audiograms should be obtained where feasible in patients old enough to be tested, particularly high risk patients . Evidence of ototoxicity (dizziness, vertigo, tinnitus , roaring in the ears and hearing loss) or nephrotoxicity requires discontinuation of the drug or dosage adjustment.

Concurrent and/or sequential systemic, oral or topical use of other neurotoxic or nephrotoxic products, particularly bacitracin, cisplatin, amphotericin B, cephaloridine, paromomycin, viomycin, polymyxin B, colistin, vancomycin, or other aminoglycosides should be avoided.

Other factors that may increase risk of toxicity are advanced age and dehydration.

The concurrent use of amikacin with potent diuretics (ethacrynic acid or furosemide) should be avoided since diuretics by themselves may cause ototoxicity. In addition, when administered intravenously, diuretics may enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue [7].

Solution Compatibility

D5W, D10W, D20W, and NS.

Terminal Injection Site Compatibility

Acyclovir, aminophylline, amiodarone, aztreonam, caffeine citrate, calcium chloride, calcium gluconate, cefazolin, cefepime, cefotaxime, cefoxitin, ceftazidime, ceftriaxone, chloramphenicol, cimetidine, clindamycin, dexamethasone, enalaprilat, epinephrine, esmolol, fluconazole, furosemide, heparin (concentrations of 1 unit/mL or less), hydrocortisone succinate, hyaluronidase, linezolid, lorazepam, magnesium sulfate, metronidazole,

midazolam, milrinone, morphine, nicardipine, penicillin g, pentobarbital, phenobarbital, potassium chloride, ranitidine, remifentanil, sodium bicarbonate, vancomycin, vitamin K1, and

zidovudine.
Terminal Injection Site Incompatibility
Fat emulsion. Amphotericin B, ampicillin, azithromycin, heparin (concentrations greater than 1 unit/mL), imipenem/cilastatin, mezlocillin, nafcillin, oxacillin, phenytoin, propofol, thiopental, and ticarcillin/clavulanate.
Monitoring
Measure serum concentrations when treating for more than 48 hours. Obtain peak concentration 30 minutes after end of infusion, and trough concentration just prior to the next dose. When treating patients with serious infections or significantly changing fluid or renal status consider measuring the serum concentration 24 hours after a dose, and use the chart below for the suggested dosing interval. Blood samples obtained to monitor serum drug concentrations should be spun and refrigerated or frozen as soon as possible.
Therapeutic serum concentrations
Peak: 20 to 30 mcg/mL (or Cmax /MIC ratio greater than 8:1)
(Draw 30 minutes after end of infusion, 1 hour after IM injection.)
Trough: 2 to 5 mcg/mL
Suggested Dosing Intervals

Level at 24 hrs (mcg/mL)	Half-life (hours)	Suggested Dosing Interval (hours)
?5	~ 9	24
5.1 to 8.0	~ 12	36
8.1 to 10.5	~ 16	48
?10.6	Measure level in 24 hours	

MECHANISM OF ACTION/PHARMACOKINETICS
Pharmacology
Mechanism of action: Amikacin, a semi-synthetic aminoglycoside [7] bactericidal antibiotic, inhibits normal protein synthesis in susceptible microorganisms [16]. Amikacin resists degradation by most aminoglycosides inactivating enzymes known to affect gentamicin, tobramycin, and kanamycin [7].

Pharmacokinetics
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https://www.micromedexsolutions.com/micromedex2/librarian/CS/B91819/ND_PR/evidencexpert/ND_P/evidencexpert/DUPLICATIONSHIELDSY 7/7
[4]
Postmenstrual Age Postnatal Age Half-life Volume of distribution
29 weeks or less
0 to 7 days (n=41) 11 hours 0.414 L/kg
8 to 28 days (n=9) 9.64 hours 0.472 L/kg
29 days or older (n=2) 4.93 hours 0.353 L/kg
30 to 34 weeks
0 to 7 days (n=49) 7.96 hours 0.462 L/kg
8 days or older (n=16) 6.20 hours 0.454 L/kg
35 weeks or more All ages (n=170) 6.21 hours 0.433 L/kg
Comorbidity
Congenital heart disease (n=38)* 6.97 hours 0.449 L/kg
*Congenital heart disease = cyanotic heart defect or acyanotic heart defect requiring surgical intervention prior to or during amikacin therapy
Hughes et al, 2017
Volume of distribution: 0.833 L in 874 neonates (postnatal age 1 to 30; gestational age 24 to 43 weeks) [6]
Clearance: 0.493 L/hr in 874 neonates (postnatal age range, 1 to 30; gestational age range, 24 to 43 weeks). Coadministration of ibuprofen reduced clearance [6].
0.84 L/hr/70 kg at 28 weeks postmenstrual age (PMA), 1.23 L/hr/70 kg at 34 weeks PMA, and 1.56 L/hr/70 kg at 40 weeks PMA in a pharmacokinetic study of 715 neonates (PMA 24 to 43 weeks; weight 0.385 to 4.78 kg). Clearance was affected the most by size (66%), PMA (17%), and renal function (9%) [17].
Therapeutic Hypothermia for Asphyxia: Clearance was reduced by 40.6% in neonates with perinatal asphyxia treated with therapeutic hypothermia (PATH) compared with neonates without PATH in model-based approach pharmacokinetic study. Volume of distribution did not change [5].
ABOUT
Special Considerations/Preparation
Availability: 250 mg/mL in 2-mL and 4-mL vials [7]
For IV use, dilute with a compatible solution to a concentration of 2.5 to 10 mg/mL [7][8].
Stability: Solutions, 0.25 and 5 mg/mL, are stable for 24 hours at room temperature.
Solutions stored for 60 days at 4 degrees C and then stored at 25 degrees C had utility times of 24 hours. At concentrations of 0.25 and 5 mg/mL, solutions frozen (-15 degrees C) for 30 days, thawed, and stored at 25 degrees C had utility times of 24 hours [7]

Aminocaproic Acid
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
Hemorrhage Prophylaxis
Extracorporeal membrane oxygenation (ECMO): 100 mg/kg followed by 30 mg/kg/hr.
Administer directly to the patient via IV or through the ECMO circuit. Duration of infusion 72 hours or longer if bleeding persists or shorter if cannula is removed [1][2]
Uses
Hemorrhage Prophylaxis
Cardiopulmonary bypass (CPB): In a neonatal subgroup analysis (n=4426) of a large observational study (n=22,258), aminocaproic acid had greater bleeding requiring surgical intervention compared with aprotinin [4]. There was higher blood loss with aminocaproic acid (46 mL/kg) compared with aprotinin (36 mL/kg), but no differences in need for transfusion or requirement for surgical revision in 235 neonates who underwent CPB in a nonrandomized study [5]. There was no difference in blood loss, requirement for surgical revision due to bleeding, or need for transfusion between tranexamic acid and aminocaproic acid in 105 neonates who underwent CPB in a nonrandomized study [6]. Various dosing regimens are available. A pharmacokinetic study in 10 neonates proposed 40 mg/kg IV loading dose followed by 30 mg/kg/hr infusion and a priming dose of 100 mg/L [7]. In clinical studies, 75 mg/kg IV over 10 minutes was administered at the beginning and end of CPB. Additionally, 75 mg/100 mL was added to the priming volume of the CPB system [5][6]. A pharmacokinetic study identified the following regimen to achieve therapeutic concentrations:
75 mg/kg IV loading dose over 10 minutes followed by 75 mg/kg/hr IV until the end of surgery. Additionally, add 75 mg/kg in the priming volume of the CPB system (venous reservoir) [8].
Hemorrhage Prophylaxis
Extracorporeal membrane oxygenation (ECMO): Empiric bleeding protocols included aminocaproic acid 100 mg/kg followed by 30 mg/kg/hr. Duration of infusion was for 72 hours or longer if bleeding persisted or shorter when cannula was removed. Administration was

either directly to the patient or through the ECMO circuit [1][2]. Surgical site bleeding was reduced with aminocaproic acid (7%) compared with no aminocaproic acid (12%) [2].
However, aminocaproic acid did not reduce the incidence of neonatal intracranial hemorrhage compared with no aminocaproic acid in 2 studies (n=327) [2][9]. Reduced circuit times due to clotting may not be a concern, as a retrospective analysis of 164 patients on ECMO demonstrated that a bleeding protocol, which included aminocaproic acid, did not shorten circuit times [1].
Administration
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IV: Rapid administration of undiluted injection into a vein is not recommended .
The manufacturer recommends a concentration of 16 to 20 mg/mL [3].
MEDICATION SAFETY
Contraindications/Precautions
Contraindicated in DIC without concomitant heparin [10][3].
Intrarenal obstruction and glomerular capillary thrombosis has been reported in patients with upper urinary tract bleeding. Avoid use in patients with hematuria of upper urinary tract origin or use with caution if benefit of therapy outweighs the risk. Rare cases of skeletal muscle weakness, necrosis of muscle fibers, and rhabdomyolysis have been reported with prolonged administration. Neurological deficits, including hydrocephalus, cerebral ischemia, and cerebral vasospasm, have been reported with the use of antifibrinolytic agents in patients with subarachnoid hemorrhage (causality is unknown). Only use when hyperfibrinolysis (hyperplasminemia) has been definitively diagnosed. Rapid injection may result in hypotension, bradycardia, and/or arrhythmia. Thrombophlebitis may occur. Avoid concomitant use with factor IX complex concentrates or anti-inhibitor coagulant concentrate [10][3].
Injection contains benzyl alcohol, which has been associated with serious adverse effects, including death, in neonates and low-birth-weight infants [3].
Adverse Effects
Renal risk (28.6% vs 36.8%), renal injury (3.6% vs 9.5%), renal failure (1.4% vs 1.2%), vascular thrombosis (12.1% vs 8.4%), seizures (2.9% vs 3.2%), intracranial bleeding (3.6%

vs 4.2%), stroke (1.4% vs 0%), and in-hospital mortality (6.4% vs 8.4%) occurred in 235 neonates undergoing cardiopulmonary bypass and administration of aminocaproic acid and aprotinin, respectively [5]. A fatal case of aortic thrombosis in a neonate on extracorporeal life support and receiving aminocaproic acid occurred [11].

Solution Compatibility

D5W, NS, Ringer injection.

Terminal Injection Site Compatibility

Aminocaproic acid 20 mg/mL

Amikacin (5 mg/mL), aminophylline (2.5 mg/mL), amphotericin B conventional colloidal (0.6 mg/mL), amphotericin B liposome 1 mg/mL), ampicillin (20 mg/mL), ampicillin/sulbactam (20/10 mg/mL), atracurium (0.5 mg/mL), azithromycin (2 mg/mL), aztreonam (40 mg/mL),

bumetanide (40 mcg/mL), calcium chloride (40 mg/mL), calcium gluconate (40 mg/mL), cefazolin (20 mg/mL), cefepime (20 mg/mL), cefotaxime (20 mg/mL), cefotetan (20 mg/mL), cefoxitin 20 (mg/mL), ceftazidime (40 mg/mL), ceftazidime (l-arginine) (40 mg/mL), ceftriaxone (20 mg/mL), cefuroxime (30 mg/mL), cimetidine (12 mg/mL), cisatracurium (0.5 mg/mL), clindamycin (10 mg/mL), cyclosporine (5 mg/mL), dexamethasone (1 mg/mL), digoxin (0.25 mg/mL), diltiazem (5 mg/mL), diphenhydramine (2 mg/mL), dobutamine (4 mg/mL), dopamine (3.2 mg/mL), enalaprilat (0.1 mg/mL), epinephrine (50 mcg/mL), erythromycin (5 mg/mL), esmolol (10 mg/mL), famotidine (2 mg/mL), fentanyl (50 mcg/mL), fluconazole (2 mg/mL), foscarnet (24 mg/mL), fosphenytoin (20 mgPE/mL), furosemide (3 mg/mL), gentamicin (5 mg/mL), granisetron (50 mcg/mL), haloperidol (0.2 mg/mL), heparin (100 units/mL), hydrocortisone (1 mg/mL), hydromorphone (0.5 mg/mL), imipenem/cilastatin (5 mg/mL), isoproterenol (20 mcg/mL), ketorolac (15 mg/mL), labetalol (2 mg/mL), levofloxacin (5 mg/mL), lidocaine (10 mg/mL), linezolid (2 mg/mL), lorazepam (0.5 mg/mL), magnesium (100 mg/mL), mannitol (150 mg/mL) (15%), meropenem (2.5 mg/mL), methylprednisolone (5 mg/mL), metoclopramide (5 mg/mL), metronidazole (5 mg/mL), milrinone (0.2 mg/mL), morphine (15 mg/mL), nalbuphine (10 mg/mL), naloxone (0.4 mg/mL), nitroglycerin (0.4 mg/mL), nitroprusside (2 mg/mL), ondansetron (1 mg/mL),

pancuronium (0.1 mg/mL), pentobarbital (5 mg/mL), phenobarbital (5 mg/mL), phenylephrine (1 mg/mL), piperacillin (40 mg/mL), piperacillin/tazobactam (40/5 mg/mL), potassium chloride (0.2 mEq/mL), procainamide (20 mg/mL), propranolol (1 mg/mL), ranitidine (2 mg/mL), rocuronium (1 mg/mL), sargramostim (10 mcg/mL), sodium bicarbonate (1 mEq/mL), succinylcholine (2 mg/mL), sulfamethoxazole/trimethoprim (4/0.8 mg/mL), tacrolimus (20 mcg/mL), ticarcillin/clavulanate (31 mg/mL), tobramycin (5 mg/mL), vancomycin (10 mg/mL), vecuronium (1 mg/mL), verapamil (2.5 mg/mL), zidovudine (4 mg/mL).

Aminocaproic acid 50 mg/mL

Amphotericin B lipid complex (1 mg/mL), argatroban (1 mg/mL), bivalirudin (5 mg/mL), daptomycin (10 mg/mL), dexmedetomidine (4 mcg/mL), ertapenem (20 mg/mL), moxifloxacin (1.6 mg/mL), octreotide (5 mcg/mL), palonosetron (50 mcg/mL), pantoprazole (0.4 mg/mL), vasopressin (1 unit/mL), voriconazole (4 mg/mL).

Terminal Injection Site Incompatibility

Acyclovir, amiodarone, caspofungin, ciprofloxacin, diazepam, dolasetron, doxycycline hyclate, filgrastim, ganciclovir, midazolam, mycophenolate mofetil, nicardipine, phenytoin, quinupristin/dalfopristin.

Compatibility information refers to physical compatibility and is derived from Trissels 2 Clinical Pharmaceutics Database. The determination of compatibility is based on concentrations for administration recommended herein. Drug compatibility is dependent on multiple factors (eg, drug concentrations, diluents, storage conditions). This list should not be viewed as all-inclusive and should not replace sound clinical judgment. The user is referred to Trissels 2 for more complete details. Trissels 2 Clinical Pharmaceutics Database, version updated on 09/15/2013.

Monitoring

Monitor CPK levels in patients on long-term therapy. Assess the amount of fibrinolysis present during therapy [10][3].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Aminocaproic acid inhibits fibrinolysis through plasminogen activator inhibition (principal) and

antiplasmin activity (lesser extent). Apparent Vd (mean +/- SD), 23.1 +/- 6.6 L (oral) and 30 +/- 8.2 L (IV). Distributes throughout extravascular and intravascular compartments, penetrating RBCs and other tissues with prolonged administration. Primarily excreted renally as unchanged drug (65%) and the metabolite adipic acid (11%). Renal clearance, 116 mL/min. Total body clearance, 169 mL/min. Terminal elimination half-life, approximately 2 hours [10][3].

A suggested regimen of aminocaproic acid 40 mg/kg IV loading dose followed by a 30 mg/kg/hr infusion and a priming dose of 100 mg/L would achieve a target concentration above 50 mg/L in most neonates during cardiopulmonary bypass surgery. The aminocaproic acid regimen was developed using aminocaproic pharmacokinetic values from 10 neonates who underwent elective cardiac surgery with cardiopulmonary bypass [7].

The minimum effective concentration of aminocaproic acid required to inhibit fibrinolysis in plasma from 20 term neonates 44.2 mcg/mL, which was significantly less than that for adults (131.4 mcg/mL) [12].

Aminocaproic acid concentration range was 39 to 433 mcg/mL (mostly within 110 to 350 mcg/mL) in 42 neonates on extracorporeal membrane oxygenation and receiving aminocaproic acid 100 mg/kg IV bolus followed by 30 mg/kg/hr IV. Concentration exceeded 1000 mcg/mL in one neonate with renal and hepatic insufficiency; no complications occurred [13].

ABOUT

Special Considerations/Preparation

IV solution: Available as an IV solution containing 250 mg/mL aminocaproic acid with 0.9% benzyl alcohol. [3].

Dilute with NS, D5W, or LR. Sterile water for injection may also be used, but will produce a hypo-osmolar solution [3].

Aminophylline

NeoFax Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Loading dose: 8 mg/kg IV infusion over 30 to 60 minutes, or orally.

Maintenance dose: 1.5 to 3 mg/kg/dose orally, or IV every 8 to 12 hours (start

maintenance dose 8 to 12 hours after the loading dose).
In preterm infants, changing from IV aminophylline to oral theophylline requires no dose adjustment.
Uses
Treatment of neonatal apnea, including post-extubation, post-anesthesia, and prostaglandin E1-induced. Bronchodilator. May improve respiratory function.
Administration
Intravenous bolus over 30 to 60 minutes [1][2][3][4][5]. May give as 25-mg/mL concentration or further dilute to as low as 1 mg/mL for continuous infusion [6].
MEDICATION SAFETY
Adverse Effects
GI irritation. Hyperglycemia. CNS irritability and sleeplessness. May be associated with renal calcifications when used concurrently with furosemide and/or dexamethasone.
Signs of toxicity: Sinus tachycardia, failure to gain weight, vomiting, jitteriness, hyperreflexia, and seizures.
Treatment of Serious Theophylline Toxicity: Activated charcoal, 1 g/kg as a slurry by gavage tube every 2 to 4 hours. Avoid sorbitol-containing preparations: They may cause osmotic diarrhea.
Solution Compatibility

D5W, D10W, and NS.
Terminal Injection Site Compatibility
Acyclovir, ampicillin, amikacin, aztreonam, caffeine citrate, calcium gluconate, ceftazidime, chloramphenicol, cimetidine, dexamethasone, dopamine, enalaprilat, erythromycin lactobionate, esmolol, famotidine, fluconazole, flumazenil, furosemide, heparin, hydrocortisone succinate, lidocaine, linezolid, meropenem, metoclopramide, midazolam, morphine, nafcillin, nicardipine, nitroglycerin, pancuronium bromide, pentobarbital, phenobarbital, piperacillin, piperacillin/tazobactam, potassium chloride, propofol, prostaglandin E1, ranitidine, remifentanil, sodium bicarbonate, vancomycin, and vecuronium.
Terminal Injection Site Incompatibility
Amiodarone, cefepime, ceftriaxone, ciprofloxacin, clindamycin, dobutamine, epinephrine, hydralazine, insulin, isoproterenol, methylprednisolone, and penicillin G.
Monitoring

Monitor heart rate and check blood glucose periodically with reagent strips. Assess for agitation and feeding intolerance.
Consider withholding next dose if heart rate is greater than 180 beats per minute.
When indicated by lack of efficacy or clinical signs of toxicity, serum trough concentration should be obtained. Therapeutic ranges are:
1) Apnea of prematurity: 7 to 12 mcg/mL.
2) Bronchospasm: 10 to 20 mcg/mL (older infants with bronchospasm may need these higher levels because of increased protein binding).
MECHANISM OF ACTION/PHARMACOKINETICS
Pharmacology
Stimulates central respiratory drive and peripheral chemoreceptor activity. May increase diaphragmatic contractility. Cerebral blood flow is acutely decreased following IV bolus dose.
Renal effects include diuresis and increased urinary calcium excretion. Stimulates gastric acid secretion and may cause gastroesophageal reflux.
Cardiac output is increased due to higher sensitivity to catecholamines. Elimination in preterm infants is primarily as unchanged drug, although significant interconversion to caffeine occurs. In the very immature neonate, the serum half-life of theophylline is prolonged (20 to 30 hours). Theophylline metabolism and clearance mature to adult values by 55 weeks postmenstrual age. Aminophylline salt is

78.9% theophylline. Theophylline administered orally is approximately 80% bioavailable; therefore, no dosage adjustment is necessary when changing from IV aminophylline to oral theophylline.
ABOUT
Special Considerations/Preparation
Availability: Aminophylline for IV use (25 mg/mL) in 10- and 20-mL vials. Dilute 1 mL (25 mg) with 4 mL NS or D5W to yield a final concentration of 5 mg/mL. Stable for 4 days refrigerated.
Oral theophylline is available only as an elixir at a concentration of 80 mg/15 mL (5.33 mg/mL) and contains 20% alcohol.
Aminophylline oral solution is no longer available.
Extemporaneous Suspension
Oral aminophylline 3 mg/mL liquid suspension made with aminophylline injection 25 mg/mL and mixed with 1:1 Ora Sweet/Ora Plus was stable for 91 days at 4C and 25 C. Store in amber glass bottle [7]

Amiodarone
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
IV Loading Dose: 5 mg/kg IV infusion given over 20 to 60 minutes, preferably in a central vein.
Maintenance Infusion: 7 to 15 mcg/kg/minute (10 to 20 mg/kg per 24 hours). Begin at 7 mcg/kg/minute and titrate by monitoring effects. For infusions lasting longer than 1 hour, amiodarone IV concentrations should not exceed 2 mg/mL unless using a central line.
Consider switching to oral therapy within 24 to 48 hours.
Correct hypokalemia, hypomagnesemia, and hypocalcemia prior to initiating treatment[1].
Oral: 5 to 10 mg/kg/dose every 12 hours.
Uses
Arrhythmias: Treatment of life-threatening or drug-resistant refractory supraventricular (SVT), ventricular tachyarrhythmias (VT), and postoperative junctional ectopic tachycardia (JET) - see Adverse Effects.
Administration
Dilute the IV loading dose to 1.5 mg/mL [2]and infusing over 20 to 60 minutes [3]. For IV infusion, dilute to a concentration of 1 to 6 mg/mL in compatible diluent. For infusions lasting longer than 1 hour (eg, continuous infusion), amiodarone IV concentrations should not exceed 2 mg/mL unless using a central line. When infusing the original amiodarone product, infusions lasting longer than 2 hours should be administered in glass or polyolefin bottles containing D5W; use of evacuated glass containers is not recommended as precipitation may occur from the buffer [4]. An in-line filter should be used during administration. Administration via a central catheter is preferred [3][5].
Extravasation ManagementNeonatal data are limited to pooled data from 10 case reports/case series (n=237) and are not specific to amiodarone extravasation; subcutaneous saline irrigation with or without hyaluronidase infiltration was commonly used. No standardized management was established. An option for more severe injuries (stages 3 and 4) is subcutaneous irrigation with saline, but this is not advocated as standard treatment.

Conservative management is appropriate for mild extravasation (stages 1 and 2) [6].
Although not neonatal-specific, the following are recommendations for extravasation of acidic or alkaline agents (amiodarone is acidic with a pH ranging from 3.5 to 4.5) [7]
General:

Stop and disconnect infusion; do not remove the cannula or needle
Attempt to gently aspirate as much extravasated agent as possible; avoid manual pressure
Remove cannula or needle
Dry heat and elevation
Closely monitor for signs of coagulation and ischemia
Avoid attempt at pH neutralization (amiodarone - pH 3.5 to 4.5)
Monitor and consider the need for surgical management such as surgical flushing with normal saline or debridement and excision of necrotic tissue (especially if pain persists for 1 to 2 weeks). In cases of compartment syndrome, surgical decompression may be required
Refractory Events:
Hyaluronidase 15 units intradermally along injection site and edematous area. Give as five, 0.2-mL intradermal injections along extravasation site and edematous tissue.
Inadvertent Intraarterial Administration:
Leave inadvertent intraarterial line in place for diagnostics
Systemic heparin titrated to therapeutic anticoagulant effect.
Stellate ganglion block
MEDICATION SAFETY
Contraindications/Precautions
Contraindications
Hypersensitivity to amiodarone including iodine, cardiogenic shock, bradycardia leading to syncope without a functioning pacemaker, sick sinus syndrome [1] or marked sinus bradycardia [8], second- or third-degree atrioventricular block [1] unless a functioning pacemaker is available .[8].
Precautions
Administration: The IV formulation should only be administered when access to facilities equipped to monitor for effectiveness and side effects are available, and by physicians experienced in the treatment of life-threatening arrhythmias [8].

Adverse events: Due to the long half-life, adverse events can persist for several weeks following discontinuation [1]
Cardiovascular: Hypotension, including some refractory and fatal cases, has been reported, particularly with IV administration; monitoring recommended [9].
Cardiovascular: Exacerbation of presenting arrhythmia, new ventricular fibrillation, incessant ventricular tachycardia, increased resistance to cardioversion, and polymorphic ventricular tachycardia with QTc prolongation (Torsade de Pointes) may occur [1]
Cardiovascular: Bradycardia or sinus arrest has been reported, especially with concomitant use of drugs that slow heart rate (eg, digoxin, beta blockers, verapamil, diltiazem, ivabradine, clonidine) [10] or by presence of electrolyte disorders [1]) and with concomitant use of ledipasvir/sofosbuvir or sofosbuvir with simeprevir [1][10]. Monitoring recommended with concomitant use or recent discontinuation of amiodarone when starting antiviral

treatment [1][10].
Cardiovascular: Preexisting implanted defibrillator or pacemaker may result in changes to electrical conduction properties (pacing or defibrillating thresholds) of heart; monitoring recommended with oral administration [1].
Concomitant use: Avoid drugs that prolong the QT interval [9].
Concomitant use: Avoid grapefruit juice [9].
Dermatologic: Photosensitivity has been reported and may be reduced with sun-barrier creams or protective clothing. Blue-gray skin discoloration may occur with prolonged use; some reversal of discoloration may occur upon discontinuation [1].
Endocrine and metabolic: Thyroid abnormalities, including hypothyroidism, hyperthyroidism and myxedema coma (sometimes fatal), thyroid nodules, and thyroid cancer, have been reported; increased risk for potentially fatal thyrotoxicosis and arrhythmia breakthrough or exacerbation; monitoring recommended and dosage adjustment or discontinuation may be necessary [1].
Endocrine and metabolic: Preexisting hypokalemia or hypomagnesemia may exaggerate degree of QT prolongation and increase potential for torsade de pointes; increased risk in patients with severe or prolonged diarrhea or those receiving diuretics, laxatives, systemic

corticosteroids, or amphotericin B. Correct prior to treatment [1] when possible [9].
Endocrine and metabolic: Prior inadequate dietary iodine intake may increase incidence of amiodarone-induced hyperthyroidism [9].
Hepatic: Elevation of liver enzymes has been reported [9]; life-threatening hepatic injury may occur with histology similar to alcoholic hepatitis or cirrhosis. Monitoring recommended and discontinuation or dose reduction may be necessary [1].
Hepatic: Hepatocellular necrosis leading to hepatic coma, acute renal failure, and death have occurred with IV administration at higher than recommended loading dose concentration and rate of infusion [9].
Immunologic: Potentially fatal anaphylactic or anaphylactoid reactions have been reported with IV administration, including shock (sometimes fatal), cardiac arrest, and the following manifestations: hypotension, tachycardia, hypoxia, cyanosis, rash, flushing, hyperhidrosis, and cold sweat [8].
Neurologic: Chronic administration may lead to peripheral neuropathy, which may not resolve when therapy is discontinued [1]
Ophthalmic: Optic neuritis and optic neuropathy, in some cases resulting in visual impairment that led to blindness, have been reported and may occur at any time during therapy. Discontinuation may be required [1]; monitoring recommended [9].
Ophthalmic: Corneal microdeposits have been reported and may result in visual halos or blurred vision; usually resolve upon dose reduction or discontinuation but asymptomatic microdeposits do not require dose change or discontinuation [1].
Ophthalmic: Corneal refractive laser surgery is contraindicated by most manufacturers of corneal refractive laser surgery devices [9].
Respiratory: Pulmonary toxicity, sometimes fatal, may occur presenting with cough and progressive dyspnea and resulting from either indirect (hypersensitivity pneumonitis, including eosinophilic pneumonia) or direct toxicity (interstitial/alveolar pneumonitis). Monitoring recommended. Consider alternative antiarrhythmic therapy if the patient experiences signs or symptoms of pulmonary toxicity [1].
Surgery: Increases sensitivity to myocardial depressant and conduction effects of halogenated inhalational anesthetics; perioperative monitoring recommended [1]

Adverse Effects

Common: In adult clinical trials: hypo- or hyperthyroidism, congestive heart failure, cardiac arrhythmias, SA node dysfunction, nausea, vomiting, constipation, anorexia, abdominal pain, solar dermatitis/photosensitivity, malaise/fatigue, tremor/abnormal involuntary movements and other neurologic adverse events, visual disturbances, abnormal liver function tests, pulmonary infiltration or fibrosis, flushing, coagulation abnormalities. Blue skin discoloration, rash, hypotension, and cardiac conduction abnormalities were reported less commonly [1].
Short-term toxicity: Bradycardia and hypotension (possibly associated with rapid rates of infusion) may occur. Hypotension may be due, in part, to the co-solvents, polysorbate 80 and benzyl alcohol, which are components of the original amiodarone product [11][12]. In a study of pediatric patients (n=61), ages 30 days to 15 years, hypotension and bradycardia were reported in 36% and 20% of patients, respectively. AV block was reported in 15% of patients. Polymorphic ventricular tachycardia may occur. Irritating to the peripheral vessels (concentrations greater than 2 mg/mL). Administration through central vein preferred.
Long-term toxicity: Hyperthyroidism (due to inhibition of T4 to T3) and hypothyroidism (due to high concentration of inorganic iodine). Generic formulation contains 2% benzyl alcohol (20 mg/mL). Hepatitis and cholestatic hepatitis (rare). Photosensitivity (10%), nausea and vomiting (10%), optic neuritis (4% to 9%), and pulmonary fibrosis (4% to 9%) have been reported with prolonged oral use in adults.
Black Box Warning
Warning: Pulmonary, Hepatic and Cardiac Toxicity
Amiodarone oral tablet is intended for use only in patients with the indicated life-threatening arrhythmias because its use is accompanied by substantial toxicity.
Amiodarone can cause pulmonary toxicity (hypersensitivity pneumonitis or interstitial/alveolar pneumonitis) that has resulted in clinically manifest disease at rates as high as 17% in some series of patients. Pulmonary toxicity has been fatal about 10% of the time. Obtain a baseline chest X-ray and pulmonary-function tests, including diffusion capacity, when therapy is initiated. Repeat history, physical exam, and chest X-ray every 3 to 6 months.
Amiodarone can cause hepatoxicity, which can be fatal. Obtain baseline and periodic liver transaminases and discontinue or reduce dose if the increase exceeds three times normal, or

doubles in a patient with an elevated baseline. Discontinue if the patient experiences signs or symptoms of clinical liver injury.
Amiodarone can exacerbate arrhythmias. Initiate in a clinical setting where continuous electrocardiograms and cardiac resuscitation are available [1].
Solution Compatibility
D5W, and NS at concentrations of 1 to 6 mg/mL.
Terminal Injection Site Compatibility
Amikacin, amphotericin B, atropine, calcium chloride, calcium gluconate, ceftizoxime, ceftriaxone, cefuroxime, clindamycin, dobutamine, dopamine, epinephrine, famotidine, fentanyl, fluconazole, furosemide, esmolol, erythromycin, gentamicin, insulin, isoproterenol,

lidocaine, lorazepam, metronidazole, midazolam, milrinone, morphine, nitroglycerin, norepinephrine, penicillin G, phentolamine, potassium chloride, procainamide, tobramycin, vancomycin, and vecuronium.
Terminal Injection Site Incompatibility
Aminophylline, ampicillin, ceftazidime, cefazolin, digoxin, heparin, imipenem-cilastatin, mezlocillin, micafungin, piperacillin, piperacillin-tazobactam, sodium bicarbonate, and sodium nitroprusside.
Monitoring
Obtain baseline chest x-ray, pulmonary function tests, thyroid function tests, and liver aminotransferases [1].
Continuous EKG and blood pressure (for IV). Follow AST and ALT. Monitor T3, T4, and TSH.
Observe IV site for extravasation.
MECHANISM OF ACTION/PHARMACOKINETICS
Pharmacology
Class III antiarrhythmic agent that is an iodinated benzofuran compound. Electrophysiologic activity is accomplished by prolonging the duration of the action potential and increasing the effective refractory period. Increases cardiac blood flow and decreases cardiac work and myocardial oxygen consumption. Highly protein bound (95%) in adults. Extensively metabolized to an active metabolite by the cytochrome CYP3A isoenzyme system (limited in preterm infants). Drug-drug interaction potentially occur when given in combination with drugs that inhibit cytochrome CYP3A: phenytoin, fosphenytoin, clarithromycin, erythromycin, azole antifungals (e.g. fluconazole, ketoconazole, itraconazole), protease inhibitors (e.g.

indinavir, ritonavir), class IA and class III antiarrhythmics (e.g. quinidine, procainamide, sotalol) and cimetidine (amiodarone levels increase). Amiodarone and its major metabolite may inhibit CYP2C9, CYP2C19, CYP2D6, CYP3A, CYP2A6, CYP2B6, and CYP2C8, as well as the transporters P-glycoprotein and organic cation transporter (OCT2). Amiodarone prevents the elimination of digoxin resulting in high digoxin levels. Half-life reported to be 26 to 107 days in adults. No data in preterm infants. Accumulates in tissues; serum levels can be detected for months. Contains 37.3% iodine by weight. Adheres to PVC tubing: low infusion rates in neonates may lead to reduced drug delivery during continuous infusions. Oral absorption is variable with approximately 50% bioavailability.

ABOUT

Special Considerations/Preparation

IV: The preferred formulation is Nexterone, available as 1.5 mg/mL (150 mg/100 mL) and 1.8 mg/mL (360 mg/200 mL) concentrations in premix bags. Nexterone does not contain benzyl alcohol or polysorbate 80, and therefore does not carry a warning regarding benzyl alcohol and fatal gasping syndrome in neonates. There are also no limitations regarding compatibility and stability with plastics and isotonic infusion fluids. Store at room temperature and protect from light.

Generic amiodarone is also available as 50 mg/mL concentration in 5, 10, and 20 mL vials. Contains 2% (20 mg/mL) of benzyl alcohol and 10% (100 mg/mL) polysorbate (Tween) 80 as a preservative. Store at room temperature and protect from light.

Oral:

Supplied in 100-mg, 200-mg, 300-mg, and 400-mg tablets.

Extemporaneous Oral Suspension (5 mg/mL)

Amiodarone 5 mg/mL oral suspension [13]:

Crush five 200-mg tablets into a mortar and make to a fine powder.

For the vehicle: Mix 100 mL of Ora-Sweet (or Ora-Sweet Sugar Free) with 100 mL of Ora-Plus, then adjust pH. Use sodium bicarbonate solution (5 gm/100 mL in distilled water) to adjust pH between 6 and 7.

Add a small amount of vehicle to powder in mortar and make a uniform paste.

Add additional vehicle in geometric portions while mixing.

Transfer to graduate and add sufficient amount of vehicle to a total volume of 200 mL
The 5 mg/mL suspension in plastic bottles is stable for at least 42 days at 25 degrees C and 91 days at 4 degrees C
Alternatively, an oral suspension with a final concentration of 5 mg/mL may be made as follows: crush a 200-mg tablet, slowly mix in 20 mL of 1% methylcellulose, and then add in 20 mL of simple syrup to make a total volume of 40 mL. Stable for six weeks at room temperature and three months refrigerated when stored in glass or plastic [14].

Amoxicillin
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
Usual dose:
Max 30 mg/kg/day orally divided every 12 hours (manufacturer recommended) . Continue for a minimum of 48 to 72 hours after patient becomes asymptomatic or bacteria has been eradicated. For infections caused by Streptococcus pyogenes, duration of treatment should be at least 10 days. Durations of several weeks may be required for some infections [1]. 100 mg/kg/day orally in 2 divided doses in neonates 2 kg or more [2][3][4][5] and 75 mg/kg/day orally in 2 divided doses in neonates less than 2 kg have been used in infants 0 to 59 days with possible serious infections [3][4][5].
Anthrax[6]
32 to 37 weeks gestational age
0 to 1 week of age: 50 mg/kg/day orally divided every 12 hours
1 to 4 weeks of age: 75 mg/kg/day orally divided every 8 hours
Term newborn
0 to 4 week of age: 75 mg/kg/day orally divided every 8 hours
Duration: For prophylaxis, continue for 60 days after exposure. For naturally acquired cutaneous infection, 7 to 10 days. As follow-up therapy for severe anthrax, complete course for 14 days or longer until clinical criteria for stability are met [6].
Urinary Tract Infection, Prophylaxis: 10 to 15 mg/kg/day orally once daily [7][8].
Dose Adjustments There are no data available for dosing amoxicillin in pediatric patients with renal impairment. In adults, based on the severity of the infection, the lower end of the

dose and/or frequency are recommended [1].
Uses
Anthrax, Treatment and Prophylaxis [6]:
Postexposure prophylaxis for Bacillus anthracis (Oral)
Penicillin-resistant strains or prior to susceptibility testing
Preferred: Ciprofloxacin or doxycycline Alternatives in order of preference:
clindamycin, levofloxacin.
Penicillin-susceptible strains
Preferred: Amoxicillin Alternative: penicillin VK.
Cutaneous Anthrax treatment, without systemic involvement (Oral)
All strains, regardless of penicillin susceptibility or if susceptibility is unknown
Preferred: Ciprofloxacin. Alternatives in order of preference: doxycycline, clindamycin, levofloxacin.
Alternatives for penicillin-susceptible strains

Preferred: Amoxicillin Alternative: penicillin VK.
Oral follow-up therapy for severe anthrax
Combination Oral Therapy
Preferred: Ciprofloxacin. Alternative: levofloxacin.
If strains are penicillin-susceptible, amoxicillin (preferred) or penicillin VK (alternative).
PLUS
Preferred: Clindamycin. Alternatives in order of preference: doxycycline or linezolid.
Urinary Tract Infection (UTI), Prophylaxis: Some experts recommend amoxicillin prophylaxis starting at birth and continuing until vesicoureteral reflux (VUR) is ruled out in neonates with hydronephrosis [7], though there are no studies in neonates to support prophylaxis.
The use of prophylactic antibiotics for VUR is controversial [11]. When no prophylactic antibiotics were administered, the 2-year rate for recurrent UTI in children (2 months to 71 months of age) was 25.4% and 17.3% with VUR and without VUR, respectively [12]. In children 2 months to 71 months with vesicoureteral reflux, trimethoprim/sulfamethoxazole prophylaxis reduced the risk of infections but did not reduce renal scarring at 2 years [13]; therefore, evidence for routine use of prophylaxis is not established [14].
Pediatric FDA Approved Indications:
For infection caused by ?-lactamase-negative organisms only
Ear, nose and throat infections caused by Streptococcus species (alpha- and betahemolytic

strains only), S pneumoniae, Staphylococcus species, or Haemophilus
influenzae[1]. For individuals without a penicillin allergy, penicillin or amoxicillin are the
agents of choice for the treatment of group A streptococcal pharyngitis [15].
Genitourinary tract infections caused by Escherichia coli, Proteus mirabilis, or
Enterococcus faecalis[1].
Skin and skin structure infections caused by Streptococcus species (alpha- and betahemolytic
strains only), Staphylococcus species, or E coli[1].
Lower respiratory tract infections caused by Streptococcus species (alpha- and betahemolytic
strains only), S pneumoniae, Staphylococcus species, or H influenza[1].
Administration
Suspension: Shake well before measuring the dose; place on tongue for swallowing; may
mix the dose with formula, milk, fruit juice, water, ginger ale, or cold drinks; after mixing,
administer immediately and completely [9]. May also dissolve amoxicillin powder in breast
milk to a concentration of 50 mg/mL [10].
MEDICATION SAFETY
Contraindications/Precautions

Endocrine and metabolic: False positive readings for glucose urine tests may occur with
Clinitest(R), Benedict Solution, or Fehling Solution. Use enzymatic glucose oxidase reactiontype
tests [1].
Gastrointestinal: Clostridium difficile-associated diarrhea, including mild diarrhea to fatal
colitis, has been reported and may occur over 2 months from last dose. Ongoing antibiotic
use not directed against c difficile may need to be discontinued [1].
Immunologic: Severe anaphylactic reactions, including fatalities, have been reported,
especially in patients with a history of penicillin hypersensitivity or sensitivity to multiple
allergens [1].
Mononucleosis: Avoid use due to a high risk of developing an erythematous skin rash [1]
Renal: Severe renal impairment (ie, GFR less than 30 mL/min) or hemodialysis; dose
adjustment recommended [1].
Adverse Effects
Common adverse effects include rash, diarrhea, nausea, and vomiting [1].
MECHANISM OF ACTION/PHARMACOKINETICS
Pharmacology

An analog of ampicillin, amoxicillin is a semisynthetic antibiotic that inhibits the biosynthesis of the cell wall. It has a broad-spectrum bactericidal activity against most strains of grampositive and gram-negative microorganisms [1].

Rapidly absorbed, with time to peak concentration of 1 to 2 hours after administration.

Widely distributed into most body tissues and fluids, except brain and spinal fluid. May penetrate brain when meninges are inflamed. Protein binding is approximately 20%, and renal excretion is mostly unchanged at approximately 60%. Half-life of immediate-release amoxicillin is 61.3 minutes [1].

Pharmacokinetics- Neonates[16][17][18][19]

Neonates Administered IV Amoxicillin*	Gestational age (GA) Postnatal age (PNA) Range (mean)	Vd (mean)	Half-life (mean)	Clearance (mean)	Author, year (N)
	GA = 25 to 42 weeks (34.6 weeks) PNA = 0 to 9 days (0.76 days)	0.65 L/kg	5.2 hours *	0.096 L/kg/hr	Pullen, 2006 N=150
	GA = 26 to 41 weeks (33.7 weeks) PNA = 10 to 52 days (24.7 days)	0.66 L/kg	3 hours *	0.18 L/kg/hr	Pullen, 2007 N=32
	GA = 24 to 32 (28.9 weeks) PNA = 1 to 3 days (1.1 day)	0.603 L/kg	6.9 hours * 5.2 hours **	0.061 L/kg/hr * 0.0805 L/hr **	Charles, 1997 N=40
	GA = (29 weeks) PNA = (3 days)	0.671 L/kg	6.7 hours **	0.066 L/kg/hr **	Huisman- de boer, 1995 N=17

*Gentamicin coadministered
**Gentamicin not coadminsitered
ABOUT
Special Considerations/Preparation
Availability: Oral suspension (125, 200, 250, or 400 mg/5mL). Also available as chewable tablets (125, 200, 250, and 400 mg), oral capsules (250 or 500 mg), or oral tablets (500 or 875 mg) [1][20][9].
Storage: Store at a controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F) [1][20][9]
Reconstitution: Tab the bottle until all of the powder flows freely. Add approximately onethird of the total amount of water for reconstitution and shake vigorously. Add remainder of water and shake again [9].
Mixed with Breast Milk
Amoxicillin suspension (50 mg/mL) reconstituted with breast milk was bioequivalent to amoxicillin reconstituted with water in 16 healthy, adult, fasted (10 hours before and 4 hours after dose) volunteers [10].

Amphotericin B Lipid Complex
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
2.5 to 5 mg/kg/dose IV infusion every 24 hours; dose based on a pharmacokinetic study in neonates; optimal regimen for hematogenous Candida meningoencephalitis is unknown [1].
Uses
Treatment of systemic fungal infections resistant to conventional amphotericin B therapy or in patients with renal or hepatic dysfunction.
Neonatal Candidiasis, Including CNS Infection[3]
Invasive candidiasis and candidemia, or very low-birth weight infants with asymptomatic candiduria .
Amphotericin B deoxycholate is recommended.
Fluconazole IV or oral is an alternative for those who have not been receiving prophylaxis with fluconazole.
Lipid formulation amphotericin B agent is an alternative; however, use with caution, especially in the presence of urinary tract involvement.
Echinocandins (caspofungin, anidulafungin, or micafungin) should be limited to salvage

therapy or scenarios of resistance or toxicity to amphotericin B deoxycholate or fluconazole

Central nervous system infections

Amphotericin B deoxycholate is recommended. Liposomal amphotericin B agent is an alternative. Salvage therapy with flucytosine may be added in those patients who have not responded to initial therapy.

Fluconazole may be used as step-down therapy for those patients who respond to initial therapy

Neonatal intensive care unit (with greater than 10% rate of invasive candidiasis)

Prophylaxis with IV or oral fluconazole for 6 weeks is recommended for neonates with birth weights of less than 1000 g

Prophylaxis with oral nystatin is an alternative in neonates with birth weights of less than 1500 g when fluconazole is unavailable or fluconazole resistance is present

Infective endocarditis: The following recommendations are based on a consensus of experts [4]. The full pediatric guidelines can be found here: https://doi.org/10.1161/CIR.0000000000000298

Organism Directed Therapy

Organism	First-Choice	Alternative Choice
Fungi		
Candida spp, Aspergillus spp	Surgical resection plus Amphotericin B With or without flucytosine	Amphotericin B followed by imidazole (eg, fluconazole, itraconazole, voriconazole) suppression if surgery cannot be performed. Lifelong suppression may be necessary if surgery cannot be performed or relapse occurs after surgery.

Baltimore, 2015

Administration

Administer by IV infusion over 2 hours (2.5 mg/kg/hour) at a concentration of 1 to 2 mg/mL.

If infusion lasts longer than 2 hours, shake the bag to mix the contents every 2 hours. Flush existing IV line with D5W prior to infusion or administer in a separate IV line. Do not infuse with saline solutions (precipitation will occur). Do not use an in-line filter to administer [2].

MEDICATION SAFETY

Adverse Effects

Anemia, thrombocytopenia, hypokalemia, nausea/vomiting, and fever/chills.

Solution Compatibility

D5W at 1 to 2 mg/mL dilution.

Solution Incompatibility

NS.

Monitoring

Serum amphotericin B concentrations are not routinely followed. Monitor urine output.

Periodic CBC for thrombocytopenia, electrolytes for hypokalemia, BUN, serum creatinine, and hepatic transaminases.

For candidemia, monitor blood cultures daily or every other day until Candida is cleared [3].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Amphotericin B lipid complex consists of amphotericin B complexed with two phospholipids in a 1:1 drug-to-lipid ratio. Acts by binding to the sterol component of a cell membrane leading to alterations in the cell wall permeability and death. Penetrates the cell wall of susceptible fungi. Concentrates in the liver and spleen. Less nephrotoxic than conventional amphotericin B. Mean serum half-life in adults 24 to 38 hours. The pharmacokinetics of amphotericin B lipid complex is nonlinear.

ABOUT

Special Considerations/Preparation

Available as a suspension containing 100-mg Abelcet in 20-mL (5 mg/mL). Shake the vial gently until there is no evidence of any yellow sediment on the bottom. Withdraw the appropriate dose into a syringe using an 18 gauge needle. Remove the needle and replace with the supplied 5 micron filter needle. Dilute the drug with D5W so that the final infusion concentration is 1 to 2 mg/mL. Shake until thoroughly mixed. Check for complete dispersion.

The diluted admixture is stable for 48 hours refrigerated and an additional 6 hours at room temperature [2].

Do not freeze. Protect from light.

Do not flush IV or mix Abelcet with saline solutions - precipitation willoccur.

Amphotericin B Liposome
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
2.5 to 7 mg/kg/dose every 24 hours IV infusion [1].
Uses
Treatment of systemic fungal infections resistant to conventional amphotericin B therapy or in patients with renal or hepatic dysfunction.
Neonatal Candidiasis, Including CNS Infection[4]
Invasive candidiasis and candidemia, or very low-birth weight infants with asymptomatic candiduria .
Amphotericin B deoxycholate is recommended.
Fluconazole IV or oral is an alternative for those who have not been receiving prophylaxis with fluconazole.
Lipid formulation amphotericin B agent is an alternative; however, use with caution, especially in the presence of urinary tract involvement.
Echinocandins (caspofungin, anidulafungin, or micafungin) should be limited to salvage therapy or scenarios of resistance or toxicity to amphotericin B deoxycholate or fluconazole
Central nervous system infections
Amphotericin B deoxycholate is recommended.
Liposomal amphotericin B agent is an alternative.
Salvage therapy with flucytosine may be added in those patients who have not responded to initial therapy.
Fluconazole may be used as step-down therapy for those patients who respond to initial therapy
Neonatal intensive care unit (with greater than 10% rate of invasive candidiasis)
Prophylaxis with IV or oral fluconazole for 6 weeks is recommended for neonates with birth weights of less than 1000 g
Prophylaxis with oral nystatin is an alternative in neonates with birth weights of less than 1500 g when fluconazole is unavailable or fluconazole resistance is present
Comparison with Echinocandins: There was no difference in clinical response between echinocandins and amphotericin B (OR 1.38; 95% CI, 0.68 to 2.8) for the treatment of suspected or confirmed invasive candidiasis in a meta-analysis (n=5; 354 neonates and children). Antifungals included were micafungin, caspofungin, amphotericin B deoxycholate,

and liposomal amphotericin B. Subanalysis demonstrated no difference in other comparisons
75

including mycological response, mortality, recurrence of candida infection, type of
echinocandin, different risk groups (high-risk, low-risk, or neutropenic groups), and type of
use (targeted or empirical). Discontinuation due to adverse effects were higher with
amphotericin B than the echinocandins (OR 0.3; 95% CI, 0.12 to 0.76) [5].
Infective endocarditis: The following recommendations are based on a consensus of
experts [6]. The full pediatric guidelines can be found here:
https://doi.org/10.1161/CIR.0000000000000298
Organism Directed Therapy
Organism First-Choice Alternative Choice
Fungi
Candida
spp,
Aspergillus
spp
Surgical
resection
plus
Amphotericin
B
With or
without
flucytosine
Amphotericin B followed by imidazole (eg, fluconazole, itraconazole,
voriconazole) suppression if surgery cannot be performed. Lifelong
suppression may be necessary if surgery cannot be performed or relapse
occurs after surgery.
Baltimore, 2015
Administration
Administer by IV infusion at a concentration of 1 to 2 mg/mL over a period of approximately
60 (if well tolerated) to 120 minutes. To provide sufficient volume for infusion, a final
concentration of 0.2 to 0.5 mg/mL may be appropriate for infants and small children [2]. The
recommended standard concentrations are 1 or 2 mg/mL [3]. May increase infusion time if
patient experiences intolerance during the infusion. Flush existing IV line with D5W prior to
infusion or administer in a separate IV line. In-line filter with pore diameter no less than 1
micron may be used [2].
MEDICATION SAFETY

Contraindications/Precautions
Precautions
Immunologic: Anaphylaxis has been reported; discontinue immediately and do not reinitiate [7].
Adverse Effects
Safety has not been established in pediatric patients younger than 1 month [7].
Common Hypokalemia (37% vs 55%), chills (29% vs 68%), vomiting (27% vs 55%), and hypertension (10% vs 21%) were reported for amphotericin liposome compared with

amphotericin B deoxycholate in a double-blind study in 95 children 16 years or younger [7].
Endocrine/Metabolic:
Hypokalemia occurred at the end of treatment in 21.2% (7 out of 33 pediatric patients) in the liposomal amphotericin B group compared with 28.6% (16 out of 56 pediatric patients) for the conventional amphotericin B group when drugs were administered as recommended (3 to 5 mg/kg/day over at least 1 hour for liposomal and 0.5 to 1.5 mg/kg/day over at least 4 hours for conventional). Potassium replacement therapy was administered to 87.9% of patients in the liposomal amphotericin B group and 89.3% of patients in the conventional group. In those younger than 90 days (n=16), 100% vs 87.5%, respectively, received potassium replacement therapy [8].
Hepatic:
Hepatotoxicity was more common in pediatric patients who received liposomal amphotericin B compared with conventional amphotericin B in a retrospective study; but when concomitant hepatotoxic drugs were accounted for there was no difference. Additionally, the majority of these children with hepatoxicity had at least 1 enzyme abnormality at baseline. Of 65 pediatric patients with baseline and end-of-treatment liver function test, amphotericinrelated hepatotoxicity was 82.8% (24/29) for liposomal amphotericin B and 55.6% (20/36) for conventional amphotericin B (OR 3.8 (1.2 to 12.3; p=0.024)). The LFTs that were different between the 2 groups were gamma-glutamyl transferase (GGT) and bilirubin; GGT was up to 5 x the upper limit of normal (ULN) in 41.4% in the liposomal group compared with 16.7% (p=0.049) in the conventional group and bilirubin was more than 3 to 10 x the ULN in 17.2% and 0%, respectively [8].
Infusion-Related Reactions:

Infusion-related reactions (rigors, fever, tachycardia, and rash) occurred in 9.1% (3 out of 33 pediatric patients) in the liposomal amphotericin B group compared with 23.2% (13 out of 56 pediatric patients; p=0.15) for the conventional amphotericin B group when drugs were administered as recommended (3 to 5 mg/kg/day over at least 1 hour for liposomal and 0.5 to 1.5 mg/kg/day over at least 4 hours for conventional). None of the reactions occurred in children younger than 90 days (n=16) [8].

Renal:

Compared with older individuals, pediatric patients appear to have more tolerance for the nephrotoxic effects of amphotericin B deoxycholate [7]. Creatinine elevation (doubling of baseline serum creatinine concentration) occurred in 21.2% (7 out of 33 pediatric patients) in the liposomal amphotericin B group compared with 14.3% (8 out of 56 pediatric patients; p=0.4) for the conventional amphotericin B group when drugs were administered as recommended (3 to 5 mg/kg/day over at least 1 hour for liposomal and 0.5 to 1.5 mg/kg/day over at least 4 hours for conventional). The mean number of concomitant nephrotoxic drugs was 2.5 for the liposomal group compared with 2 for the conventional group [8].

Solution Compatibility

D5W, D10W, D20W, D25W.

Solution Incompatibility

NS.

Monitoring

Laboratory Exam: Monitor renal function frequently during therapy. Liver function, serum electrolytes (especially magnesium and potassium), and CBC should be assessed regularly during therapy [7].

For candidemia, monitor blood cultures daily or every other day until Candida is cleared [4].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

AmBisome consists of amphotericin B intercalated within a single bilayer liposomal drug delivery system. Acts by binding to the sterol component of a cell membrane leading to alterations in the cell wall permeability and death. Penetrates the cell wall of susceptible fungi. Concentrates in the liver and spleen but penetrates the CNS less than conventional amphotericin B. Less nephrotoxic than conventional amphotericin B. Mean serum half-life in

adults 24 to 38 hours. The pharmacokinetics of amphotericin B liposome is nonlinear.
ABOUT
Special Considerations/Preparation
Available as powder for injection in 50 mg vials. Reconstitute by adding 12 mL of sterile water for injection to a yield a concentration of 4 mg/mL. Immediately shake vial vigorously for 30 seconds. Check for complete dispersion. Reconstituted suspension stable for 24 hours refrigerated.
Do not freeze. Protect from light.
Before administration, AmBisome must be diluted with D5W to a final concentration less than 2 mg/mL. A 1 mg/mL dilution may be made by filtering (using 5 micron filter) 1 mL of reconstituted solution into 3 mL of D5W. Use one filter per vial of AmBisome. Use solution within 6 hours of dilution.
Do not flush IV or mix Ambisome with saline solutions-precipitation will occur.

Amphotericin B
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
Fungal Infections, Suspected or Documented
1 to 1.5 mg/kg every 24 hours IV infusion [1][2][3][4]. Doses of 1.5 mg/kg/dose are administered on alternate days [5]. 1 mg/kg/dose IV every 24 hours for neonates with disseminated candidiasis, including CNS infections [6]. Duration of therapy for candidemia, without metastatic complications, is 2 weeks after documented clearance of Candida from the bloodstream and resolution of symptoms. For CNS infection, continue until all signs, symptoms, and CSF and radiological abnormalities have resolved [6].
Uses
Treatment of systemic fungal infections and severe superficial mycoses.
Neonatal Candidiasis, Including CNS Infection[6]
Invasive candidiasis and candidemia, or very low-birth weight infants with asymptomatic candiduria .
Amphotericin B deoxycholate is recommended.
Fluconazole IV or oral is an alternative for those who have not been receiving prophylaxis with fluconazole.
Lipid formulation amphotericin B agent is an alternative; however, use with caution,

especially in the presence of urinary tract involvement.
Echinocandins (caspofungin, anidulafungin, or micafungin) should be limited to salvage therapy or scenarios of resistance or toxicity to amphotericin B deoxycholate or fluconazole
Central nervous system infections
Amphotericin B deoxycholate is recommended.
Liposomal amphotericin B agent is an alternative.
Salvage therapy with flucytosine may be added in those patients who have not responded to initial therapy.
Fluconazole may be used as step-down therapy for those patients with fluconazolesusceptible isolates who respond to initial therapy
Neonatal intensive care unit (with greater than 10% rate of invasive candidiasis)
Prophylaxis with IV or oral fluconazole for 6 weeks is recommended for neonates with birth weights of less than 1000 g
Prophylaxis with oral nystatin is an alternative in neonates with birth weights of less than 1500 g when fluconazole is unavailable or fluconazole resistance is present

Comparison with Echinocandins: There was no difference in clinical response between echinocandins and amphotericin B (OR 1.38; 95% CI, 0.68 to 2.8) for the treatment of suspected or confirmed invasive candidiasis in a meta-analysis (n=5; 354 neonates and children). Antifungals included were micafungin, caspofungin, amphotericin B deoxycholate, and liposomal amphotericin B. Subanalysis demonstrated no difference in other comparisons including mycological response, mortality, recurrence of candida infection, type of echinocandin, different risk groups (high-risk, low-risk, or neutropenic groups), and type of use (targeted or empirical). Discontinuation due to adverse effects were higher with amphotericin B than the echinocandins (OR 0.3; 95% CI, 0.12 to 0.76) [12].
Infective endocarditis: The following recommendations are based on a consensus of experts [13]. The full pediatric guidelines can be found here:
https://doi.org/10.1161/CIR.0000000000000298
Organism Directed Therapy
Organism First-Choice Alternative Choice
Fungi
Candida spp,

Aspergillus
spp
Surgical
resection
plus
Amphotericin
B
With or
without
flucytosine
Amphotericin B followed by imidazole (eg, fluconazole, itraconazole,
voriconazole) suppression if surgery cannot be performed. Lifelong
suppression may be necessary if surgery cannot be performed or relapse
occurs after surgery.
Baltimore, 2015
Administration
Infuse over 2 to 6 hours [7][8][9] at a concentration not to exceed 0.1 mg/mL [7]; some
institutions have used 0.5 mg/mL concentrations in pediatric patients [10]. Avoid rapid
administration (hypotension, hypokalemia, arrhythmias, and shock can occur). Do not flush
IV or mix amphotericin with saline solution; precipitation will occur. In-line filter
with pore diameter no less than 1 micron may be used [7].
To avoid febrile reactions, administration of acetaminophen or diphenhydramine may be
considered [11]. Some suggest starting with 0.25 mg/kg/day, followed by increases of 0.25
mg/kg/day until the target dose is reached[4]. However, for patients with severe infections
the dose should be initiated at the target dose [11].
MEDICATION SAFETY
Contraindications/Precautions
Precautions
Administration: Rapid infusion may result in hypotension, hypokalemia, arrhythmias, and
shock; infuse over 2 to 6 hours [5].
Administration: If therapy is interrupted for a period longer than 7 days, therapy should be

resumed by starting with the lowest dosage level and increased gradually [5].
Infusion Reactions: Acute reactions (fever, shaking, chills, hypotension, anorexia, nausea,
vomiting, headache, and tachypnea) are common 1 to 3 hours after initiating infusion.
Pretreatment with antipyretics, antihistamines, corticosteroids, or meperidine may improve

tolerance to treatment. A single test dose is recommended in some patients to assess tolerance [5].
Neurological: Leukoencephalopathy has occurred; total body irradiation may put patient at risk [5].
Renal: Use with caution in patients with reduced renal function; some patients may need hydration and sodium repletion prior to administration to reduce risk of nephrotoxicity [5].
Adverse Effects
Common Hypokalemia (37% vs 55%), chills (29% vs 68%), vomiting (27% vs 55%), and hypertension (10% vs 21%) were reported for amphotericin liposome compared with amphotericin B deoxycholate in a double-blind study in children 16 years or younger [14].
Other common events with amphotericin B include fever, malaise, weight loss, hypotension, tachypnea, anorexia, nausea, diarrhea, dyspepsia, cramping epigastric pain, anemia (normochromic, normocytic), pain at the injection site with or without phlebitis or thrombophlebitis, generalized pain (including muscle and joint pains), headache, decreased renal function, and renal function abnormalities [5]
Endocrine/Metabolic:
Hypokalemia (serum K+ less than 3 mmol/L) occurred in 17% of infants, younger than 30 days of age who received amphotericin B deoxycholate, in the neonatal intensive care unit.
The median gestational age was 26 weeks (range, 23 to 41 weeks) and median birth weight was 863 g (range, 546 to 4000 g) [15].
Hypokalemia occurred at the end of treatment in 21.2% (7 out of 33 pediatric patients) in the liposomal amphotericin B group compared with 28.6% (16 out of 56 pediatric patients) for the conventional amphotericin B group when drugs were administered as recommended (3 to 5 mg/kg/day over at least 1 hour for liposomal and 0.5 to 1.5 mg/kg/day over at least 4 hours for conventional). Potassium replacement therapy was administered to 87.9% of patients in the liposomal amphotericin B group and 89.3% of patients in the conventional group. In those younger than 90 days (n=16), 100% vs 87.5%, respectively, received potassium replacement therapy [16].
Hepatic:
Hepatotoxicity was more common in pediatric patients who received liposomal amphotericin B compared with conventional amphotericin B in a retrospective study; but when concomitant hepatotoxic drugs were accounted for there was no difference. Additionally, the majority of these children with hepatoxicity had at least 1 enzyme abnormality at baseline. Of

65 pediatric patients with baseline and end-of-treatment liver function test, amphotericinrelated hepatotoxicity was 82.8% (24/29) for liposomal amphotericin B and 55.6% (20/36) for conventional amphotericin B (OR 3.8 (1.2 to 12.3; p=0.024)). The LFTs that were different between the 2 groups were gamma-glutamyl transferase (GGT) and bilirubin; GGT was up to 5 x the upper limit of normal (ULN) in 41.4% in the liposomal group compared with 16.7% (p=0.049) in the conventional group and bilirubin was more than 3 to 10 x the ULN in 17.2% and 0%, respectively [16].

Infusion-Related Reactions:

Infusion-related reactions (rigors, fever, tachycardia, and rash) occurred in 9.1% (3 out of 33 pediatric patients) in the liposomal amphotericin B group compared with 23.2% (13 out of 56 pediatric patients; p=0.15) for the conventional amphotericin B group when drugs were

administered as recommended (3 to 5 mg/kg/day over at least 1 hour for liposomal and 0.5 to 1.5 mg/kg/day over at least 4 hours for conventional). None of the reactions occurred in children younger than 90 days (n=16) [16].

Renal:

Serum creatinine increased at least 0.4 mg/dL at any time during amphotericin B therapy in 16% (15 out of 92) of infants, 90 days or younger, in the neonatal intensive care unit. None of the values exceeded 2 mg/dL. By the end of therapy, elevated creatinine values normalized in 8 of the 15 infants; 3 had resolving values, and 4 had values that remained elevated. The median gestational age was 26 weeks (range, 23 to 41 weeks) and median birth weight was 863 g (range, 546 to 4000 g). The mean cumulative dose was 13.5 mg/kg and duration was 16.3 days for infants who both developed and did not develop nephrotoxicity; no difference in dose or duration between groups [15].

Compared with older individuals, pediatric patients appear to have more tolerance for the nephrotoxic effects of amphotericin B deoxycholate [17]. Creatinine elevation (doubling of baseline serum creatinine concentration) occurred in 21.2% (7 out of 33 pediatric patients) in the liposomal amphotericin B group compared with 14.3% (8 out of 56 pediatric patients; p=0.4) for the conventional amphotericin B group when drugs were administered as

recommended (3 to 5 mg/kg/day over at least 1 hour for liposomal and 0.5 to 1.5 mg/kg/day over at least 4 hours for conventional). The mean number of concomitant nephrotoxic drugs was 2.5 for the liposomal group compared with 2 for the conventional group [16].
Sodium intake of more than 4 mEq/kg/day was associated with a decrease in the incidence of amphotericin B-induced nephrotoxicity in extremely premature infants with a birth weight of less than 1250 g [18][19]. Nephrotoxicity developed in 13 out of 21 neonates in the control group compared with 3 out of 16 in the high-sodium intake group (p=0.02). The additional sodium was administered by either increasing the amount of sodium in the total parenteral nutrition (TPN) or normal saline in those who could tolerate excess fluid until sodium could be adjusted in the TPN. All neonates in the high sodium group received 1 mg/kg/day by 2 days of age [19].
Black Box Warning
This drug should be used primarily for treatment of patients with progressive and potentially life-threatening fungal infections; it should not be used to treat noninvasive forms of fungal disease such as oral thrush, vaginal candidiasis and esophageal candidiasis in patients with normal neutrophil counts [5]
The product name and dosage should verified if the prescribed dose exceeds 1.5 mg/kg.
Overdose can result in potentially fatal cardiac or cardiorespiratory arrest [5].
Solution Compatibility
D5W, D10W, D15W, and D20W.
Solution Incompatibility
NS

Terminal Injection Site Compatibility
Amiodarone, heparin, hydrocortisone, sodium bicarbonate, and zidovudine.
Terminal Injection Site Incompatibility
Fat emulsion. Amikacin, aztreonam, calcium chloride, calcium gluconate, cefepime, cimetidine, ciprofloxacin, dopamine, enalaprilat, fluconazole, gentamicin, linezolid, magnesium sulfate, meropenem, penicillin G, piperacillin/tazobactam, potassium chloride, propofol, ranitidine, remifentanil, and tobramycin.
Monitoring
Laboratory Parameters: Monitor renal function frequently during therapy. Liver function, serum electrolytes (especially magnesium and potassium), CBC, and hemoglobin should be

assessed regularly during therapy [5].
For candidemia, monitor blood cultures daily or every other day until Candida is cleared [6].
MECHANISM OF ACTION/PHARMACOKINETICS
Pharmacology
Mechanism of Action: Amphotericin B binds to ergosterol in the membrane of sensitive fungi and may be fungicidal or fungistatic depending on the concentrations achieved in body fluids/tissue [14].
The therapeutic concentration range is not well-defined. Highly protein-bound (greater than 90%). Elimination half-life is approximately 15 days. Drug may accumulate in tissues to a significant concentration and be excreted renally for months [5].
After 5 days of amphotericin B IV in 13 neonates (2 to 55 days of life; mean gestational age 27.4 +/- 5 weeks (24 to 40 weeks)). Dose was increased from 0.1 to 0.5 mg/kg/day over the first 4 to 6 days in 10 infants. The other 3 infants started on 0.8 to 1 mg/kg/day which was reduced to 0.5 mg/kg/day. The mean dose for all patients was 0.54+/-0.16 mg/kg/day. Oral 5-fluorocytosine was started on the same day as amphotericin B [20]
Peak concentration: 0.96 mcg/mL (range 0.5 to 4 mcg/mL) [20]
Vd: 1.5 L/kg (range, 0.1 to 17.5 hours) [20]
CSF Distribution: 40% to 90% of serum (n=5) [20]
Clearance: 18 mL/min/1.73 m2(range 7.7 to 72.3 mL/min/1.73 m2) [20]
Half-life: 14.8 hours (range 5 to 82 hours) beta half-life, weeks to months for alpha elimination phase [20]

ABOUT
Special Considerations/Preparation
Available as powder for injection in 50-mg vials. Protect the vials from light. Reconstitute with 10 mL of D5W or preservative free sterile water to a concentration of 5 mg/mL, then dilute further using D5W to a concentration no greater than 0.1 mg/mL for infusion.
Reconstituted solution stable for 24 hours at room temperature or 7 days in refrigerator. Do not flush IV or mix amphotericin with saline solution; precipitation will occur. May filter if necessary; mean pore diameter should not be less than 1 micron. The manufacturer recommends protecting the solution from light during administration [7]. However, there are available data that demonstrate protection from light to be unnecessary in typical hospital

lighting if administered within 24 hours of preparation [21].
Intravitreal injection: amphotericin B deoxycholate 5 to 10 mcg/0.1 mL of sterile water
[6].

Ampicillin
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
Usual dose, 25 to 50 mg/kg/dose [1][2] by IV slow push, or IM.
Renal function and drug elimination are most strongly correlated with postmenstrual age
(PMA; equivalent to gestational age plus postnatal age). PMA is the primary determinant of
dosing interval, with postnatal age as the secondary qualifier.
Dosing Interval Chart
PMA
(weeks)
PostNatal
(days)
Interval
(hours)
?29 0 to 28
>28
12
8
30 to 36 0 to 14
>14
12
8
37 to 44 0 to 7
>7
12
8
?45 ALL 6
Anthrax[3]
32 up to 34 weeks gestational age
0 to 1 week: 50 mg/kg/dose IV every 12 hours
1 to 4 weeks: 50 mg/kg/dose IV every 8 hours
34 weeks gestational age or older
0 to 1 week: 50 mg/kg/dose IV every 8 hours
1 to 4 weeks: 50 mg/kg/dose IV every 6 hours
Duration: 2 to 3 weeks or more until stable. Continue antimicrobial course of prophylaxis
(usually oral therapy) for up to 60 days from onset of illness [3].
Bacteremia, Group B Streptococcal Disease; Empiric and Definitive Therapy (Earlyand
late-onset) [4]
Guideline Dosage

Gestational
Age
Postnatal age Duration
7 days or
younger
Older than 7
days
34 weeks
or less
50 mg/kg/dose
IV every 12
hours
75 mg/kg/dose
IV every 12
hours 10 days for bacteremia without a focus; longer durations may be necessary for prolonged or
Greater complicated courses.
than 34
weeks
50 mg/kg/dose
IV every 8
hours
50 mg/kg/dose
IV every 8
hours
Use with an aminoglycoside for empirical therapy in full-term newborns 7 days or younger.
Use with ceftazidime for empirical therapy for previously healthy infants, 8 to 28 days of age, in the community when critical illness and meningitis are absent.
Puopolo, 2019

Bacteremia (Septicemia)
FDA Dosage[5]
Gestational
Age
Postnatal Age Duration
7 days or
younger
8 days to
younger
than 28
days
Continue for a minimum of 48 to 72 hours after asymptomatic
or evidence of bacterial eradication. For group A betahemolytic
streptococci, treat for at least 10 days.
34 weeks
or less
50
mg/kg/dose
IV every 12

hours
75
mg/kg/dose
IV every 12
hour
Greater
than 34
weeks
28 days or younger
50 mg/kg/dose IV every
8 hours
Product Information, 2017
Meningitis, Group B Streptococcal Disease; Empiric and
Definitive Therapy (Earlyand
late-onset) [4]
Guideline Dosage
Postnatal
age
Dosage Duration
7 days or
younger
100 mg/kg/dose IV
every 8 hours 14 days for uncomplicated meningitis;
longer durations may be
Older than necessary for prolonged or complicated
courses.
7 days
75 mg/kg/dose IV
every 6 hours
Use with an aminoglycoside for empirical therapy in
full-term newborns 7 days or younger.
Use with ceftazidime and vancomycin for empirical
therapy for previously healthy infants, 8 to 90
days of age.
Puopolo, 2019
Meningitis, Bacterial
FDA Dosage[5]
Gestational
Age
Postnatal Age Duration
7 days or
younger
8 days to
younger
than 28
days
Continue for a minimum of 48 to 72 hours after
asymptomatic
or evidence of bacterial eradication. For group A
betahemolytic
streptococci, treat for at least 10 days.
34 weeks
or less
50
mg/kg/dose
IV every 12
hours
75

mg/kg/dose
IV every 12
hour
Greater
than 34
weeks
28 days or younger
50 mg/kg/dose IV every
8 hours
Product Information, 2017
Uses

Broad-spectrum antibiotic useful against group B
streptococcus, Listeria monocytogenes, and
susceptible E coli species.
Anthrax[3]:
Systemic Anthrax when meningitis can be ruled out (IV)
Combination IV Therapy
Preferred: Ciprofloxacin. Alternatives in order of
preference: meropenem, levofloxacin,
imipenem/cilastatin, or vancomycin. If strains are
penicillin-susceptible, then penicillin G
(preferred) or ampicillin (alternative).
Plus
Preferred: Clindamycin. Alternatives in order of
preference: linezolid, doxycycline (not
for neonates 37 weeks gestation or younger), or
rifampin.
Systemic Anthrax (meningitis or disseminated infection
and meningitis cannot be
ruled out) (IV)
Triple IV Therapy
Preferred: Ciprofloxacin. Alternatives in order of
preference: levofloxacin or
moxifloxacin
Plus
Preferred: Meropenem. Alternatives in order of
preference: imipenem/cilastatin or
doripenem. If strains are penicillin-susceptible, then
penicillin G (preferred) or ampicillin
(alternative).
Plus
Preferred: Linezolid. Alternatives in order of
preference: clindamycin or rifampin or as
a last resort, chloramphenicol
Group B Streptococcal (GBS) Disease:
Definitive
The preferred antibiotic for early-onset and late-
onset, culture confirmed-GBS disease is
penicillin G and the alternative is ampicillin [4].
Empiric
Preterm infants: The choice is based on multiple
factors in those continuously hospitalized

beyond 72 hours of age. Empirical choices include group B streptococci-susceptible antibiotics including a ?-lactam, cephalosporin, or vancomycin [4].
7 days or younger: The preferred empiric therapy is ampicillin plus an aminoglycoside. If there is compelling reason to suspect an ampicillin-resistant infection in a critically ill neonate, especially very-low-birth-weight neonates, then consider the addition of a broaderspectrum antibiotic [4].
8 to 28 days: Ampicillin plus ceftazidime is preferred for previously healthy infants in the community when critical illness and meningitis are absent [4].
29 to 90 days: Ceftriaxone is recommended for critically ill infants with meningitis [4].
8 to 90 days: Adding vancomycin to empiric therapy is recommended for previously healthy infants in the community if there is evidence of meningitis or critical illness to expand coverage, including for ?-lactam-resistant Streptococcus pneumoniae[4].
Infective endocarditis: The following recommendations are based on a consensus of experts [8]. The full pediatric guidelines can be found here:
https://doi.org/10.1161/CIR.0000000000000298
Organism Directed Therapy
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Organism First-Choice Alternative Choice
Streptococci
Highly susceptible to penicillin G (MBC 0.1 mcg/mL or less); includes most viridans streptococci, groups A, B, C, G nonenterococcal, group D streptococci (S bovis, S equinus)
Penicillin G or CefTRIAXone
Vancomycin or First-generation cephalosporin or CefTRIAXone
Relatively resistant to penicillin (MBC 0.2 mcg/mL or more); less-susceptible viridans streptococci or enterococci
Penicillin G or Ampicillin + Gentamicin (for first 2 weeks, or entire course for enterococci)
Vancomycin + Gentamicin for

enterococci
Ampicillin +
CefTRIAXone (for
aminoglycoside (AMG)-
resistant enterococci or
AMG-intolerant patient)
CefTRIAXone +
gentamicin (not for
enterococcal endocarditis)
Resistant to penicillin Consult an infectious
disease specialist.

Staphylococci (S aureus or coagulase-negative
staphylococci)
Penicillin G susceptible (1 mcg/mL or less) (rare)
Penicillin G Oxacillin or
Nafcillin or
First-generation
cephalosporin or
Vancomycin
Penicillin G resistant (0.1 mcg/mL)
Oxacillin or
Nafcillin
with or without
Gentamicin
Vancomycin (for those
highly allergic to betalactam
antibiotics) or
First-generation
cephalosporin
Oxacillin (MRSA) resistant (4 mcg/mL)
Vancomycin Daptomycin for rightsided
endocarditis, maybe
for left-sided
Vancomycin resistant or intolerant Daptomycin Unknown
When prosthetic material present add riFAMpin
+ gentamicin (for first 2 weeks) for all
staphylococci
Gram-negative enteric bacilli
CefTAZidime or
Cefepime or
Cefotaxime or
CefTRIAXone
Plus gentamicin (or
tobramycin or
amikacin, depending
on susceptibility)
Broad-spectrum penicillin
Plus gentamicin (or
tobramycin or amikacin)
HACEK group
CefTRIAXone or
Cefotaxime or
Ampicillin-sulbactam
Ampicillin (when
susceptible)
Plus aminoglycoside

KEY: AMG = aminoglycosides; HACEK = Haemophilus species, Aggregatibacter species, Cardiobacterium hominis, Eikenella corrodens, and Kingella species; MBC = minimum bactericidal concentration, MRSA = methicillin-resistant Staphylococcus aureus (includes resistance to oxacillin, nafcillin, and cephalosporins)
Baltimore, 2015

Meningitis: Empiric agents for the treatment of meningitis in neonates are ampicillin, gentamicin, and cefotaxime [9]. Reassess therapy based on culture and sensitivity results [10].
Sepsis, Early-Onset
Ampicillin plus gentamicin are the agents of choice for empirical treatment of early-onset sepsis (EOS) in neonates at most risk for EOS. Broad-spectrum antibiotics may be necessary in neonates who are severely ill, particularly preterm neonates at high risk for EOS after prolonged antepartum maternal antibiotic treatment [11][12].
Gestational age 34 6/7 weeks or younger
Highest risk for EOS: Administer empirical antibiotics in those at highest risk; neonates born preterm because of maternal cervical incompetence, preterm labor, premature rupture of membranes, clinical concern for intraamniotic infection, or acute onset of unexplained nonreassuring fetal status [11]
Low risk: Consider empirical antibiotics based on the risks and benefits. Those at low risk are those born preterm by cesarean delivery because of maternal noninfectious illness or placental insufficiency in the absence of labor, attempts to induce labor, or rupture of membranes before delivery [11]
Gestational age 35 0/7 weeks or older: Administer empirical antibiotics based on level of risk. Multiple approaches of determining risk may be used including categorical algorithms, multivariate risk assessments, or serial physical examinations [12].
Duration:
Discontinue antibiotics by 36 to 48 hours when blood cultures are sterile, unless a sitespecific infection has been identified, for preterm and full term neonates [11][12].
Procalcitonin values in addition to perinatal risk factors, signs and symptoms, and laboratory values may aid in the determination to discontinue antibiotic therapy in neonates with

suspected early-onset sepsis. The duration of antibiotic therapy was reduced by 9.9 hours with a procalcitonin-guided algorithm compared with standard care in a multicenter randomized control trial of 1710 neonates born after 34 weeks of gestational age with possible or unlikely sepsis. Re-infection and mortality was not different between the groups (risk difference 0.1% (95% CI, -5.2% to 5.3%) [13].

Pediatric FDA Approved Indications

Bacterial meningitis caused by E coli, group B streptococci, and other gram-negative bacteria (Listeria monocytogenes, N meningitides). Addition of an aminoglycoside may increase effectiveness against gram-negative bacteria [5].

Septicemia caused by susceptible gram-positive organisms including Streptococcus species, penicillin G-susceptible staphylococci, and enterococci. Gram-negative sepsis caused by E coli, P mirabilis and Salmonella species. Addition of an aminoglycoside may enhance effectiveness [5].

Administration

Intravenous

Doses 500 mg or less should be administered slowly over 3 to 5 minutes IV and over at least 10 to 15 minutes for doses 1 g or greater [6].

Recommended concentrations are 30, 40, 50, and 100 mg/mL for intermittent IV [7].

Intramuscular

Mix to a final concentration of 250 mg/mL for IM administration [6].

MEDICATION SAFETY

Adverse Effects

Very large doses may result in CNS excitation or seizure activity. Moderate prolongation of bleeding times (by approximately 60 seconds) has been reported after the third or fourth dose in neonates 33 to 41 weeks GA receiving 50 to 100 mg/kg every 12 hours[15].

Prolongation of bleeding times (by approximately 2 minutes) has also been reported after at least 10 doses in preterm very low birth-weight neonates 23 to 30 weeks GA receiving 50 to 100 mg/kg every 12 hours [16]. The clinical implications of the prolonged bleeding time is unknown. Hypersensitivity reactions (maculopapular rash, urticarial rash, or fever) are rare in neonates.

Solution Compatibility

D5W, D5W in 0.45% sodium chloride, lactated ringer's solution, NS, sterile water.

Stability is dependent on storage temperature and duration, and concentration of ampicillin[6].
Solution Incompatibility
D10W, D5NS, D5W in 0.45% sodium chloride (Trissel's 2 Clinical Pharmaceutics Database).
Ampicillin may be compatible with D5W in 0.45% sodium chloride, depending upon storage temperature and duration, and concentration of ampicillin[6]
Terminal Injection Site Compatibility
Acyclovir, alprostadil, aminophylline, aztreonam, calcium gluconate, cefepime, chloramphenicol, cimetidine, clindamycin, enalaprilat, famotidine, furosemide, heparin, hydrocortisone succinate, insulin, lidocaine, linezolid, magnesium sulfate, metronidazole, milrinone, morphine, phytonadione, potassium chloride, propofol, ranitidine, remifentanil, and vancomycin.
Terminal Injection Site Incompatibility
Amikacin, amiodarone, dopamine, epinephrine, erythromycin lactobionate, fluconazole, gentamicin, hydralazine, metoclopramide, midazolam, nicardipine, sodium bicarbonate, and

tobramycin.
Ampicillin 100 mg/mL: TPN formulas with TrophAmine 2% and TrophAmine 3%
Monitoring
Periodic assessment of renal, hepatic, and hematopoietic function in patients receiving extended treatment [14].
After 2 consecutive procalcitonin measurements within the normal range and when there is a low risk for infection (assessed by perinatal risk factors, clinical symptoms, and other laboratory findings), consider discontinuation of antibiotics for suspected early-onset sepsis in neonates (34 weeks or older) categorized as infection possible or unlikely. All neonates should receive a minimum of 24 hours of antibiotics before discontinuation [13].
MECHANISM OF ACTION/PHARMACOKINETICS
Pharmacology
Ampicillin is a semisynthetic penicillin that is bactericidal. Clearance is primarily by the renal route and is inversely related to postnatal age. Serum half-life in term infants younger than 7 days is approximately 4 hours.
Population pharmacokinetic parameters were determined in a multicenter trial [17]:
Pharmacokinetic Parameters

Gestational Age Postnatal Age Clearance* Volume* Half-life*
34 weeks or less
7 days or less
(n=21)
0.055 (0.03 to 0.07)
L/hr/kg
0.4 (0.4 to 0.4)
L/kg
5 (3.9 to 9.4)
hours
8 to 28 days
(n=7)
0.07 (0.03 to 0.07)
L/hr/kg
0.4 (0.4 to 0.41)
L/kg
4 (3.8 to 8.3)
hours
Greater than 34 weeks
7 days or less
(n=27)
0.086 (0.04 to 0.13)
L/hr/kg
0.4 (0.4 to 0.4)
L/kg
3.2 (2.2 to 6.2)
hours
8 to 28 days
(n=18)
0.11 (0.06 to 0.13)
L/hr/kg
0.4 (0.4 to 0.41)
L/kg
2.4 (2.1 to 4.7)
hours
*median (ranges)

Controlled Hypothermia

Pharmacokinetic Parameters: The mean (+/-SD) pharmacokinetic parameters in 13 neonates (median gestational age 39 weeks and mean estimated glomerular filtration rate of 43 mL/min/1.732) with hypoxic-ischemic encephalopathy undergoing controlled hypothermia were 0.43+/-0.12 mL/min/kg for total body clearance, 0.35+/-0.46 L/kg for volume of the central compartment, and 0.52+/-0.28 L/kg for total volume of distribution [18].

Potential Dosage: Doses of 25 mg/kg or 50 mg/kg IV every 24 hours achieved optimal trough concentrations in dose simulations using gestational age of 36 to 41 weeks, estimated creatinine clearance of 27 to 76 mL/min/1.732, and weight of 2.4 to 4.85 kg (mimicking neonates with hypoxic-ischemic encephalopathy undergoing controlled hypothermia). Steady

state trough concentrations remained above an MIC of 8 mcg/mL for 100% of the dosing

interval with a probability of at least 94% [18].
ABOUT
Special Considerations/Preparation
Available as powder for injection in 125-, 250-, 500-mg, 1-g, 2-g, and 10-g vials.
Reconstitute using sterile water for injection. Maximum concentration for IV infusion is 100 mg/mL. Mix to a final concentration of 250 mg/mL for IM administration.
Reconstituted solution must be used within 1 hour of mixing because of loss of potency.

Anidulafungin
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
Candidiasis
Full term infants when intolerant to or resistant to fluconazole or amphotericin B
Loading dose: 3 mg/kg IV for 1 dose [1][2]. A higher dose may be required in patients receiving extracorporeal membrane oxygenation (ECMO) [1].
Maintenance dose: 1.5 mg/kg IV once daily [1][2]. Higher doses may be required in patients receiving extracorporeal membrane oxygenation (ECMO) [1]. Duration of therapy for candidemia, without metastatic complications, is 2 weeks after documented clearance of Candida from the bloodstream and resolution of symptoms [3].
Uses
Neonatal Candidiasis, Including CNS Infection[3]
Invasive candidiasis and candidemia, or very low-birth weight infants with asymptomatic candiduria .
Amphotericin B deoxycholate is recommended.
Fluconazole IV or oral is an alternative for those who have not been receiving prophylaxis with fluconazole.
Lipid formulation amphotericin B agent is an alternative; however, use with caution, especially in the presence of urinary tract involvement.

Echinocandins (caspofungin, anidulafungin, or micafungin) should be limited to salvage therapy or scenarios of resistance or toxicity to amphotericin B deoxycholate or fluconazole

Central nervous system infections

Amphotericin B deoxycholate is recommended.

Liposomal amphotericin B agent is an alternative.

Salvage therapy with flucytosine may be added in those patients who have not responded to initial therapy.

Fluconazole may be used as step-down therapy for those patients who respond to initial therapy

Neonatal intensive care unit (with greater than 10% rate of invasive candidiasis)

Prophylaxis with IV or oral fluconazole for 6 weeks is recommended for neonates with birth weights of less than 1000 g

Prophylaxis with oral nystatin is an alternative in neonates with birth weights of less than 1500 g when fluconazole is unavailable or fluconazole resistance is present

In a safety and pharmacokinetic study, doses of 1.5 mg/kg/day for 5 days in 8 neonates (6 out of 8 preterm) provided similar anidulafungin exposures compared to children and adults

(100 mg/day) [1]. Despite sensitivity to amphotericin B, fungal peritonitis was not cleared in a full-term neonate until anidulafungin was added to liposomal amphotericin B; Candida albicans had been cultured from the peritoneum while the patient was receiving amphotericin B monotherapy [2]. Doses for hematogenous Candida meningoencephalitis (HCME) are expected to be much higher than those used for other indications, based upon a translational study which used neonatal (6 out of 8 were preterm) pharmacokinetic data applied to an animal model of the disease [5].

FDA Approved Indications

Treatment of candidemia, esophageal candidiasis, and intra-abdominal abscess and peritonitis due to Candida in patients older than 16 years [4].

Administration

Administer by IV Infusion (0.8 mg/mL) [4]over 60 minutes [1]; not to exceed 1.1 mg/minute [4].

MEDICATION SAFETY

Contraindications/Precautions

Contraindicated in patients with hypersensitivity to other echinocandins [4].

Hepatitis, hepatic failure, and significant hepatic dysfunction have been reported.
Anaphylactic reactions, including shock, have also been reported; discontinue use if reactions occur. Infusion-related reactions (eg, rash, urticaria, flushing, pruritus, bronchospasm, dyspnea, and hypotension) have been reported; to reduce occurrence, do not exceed an infusion rate of 1.1 mg/minute [4].
Adverse Effects
Adverse events reported were hypotension (1), adrenal insufficiency (1), abnormal X-ray of kidneys, ureter, and bladder (1), death (1), infection (1), pulmonary edema (1), and oliguria or uremia (2) in a safety study of 8 neonates [1].
Solution Compatibility
D5W, NS.
Terminal Injection Site Compatibility

Anidulafungin 0.5 mg/mL
Acyclovir (7 mg/mL), amikacin (5 mg/mL), aminocaproic acid (50 mg/mL), aminophylline (2.5 mg/mL), amiodarone (4 mg/mL), amphotericin B lipid complex (1 mg/mL), amphotericin B liposome (1 mg/mL), ampicillin (20 mg/mL), ampicillin/sulbactam (20 and 10 mg/mL), argatroban (1 mg/mL), atracurium (0.5 mg/mL), azithromycin (2 mg/mL), aztreonam (40 mg/mL), bivalirudin (5 mg/mL), bumetanide (40 mcg/mL), calcium chloride (40 mg/mL), calcium gluconate (40 mg/mL), caspofungin (0.5 mg/mL), cefazolin (20 mg/mL), cefepime (20 mg/mL), cefotaxime (20 mg/mL), cefotetan (20 mg/mL), cefoxitin (20 mg/mL), ceftazidime (40 mg/mL), ceftriaxone (20 mg/mL), cefuroxime (30 mg/mL), chloramphenicol (20 mg/mL), cimetidine (12 mg/mL), ciprofloxacin (2 mg/mL), cisatracurium (0.5 mg/mL), clindamycin (10 mg/mL), cyclosporine (5 mg/mL), dexamethasone (1 mg/mL), dexmedetomidine (4 mcg/mL), digoxin (0.25 mg/mL), diltiazem (5 mg/mL), diphenhydramine (2 mg/mL), dobutamine (4 mg/mL), dolasetron (2 mg/mL), dopamine (3.2 mg/mL), doxycycline hyclate (1 mg/mL), enalaprilat (0.1 mg/mL), epinephrine (50 mcg/mL), erythromycin (5 mg/mL), esmolol (10 mg/mL), famotidine (2 mg/mL), fentanyl (50 mcg/mL), fluconazole (2 mg/mL), foscarnet (24 mg/mL), fosphenytoin (20 mgPE/mL), furosemide (3 mg/mL), ganciclovir (20 mg/mL), gentamicin (5 mg/mL), glycopyrrolate (0.2 mg/mL), granisetron (50 mcg/mL), haloperidol (0.2 mg/mL), heparin (100 units/mL), hydralazine (1

mg/mL), hydrocortisone (1 mg/mL), hydromorphone (0.5 mg/mL), imipenem/cilastatin (5 mg/mL), insulin (1 unit/mL), isoproterenol (20 mcg/mL), ketorolac (15 mg/mL), labetalol (2 mg/mL), levofloxacin (5 mg/mL), lidocaine (10 mg/mL), linezolid (2 mg/mL), lorazepam (0.5 mg/mL), mannitol (150 mg/mL; 15%), meropenem (2.5 mg/mL), methotrexate (12.5 mg/mL), methyldopate (10 mg/mL), methylprednisolone (5 mg/mL), metoclopramide (5 mg/mL), metronidazole (5 mg/mL), midazolam (1 mg/mL), milrinone (0.2 mg/mL), morphine (15 mg/mL), moxifloxacin (1.6 mg/mL), mycophenolate mofetil (6 mg/mL), nafcillin (20 mg/mL), naloxone (0.4 mg/mL), nicardipine (1 mg/mL), nitroglycerin (0.4 mg/mL), nitroprusside (2 mg/mL), norepinephrine (0.12 mg/mL), octreotide (5 mcg/mL), ondansetron (1 mg/mL), palonosetron (50 mcg/mL), pancuronium (0.1 mg/mL), pantoprazole (0.4 mg/mL), pentobarbital (5 mg/mL), phenobarbital (5 mg/mL), phenylephrine (1 mg/mL), piperacillin/tazobactam (40 and 5 mg/mL), potassium chloride (0.1 mEq/mL), procainamide (20 mg/mL), propranolol (1 mg/mL), quinupristin/dalfopristin (5 mg/mL), ranitidine (2 mg/mL), rocuronium (1 mg/mL), succinylcholine (2 mg/mL), sulfamethoxazole-trimethoprim (4 and 0.8 mg/mL), tacrolimus (20 mcg/mL), ticarcillin/clavulanate (31 mg/mL), tobramycin (5 mg/mL), vancomycin (10 mg/mL), vasopressin (1 unit/mL), vecuronium (1 mg/mL), verapamil (2.5 mg/mL), voriconazole (4 mg/mL), zidovudine (4 mg/mL).

Terminal Injection Site Incompatibility

Amphotericin B conventional colloidal, diazepam, ertapenem, magnesium sulfate, nalbuphine, phenytoin, sodium bicarbonate.

Compatibility information refers to physical compatibility and is derived from Trissels 2 Clinical Pharmaceutics Database. The determination of compatibility is based on concentrations for administration recommended herein. Drug compatibility is dependent on multiple factors (eg, drug concentrations, diluents, storage conditions). This list should not be viewed as all-inclusive and should not replace sound clinical judgment. The user is referred to Trissels 2 for more complete details.

Trissels 2 Clinical Pharmaceutics Database, version updated on 06/15/2012.

Monitoring

For candidemia, monitor blood cultures daily or every other day until Candida is cleared [3].
Monitor liver function tests. Also monitor for signs and symptoms of worsening hepatic function in patients who develop abnormal liver function tests during therapy [4].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Anidulafungin, a semi-synthetic echinocandin, is a non-competitive inhibitor of beta-(1,3)-Dglucan synthase; this enzyme is responsible for formation of the polysaccharide, beta-(1,3)-glucan, an essential fungal cell wall component [4]. Anidulafungin is most active (MIC90 in mcg/mL) against Candida albicans (0.06), C glabrata (0.12), C tropicalis (0.06), and C krusei (0.12) isolates, but less potent against C parapsilosis (2) and C guilliermondii (2). It has demonstrated activity against the biofilms of C. albicans and C. parapsilosis. The minimum effective concentration 90 against Aspergillus fumigatus is 0.008 mcg/mL [6]. Candida isolates with reduced susceptibility to anidulafungin have been reported. The clinical relevance of these reports is unknown, but the development of drug resistance may be possible. Extensively bound to plasma proteins (greater than 99%). No hepatic metabolism; not a substrate, inducer, or inhibitor of CYP450. Undergoes slow chemical degradation at physiologic temperature and pH to a ring-opened peptide (inactive). In a single-dose study, less than 1% was recovered in urine and approximately 30% was recovered in the feces over 9 days, of which less than 10% was intact anidulafungin. Not removed by hemodialysis [4].
In a pharmacokinetic and safety study following 3 to 5 days of anidulafungin (n=15; age 2 days to 2 years), neonates (n=8; 6 out of 8 premature) demonstrated a median weight adjusted clearance of 0.02 L/kg/hr (range 0.013 to 0.049), median half-life of 78 hours (range 40 to 219), and median exposure of 74.9 mcg*hr/mL (30.4 to 108.9). The lowest exposure was seen in 2 neonates who received extracorporeal membrane oxygenation (ECMO), a process which may alter volume of distribution and/or clearance, and therefore drug exposure. The inclusion of data from the ECMO patients in the calculations likely skewed the median pharmacokinetic values for the entire neonatal study population [1].

ABOUT

Special Considerations/Preparation

Available as 50-mg and 100-mg single-use vials of anidulafungin lyophilized powder for solution. The 50-mg and 100-mg vials also contain fructose (50 mg and 100 mg,

respectively) and mannitol (250 mg and 500 mg, respectively). Refrigerate unopened vials between 2 and 8 degrees C (36 and 46 degrees F). Do not freeze. Excursions to 25 degrees C (77 degrees F) are permitted for 96 hours; then, vial may be returned to refrigerator [4]. Reconstitute 50-mg and 100-mg vials with 15 mL and 30 mL, respectively, of sterile water for injection (3.33 mg/mL). Reconstituted solution may be stored up to 24 hours at 25 degrees C

(77 degrees F) or less. For infusion, dilute appropriate dose in sufficient volume of D5W or NS to final concentration of 0.8 mg/mL. Diluted solution for infusion may be stored at room temperature, up to 25 degrees C (77 degrees F), for up to 48 hours or frozen for at least 72 hours prior to administration [4].

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Arginine
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
Acute Hyperammonemia - Urea Cycle Disorders
Pending Definitive Diagnosis of Urea Cycle Enzyme Deficiency:
Loading dose: Arginine hydrochloride 600 mg/kg in combination with sodium phenylacetate 250 mg/kg and sodium benzoate 250 mg/kg as an IV infusion over 90 to 120 minutes [1][2][3][4].
Maintenance dose: Arginine hydrochloride 600 mg/kg in combination with sodium phenylacetate 250 mg/kg and sodium benzoate 250 mg/kg as an IV infusion over 24 hours [1][2][3][4].
Known CPS, OTC, or NAGS Deficiency:
Loading dose: Arginine hydrochloride 200 mg/kg in combination with sodium phenylacetate 250 mg/kg and sodium benzoate 250 mg/kg as an IV infusion over 90 to 120 minutes [1][2][5][3][4].
Maintenance dose: Arginine hydrochloride 200 mg/kg in combination with sodium phenylacetate 250 mg/kg and sodium benzoate 250 mg/kg as an IV infusion over 24 hours [1][2][5][3][4].
Known ASS or ASL Deficiency:
Loading dose: Arginine hydrochloride 600 mg/kg in combination with sodium phenylacetate 250 mg/kg and sodium benzoate 250 mg/kg as an IV infusion over 90 to 120 minutes [1][2][5][3][4].
Maintenance dose: Arginine hydrochloride 600 mg/kg in combination with sodium phenylacetate 250 mg/kg and sodium benzoate 250 mg/kg as an IV infusion over 24 hours [1][2][5][3][4].
Repeating the loading dose within 24 hours of the initial loading dose should be considered only for patients with a severe disorder receiving dialysis[4].
CPS = carbamyl phosphate synthetase; OTC = ornithine transcarbamylase; NAGS = N-acetyl glutamate synthase; ASS = argininosuccinic acid synthetase; ASL = argininosuccinic acid lyase

Uses
Adjunctive treatment of acute hyperammonemia in neonates with urea cycle disorders.
Sodium phenylacetate/sodium benzoate should be used concomitantly with arginine hydrochloride. Hemodialysis is the primary treatment of acute hyperammonemia during the early management period [2][5][3][4][6].

Administration
For treatment of acute hyperammonemia, must be administered through a central line.
For loading and maintenance doses, dilute arginine and sodium phenylacetate/sodium benzoate in 25 to 35 mL/kg of D10W prior to administration [4].
MEDICATION SAFETY
Contraindications/Precautions
Arginine hydrochloride contains 47.5 mEq of chloride in 100 mL. Hyperchloremic metabolic acidosis has been reported in 2 pediatric patients receiving excessive arginine. Extravasation can cause tissue necrosis. Arginine is a nitric oxide precursor. Excessive arginine accumulation can result in nitric oxide overproduction with potential for vasodilation and hypotension [5][3][4][7].
Solution Compatibility
D10W and sodium phenylacetate/sodium benzoate 10%.
Monitoring
Plasma ammonia levels every hour during dialysis until levels stabilize to less than 200 to 300 micromoles/L. Capillary blood should not be used for monitoring ammonia levels. Monitor electrolytes and acid-base status closely during the acute phase (eg, every 4 hours). Monitor amino acids daily to assess the effectiveness of citrulline/arginine replacement and glutamine removal [3][4].
MECHANISM OF ACTION/PHARMACOKINETICS
Pharmacology
The use of arginine provides an alternative pathway for waste nitrogen excretion in patients with urea cycle disorders, attenuating the risk for ammonia- and glutamine-induced neurotoxicity. Arginine increases the synthesis of citrulline which contains a nitrogen from ammonia and is efficiently excreted in the urine. In addition, certain defects in the urea cycle prevent the formation of citrulline which decreases the synthesis of arginine. This results in arginine becoming an essential amino acid in patients with urea cycle disorders [5][3][6].

ABOUT
Special Considerations/Preparation
Arginine hydrochloride is supplied as a 10% solution. The product is hypertonic (950 mOsmol/liter), acidic (average pH 5.6), and contains 47.5 mEq of chloride in 100 mL. The product should be stored at room temperature. Solution that has been frozen should not be used [7].

Ascorbic Acid
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
Adequate Intake:
40 mg/day orally or enterally [1].
Enteral Nutrition
Preterm: 18 to 24 mg/kg/day enterally [1].
Term:40 mg/day enterally [1].
Parenteral Nutrition
Preterm: 15 to 25 mg/kg/day IV. Multivitamin formulations (80 mg/5 mL): 5 mL for infants 3 kg or more; 3.25 mL for infants 1 to 3 kg, and 1.5 mL for infants less than 1 kg [1]
Term: 80 mg/day IV [1].
Uses
Pediatric FDA Approved Indications
Ascor is indicated for the short-term (up to 1 week) treatment of scurvy in patients 5 months or older for whom oral administration is not possible, is insufficient, or is contraindicated [3].
Limitations of Use
Not indicated for the treatment of vitamin C deficiency not associated with signs and symptoms of scurvy [3].
Administration
Injection
Dilute into a large volume such as normal saline or dextrose [2].
Too rapid administration should be avoided [2].
MEDICATION SAFETY
Contraindications/Precautions
CONTRAINDICATIONS
None [2]
PRECAUTIONS

Administration: Avoid rapid administration [2]
Adverse Effects
Too rapid IV administration of the solution may cause temporary faintness or dizziness [2].
MECHANISM OF ACTION/PHARMACOKINETICS
Pharmacology
Mechanism of action
Ascorbic acid (vitamin C) is a water-soluble vitamin. Ascorbic acid is involved in tyrosine metabolism, conversion of folic acid to folinic acid, carbohydrate metabolism, synthesis of lipids and proteins, iron metabolism, resistance to infections, and cellular respiration [2].
Distribution
Ascorbic acid is widely distributed in the body. Large concentrations are found in the liver, leukocytes, platelets, glandular tissues, and eye lens [3].
Metabolism
The major route of metabolism involves conversion of ascorbic acid to urinary oxalate, presumably through intermediate formation of dehydroascorbic acid [3].
Excretion
Ascorbic acid is excreted by the kidney in large amounts only when plasma concentrations exceed 1.4 mg/100 mL [3].
Half-life: 7.4 +/- 1.4 hours [3]
ABOUT
Special Considerations/Preparation
Injection
Availability: Ascorbic acid 500 mg/mL [2]
Storage: Store under refrigerated conditions between 2 and 8 degrees C (36 and 46 degrees F). Protect from light [2]
Preparation:[2]
Pressure may develop within vial during storage; relieve pressure by first inserting sterile empty syringe into vial to allow pressure to equilibrate.
Once vial is punctured, complete all dispensing from the vial within 4 hours and use each dose immediately; discard unused portion .
Dilute dose in compatible infusion solution.

Oral
Availability: Multiple forms and strengths, such as 100 mg, 250 mg, 500 mg, 1000 mg oral tablets; 500 mg chewable tablet; 500 mg and 1000 mg extended-release oral tablet; 60 mg mucous membrane lozenge/troche; 500 mg oral wafer.

Aspirin
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
Acute Ischemic Stroke (AIS), Recurrent: 1 to 5 mg/kg orally once daily [1][2].
Thrombosis; Prophylaxis
1 to 5 mg/kg orally once daily [1][3][4][5]. Higher doses (6 to 10 mg/kg/day) have been used in neonates undergoing heart surgery [1][6][7][8].
Uses
Acute Ischemic Stroke (AIS): Secondary prevention of recurrent AIS [1][2][5].
Thrombosis; Prophylaxis: Aspirin is recommended as thromboprophylaxis after Fontan surgery, in patients with systemic-to-pulmonary shunts, in patients after ventricular assist device placement, and in patients with mechanical heart valves who have had thrombotic events while receiving therapeutic antithrombotic therapy or patients in whom there is a contraindication to full-dose vitamin K antagonists [1][3][4][5][9]. In a prospective, multicenter, randomized study (n=111) of warfarin vs aspirin for primary thromboprophylaxis in children after Fontan surgery, the thrombosis event rate at 2 years was 19% with no significant difference between warfarin and aspirin therapy (24% vs 14%; p=0.45); minor bleeding was more common in the warfarin group (33% vs 14%) [3].
Administration
Administer without regard to feedings.
MEDICATION SAFETY
Contraindications/Precautions
Aspirin use has been associated with a potentially fatal condition called Reye's syndrome. Association has been shown to be mainly dose dependent, occurring with anti-inflammatory doses (greater than 40 mg/kg/day), rather than lower doses used for antiplatelet effects [11][12][5][13][14]. Use caution in patients with bleeding disorders, peptic ulcer disease, renal impairment, or severe hepatic impairment. Severe allergic reactions, including asthma, hives, and facial swelling, may occur [15].

Adverse Effects

Mild gastrointestinal symptoms (nausea, vomiting, abdominal pain, GI upset) are the most common adverse effects. Headache and tinnitus have also been reported frequently in children. Elevations in serum transaminases may occur [16][17]. Mild salicylism is characterized by headache, dizziness, tinnitus, hearing and vision impairment, sweating, nausea, vomiting, nasal congestion, and slight hyperpyrexia. Symptoms of severe salicylate toxicity include hyperventilation, mental confusion, restlessness, irritability, hyperthermia, and alterations in acid-base balance, primarily respiratory alkalosis [10].

Monitoring

Mild salicylism is characterized by headache, dizziness, tinnitus, hearing and vision impairment, sweating, nausea, vomiting, nasal congestion, and slight hyperpyrexia. Symptoms of severe salicylate toxicity include hyperventilation, mental confusion, restlessness, irritability, hyperthermia, and alterations in acid-base balance, primarily respiratory alkalosis [10].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of action: The main mechanism of action of aspirin is through inhibition of prostaglandin biosynthesis. Prostaglandins are produced from arachidonic acid via COX (cyclooxygenase; also known as prostaglandin endoperoxide synthase). Aspirin is a more specific inhibitor against COX-1 over COX-2 [18]. Aspirin is a more potent inhibitor of both prostaglandin synthesis and platelet aggregation than its other salicylic derivatives due to the acetyl group on the aspirin molecule, which inactivates cyclooxygenase via acetylation [19]. The antithrombotic effect of aspirin occurs by an irreversible inhibition of platelet cyclooxygenase. This enzyme inhibition blocks the formation of thromboxane A2 from arachidonic acid which would reduce platelet shape change, aggregation, and the release reaction [20][21][22][23].

Platelet inhibition occurs at lower doses (1 to 5 mg/kg/day). Rapidly absorbed following oral administration with peak concentration achieved in 2 hours. Rapidly hydrolyzed by esterases in the liver, intestine, and blood to salicylic acid. Has a low Vd and is extensively bound to albumin (80% to 90%). Eliminated through hepatic metabolism and renal excretion with elimination pathways dependent on dose. At therapeutic doses, most elimination occurs through hepatic metabolism to 3 major metabolites (all inactive); less than 10% is excreted

unchanged in the urine. At higher doses, when saturation of metabolic pathways occurs, renal excretion dominates with greater than 50% of unchanged salicylic acid eliminated in the urine. Renal excretion dependent on urinary pH (alkaline urine increases elimination). Elimination half-life is approximately 2 to 3 hours at low dose and 12 hours at antiinflammatory doses [18].

ABOUT

Special Considerations/Preparation

Available: 81-mg chewable tablets; 300- and 600-mg rectal suppositories.

Atropine

NeoFax Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Bradycardia

IV: 0.01 to 0.03 mg/kg/dose IV [1]over 1 minute, or IM. Dose can be repeated every 10 to 15 minutes to achieve desired effect, cumulative maximum dose of 0.04 mg/kg.

ET: 0.01 to 0.03 mg/kg/dose immediately followed by 1 mL NS.

Oral: Begin with 0.02 mg/kg/dose given every 4 to 6 hours. May increase gradually to 0.09 mg/kg/dose.

Premedication for Intubation

0.01 to 0.02 mg/kg IV over 1 minute immediately prior to other premedications [2][3][4][5][6].

Uses

Bradycardia: Reversal of severe sinus bradycardia, particularly when parasympathetic influences on the heart (digoxin, beta-blocker drugs, hyperactive carotid sinus reflex) predominate. Prevention of bradycardia during endotracheal or nasotracheal intubation [2][3][4][5][6].

Used to reduce the muscarinic effects of neostigmine when reversing neuromuscular blockade.

Administration

Intramuscular: Available strengths are 0.25-mg, 0.5-mg, 1-mg, and 2-mg strengths.

Should be administered in the outer thigh with auto-injector left in place for at least 10

seconds. Massage injection site for several seconds after administration [7].
Intravenous: Concentrations are 0.05-, 0.1-, 0.4-, and 1-mg/mL [8]. Administer IV over 1 minute [5] as undiluted drug (0.05- or 0.1-mg/mL). Atropine may also be diluted in 4 mL of D5 W or NS when used as a premedication [9].
Oral: May give IV dosage form orally.
MEDICATION SAFETY
Adverse Effects

Cardiovascular effects: Cardiac arrhythmias can occur, particularly during the first 2 minutes following IV administration; usually a simple A-V dissociation, more often caused by smaller rather than larger doses.
Gastrointestinal: Abdominal distention with decreased bowel activity, esophageal reflux.
Ophthalmic: Mydriasis and cycloplegia.
Other: Fever, especially in brain-damaged infants.
Respiratory: Post-operative respiratory acidosis was associated with pre-operative atropine 0.01 mg/kg IV compared with no atropine (22.9% vs 7.3%; p=0.016) in a retrospective analysis of 150 Asian neonates undergoing surgical ligation for patent ductus arteriosus. The mean capillary CO2 was higher in the atropine compared with no atropine group (49.35 vs 38.85 mmHg; p=0.0004). The mean capillary pH was lower in the atropine compared with no atropine group (7.33 vs 7.43 mmHg; p=0.0001) [10].
Solution Compatibility
D5W and NS.
Terminal Injection Site Compatibility
Amiodarone, cimetidine, dobutamine, famotidine, fentanyl, furosemide, glycopyrrolate, heparin, hydrocortisone succinate, meropenem, methadone, metoclopramide, midazolam, milrinone, morphine, nafcillin, netilmicin, pentobarbital, potassium chloride, propofol, ranitidine, and sodium bicarbonate.
Terminal Injection Site Incompatibility
Phenytoin, sulfamethoxazole/trimethoprim.
Monitoring
Heart rate.
MECHANISM OF ACTION/PHARMACOKINETICS
Pharmacology

Anticholinergic. Increases heart rate by decreasing the effects of the parasympathetic system

while increasing the effects of the sympathetic system. Peak tachycardia is 12 to 16 minutes after dose is given. Relaxes bronchial smooth muscle, thus reducing airway resistance and increasing dead space by 30%. Motor activity in the stomach and small and large intestines is reduced. Esophageal sphincter tone is reduced. Salivary secretion is inhibited. Duration of action is 6 hours. Primarily excreted renally unchanged.

ABOUT

Special Considerations/Preparation

Supplied in multiple concentrations (0.05-, 0.1-,0.4-, and 1-mg/mL) for injection. May give IV dosage form orally.

Azithromycin

NeoFax Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Treatment and Prophylaxis of Pertussis Infections: 10 mg/kg/dose orally once daily for 5 days [1]; IV dose is unknown.

Ophthalmia neonatorum caused by Chlamydia trachomatis: 20 mg/kg/dose orally once daily for 3 days [2][3].

Uses

Bordetella; Treatment and Postexposure Prophylaxis: Azithromycin is the preferred agent for the treatment and postexposure prophylaxis of pertussis in infants younger than 1 month of age. Treat infants younger than 1 year within 6 weeks of cough onset. Prophylaxis should be administered within 21 days of onset of cough in the index patient [1].

Bronchopulmonary Dysplasia (BPD), Prevention: Azithromycin compared with no treatment reduced the risk of BPD (55% vs 67% (RR = 0.83, 95% CI 0.71 to 0.98)) in extremely premature neonates in 3 randomized controlled studies. Dosages were 10 mg/kg/day IV for 1 week, then 5 mg/kg/day IV for 1 to 5 weeks [6].

Chlamydia Infections: Erythromycin base or ethylsuccinate is the first-line agent and azithromycin a second-line agent for the treatment of ophthalmia neonatorum caused by Chlamydia trachomatis ; however, data are limited on azithromycin [2]

Administration

Intravenous: Dilute reconstituted solution (100 mg/mL) to a final concentration of 1 to 2

mg/mL. Give the 1 mg/mL concentration over 3 hours or 2 mg/mL concentration over 1 hour [4].
Oral: Oral suspension can be given with or without feeding [5].

MEDICATION SAFETY

Contraindications/Precautions

Contraindicated in patients allergic to macrolide or ketolide antibiotics and patients with a history of cholestatic jaundice/hepatic dysfunction associated with prior use of azithromycin [7].

Cardiovascular: QT-interval prolongation has been reported including cases of torsade de pointes. Patients with known or congenital QT prolongation, history of torsade de pointes, bradyarrhythmias, uncompensated heart failure, ongoing proarrhythmic conditions (eg, significant bradycardia, uncorrected hypokalemia or hypomagnesemia, or those receiving class IA or class III antiarrhythmic agents), or concomitant drugs known to prolong the QT interval are at increased risk [8][9][10].
Cardiovascular: Compared with penicillin or a cephalosporin, azithromycin was not associated with greater prevalence of cardiac arrest, overall mortality, or ventricular arrhythmias in a retrospective cohort study of 82,982 pediatric patients (median age 2.6 years) with community acquired pneumonia [11].
Gastrointestinal: Infantile hypertrophic pyloric stenosis has been reported in neonates up to 42 days of life treated with azithromycin [12].
Hepatic: Hepatotoxicity (eg, abnormal liver function, hepatitis, cholestatic jaundice, hepatic necrosis, and hepatic failure), including fatalities, has been reported; if signs and symptoms of hepatitis occur, discontinue therapy [7].
Immunologic: Serious and sometimes fatal allergic reactions, including angioedema, anaphylaxis, and dermatologic reactions such as acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported. Immediate discontinuation recommended; however, recurrence of allergic symptoms without further azithromycin exposure may occur [13][14].
Long-term use: Avoid long-term azithromycin use for prophylaxis of bronchiolitis obliterans syndrome (unapproved use) to patients who undergo donor stem cell transplants due to the

increased potential for cancer relapse and death [15].
Neurologic: Worsening of myasthenia gravis symptoms as well as new onset of myasthenia
gravis has been reported rarely in association with azithromycin [7][16].
Adverse Effects
Diarrhea and/or vomiting occur in 5% to 12% of patients. Irritability, rash, and blood in stool have also been reported.
The most frequently reported gastrointestinal symptoms were vomiting, diarrhea, abdominal
tenderness, and feeding intolerance in a systematic review of 11 articles (n=473 neonates)
[6]
The use of macrolide antibiotics was associated with infantile hypertrophic pyloric stenosis
with a 30-fold increased risk in infants exposed at 0 to 13 days of age and 3-fold increased
risk in infants exposed at 14 to 120 days of age in an observational study (n=6591) [17].
Similar outcomes (highest risk of pyloric stenosis when exposed within the first couple weeks
of life; although risk still present at 6 weeks of life) were demonstrated in another
observational study (n= 4875 exposed to azithromycin) [18].
Solution Compatibility
D5W, NS, 5% Dextrose in 0.45% NaCl with 20 mEq/L KCl, and Lactated Ringer's.

Terminal Injection Site Compatibility
Caspofungin.
Terminal Injection Site Incompatibility
Amikacin, aztreonam, cefotaxime, ceftazidime, ceftriaxone, cefuroxime, clindamycin,
famotidine, fentanyl, furosemide, gentamicin, imipenem-cilastatin, morphine, piperacillintazobactam, potassium chloride, ticarcillin-clavulanate, and tobramycin.
Monitoring
Assess gastrointestinal tolerance.
MECHANISM OF ACTION/PHARMACOKINETICS
Pharmacology
Azithromycin is classified as an azalide, a subclass of macrolide antibiotics. In vitro activity
has been demonstrated against Bordetella pertussis, as well as Streptococci (Groups C, F, G
and Viridans), Ureaplasma urealyticum, and Peptostreptococcus species. Eradication of B.
pertussis in unimmunized individuals (e.g., neonates) takes longer and requires higher doses
than immunized individuals. Oral bioavailability is 38% in adults and children and is not

affected by food. Primarily excreted unchanged in the bile, with some hepatic metabolism to inactive metabolites. The prolonged terminal half-life (approximately 80 hours) is thought to be due to extensive uptake and subsequent release of drug from tissues.
ABOUT
Special Considerations/Preparation
Oral
Availability: Oral suspension is available in 300, 600, 900, and 1,200 mg bottles.
Reconstitute 300 mg bottle with 9 mL of water to provide a final concentration of 100 mg per 5 mL (20 mg/mL). Shake well before administration.
Storage: Do not refrigerate. Use within 10 days once bottle has been opened.
Injection
Availability: Azithromycin for intravenous injection is supplied in single use vials containing 500 mg lyophilized powder. Reconstitute by adding 4.8 mL Sterile Water for Injection, then shake the vial until all the drug is dissolved. The concentration of the reconstituted solution is

100 mg/mL.
Storage: It is stable at room temperature for 24 hours.
Dilute prior to administration using a compatible solution to a final concentration of 1 to 2 mg/mL. Diluted solution stable for 24 hours at room temperature or 7 days in refrigerator.
Do not use higher concentrations due to local IV site reactions. Infuse over at least 60 minutes.

Aztreonam
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
30 mg/kg/dose IV or IM.
Antibiotic Dosing Chart:
Renal function and drug elimination are most strongly correlated with Postmenstrual Age (PMA; equivalent to Gestational Age plus Postnatal Age). PMA is the primary determinant of dosing interval, with Postnatal Age as the secondary qualifier.
Dosing Interval Chart
PMA

(weeks)
PostNatal
(days)
Interval
(hours)
?29 0 to 28
>28
12
8
30 to 36 0 to 14
>14
12
8
37 to 44 0 to 7
>7
12
8
?45 ALL 6
Uses
Treatment of neonatal sepsis caused by susceptible gram-negative organisms (e.g. E coli, H influenzae, Klebsiella, Pseudomonas, and Serratia). Generally used in combination with ampicillin (empirical treatment of sepsis) or an aminoglycoside (for synergism against Pseudomonas and Enterobacteriaceae).
Administration
Intravenous
Give IV push over 3 to 5 minutes, or IV infusion over 20 to 60 minutes at a final concentration not to exceed 20 mg/mL[1][2].
Intramuscular
For IM administration, concentrations range from 66 mg/mL to 333 mg/mL [1].
MEDICATION SAFETY
Adverse Effects

Aztreonam contains 780 mg L-arginine per gram of drug (23.4 mg/kg body weight per dose).
Adequate amounts of glucose must be provided to prevent hypoglycemia. Side effects are rare but include eosinophilia, elevation of serum transaminases, and phlebitis at the injection site.
Solution Compatibility
D5W, D10W, and NS.
Terminal Injection Site Compatibility
Amikacin, aminophylline, ampicillin, bumetanide, calcium gluconate, caspofungin, cefazolin, cefepime, cefotaxime, cefoxitin, ceftazidime, ceftriaxone, cimetidine, clindamycin, dexamethasone, dobutamine, dopamine, enalaprilat, famotidine, fluconazole, furosemide,

gentamicin, heparin, hydrocortisone succinate, imipenem, insulin, linezolid, magnesium sulfate, metoclopramide, mezlocillin, morphine, netilmicin, nicardipine, piperacillin, piperacillin/tazobactam, potassium chloride, propofol, quinupristin/dalfopristin, ranitidine, remifentanil, sodium bicarbonate, ticarcillin/clavulanate, tobramycin, vancomycin, and zidovudine.

Terminal Injection Site Incompatibility

Acyclovir, amphotericin B, azithromycin, ganciclovir, lorazepam, metronidazole, and nafcillin.

Monitoring

Check serum glucose one hour after administration. Measuring serum concentration is not usually necessary. Periodic CBC, AST, ALT.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of action: Aztreonam is a synthetically-produced monocyclic beta-lactam antibiotic. Although bactericidal against aerobic gram-negative bacteria, it has virtually no activity against aerobic gram-positive and anaerobic bacteria, thereby producing little alteration of bowel flora [1].

Good tissue and fluid penetration has been demonstrated in adults, along with proteinbinding of 50 to 65%. Eliminated renally, primarily as unchanged drug. Serum half-life in neonates is 3 to 9 hours. Aztreonam does not interfere with bilirubin-albumin binding.

ABOUT

Special Considerations/Preparation

Availability: Powder for injection in 1-g and 2-g vials [3]

Reconstitution (Shake immediately and vigorously):

For infusion, reconstitute 1-g with at least 3 mL of sterile water for injection (SWFI) and further dilute to a concentration of no greater than 20 mg/mL.

For bolus, reconstitute 1-g or 2-g vial with 6 to 10 mL of SWFI.

For IM administration, dilute 1-g with at least 3 mL of appropriate diluent.

Storage: Prior to reconstitution, store in original package at a controlled room temperature; avoid excessive heat [3].

Solutions at concentrations not exceeding 2% weight/volume must be used within 48 hours if stored at a controlled room temperature between 15 and 30 degrees C (59 and 86 degrees F) or within 7 days if refrigerated between 2 and 8 degrees C (36 and 46 degrees). Discard

any unused portion. [3].
Solutions at concentrations exceeding 2%
weight/volume, except those prepared with Sterile
Water for Injection or Sodium Chloride Injection,
should be used promptly after preparation;
the 2 excepted solutions must be used within 48 hours
if stored at a controlled room
temperature between 15 and 30 degrees C (59 and 86
degrees F) or within 7 days if
refrigerated between 2 and 8 degrees C (36 and 46
degrees). Discard any unused portion
[3].

Beractant
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
Respiratory Distress Syndrome (RDS)
4 mL/kg/dose (100 mg of phospholipids/kg/dose)
intratracheally in 4 quarter-dose aliquots
with the infant in a different position for each
aliquot [1]
Prophylaxis: First dose is given as soon as possible,
preferably within 15 minutes of birth,
up to 4 doses may be administered in first 48 hours of
life, if indicated. Do not give more
frequently than every 6 hours. Obtain radiographic
confirmation of respiratory distress
syndrome before administering additional doses[1].
Rescue treatment of RDS : First dose is as soon as
possible, preferably by 8 hours of age;
up to 4 doses may be administered in first 48 hours of
life, if indicated. Do not give more
frequently than every 6 hours [1]
Uses
Prevention and treatment of respiratory distress
syndrome (RDS) in premature
infants. Routine continuous positive airway pressure
(CPAP) is considered superior to
prophylactic surfactant therapy. It is strongly
recommended that CPAP immediately after
birth with subsequent selective surfactant
administration be considered as an alternative to
routine intubation with prophylactic or early
surfactant administration in preterm infants.
Severe RDS in preterm infants born younger than 30
weeks gestation who need mechanical
ventilation should be administered surfactant after
initial stabilization. Consider the use of
rescue surfactant for infants with hypoxic respiratory
failure attributable to secondary
surfactant deficiency, such as meconium aspiration
syndrome or sepsis/pneumonia[2].

Animal-derived surfactants (beractant, calfactant, and poractant alfa) had comparable outcomes for air leak syndromes, death, and bronchopulmonary dysplasia in a retrospective study (n=51,282; median birth weight of 1435 g; median gestational age of 30 weeks (27 to 33 weeks)) [3].

Neonatal FDA-Approved Indications: Indicated for prevention and treatment (rescue) of Respiratory Distress Syndrome (RDS) (hyaline membrane disease) in premature infants. Beractant significantly reduces the incidence of RDS, mortality due to RDS, and air leak complications [1].

Administration

Administration is facilitated if one person administers the dose while another person positions and monitors the infant [1].

At discretion of the clinician, the endotracheal tube may be suctioned prior to administration of beractant; allow infant to stabilize before proceeding with dosing [1].

Slowly withdraw the contents of the vial into a plastic syringe through a large gauge needle

(eg, at least 20 gauge). Attach the premeasured 5 French end-hole catheter to the syringe and fill the catheter with beractant, discarding any excess product through the catheter so that only the total dose to be given remains in the syringe [1].

Administer in 4 quarter-dose aliquots with the infant in a different position for each aliquot as follows: 1) head and body inclined 5 to 10 degrees down, head turned to right; 2) head and body inclined 5 to 10 degrees down, head turned to left; 3) head and body inclined 5 to 10 degrees up, head turned to right; 4) head and body inclined 5 to 10 degrees up, head turned to left [1]

For each quarter-dose aliquot, insert the 5-French end-hole catheter into the endotracheal tube with the tip of the catheter protruding just beyond the end of the endotracheal tube above the infant's carina; do not instill product into a mainstem bronchus. Gently inject the aliquot through the catheter over 2 to 3 seconds then remove the catheter and manually ventilate the infant for at least 30 seconds or until clinically stable. Use sufficient oxygen to prevent cyanosis and sufficient positive pressure to provide adequate air exchange and chest wall excursion [1].

When the infant is stable following administration of an aliquot, reposition for instillation of the next quarter dose and then instill the dose using the same procedures [1].
Once the final quarter-dose is administered, remove the catheter without flushing it. Do not suction the infant for 1 hour after dosing unless signs of significant airway obstruction occur [1].
Each vial is for single-use only; discard unused product [1]
MEDICATION SAFETY
Contraindications/Precautions
Contraindications
No specific contraindications have been determined [1]
Precautions
Administration: For intratracheal use only [1]
Cardiovascular: Transient bradycardia and decreased oxygen saturation have been reported. Interrupt therapy and institute treatment as necessary [1]
Respiratory: Rapid effects on oxygenation and lung compliance occur with administration; intubation and ventilator management must be immediately available and frequent monitoring is required [1]
Immunologic: Post-treatment nosocomial sepsis may occur [1]
Respiratory: Rales and moist breath sounds have been reported after administration; endotracheal suctioning is not necessary unless airway obstruction present [1]
Adverse Effects
Most common reactions reported include transient bradycardia (11.9% of doses) and oxygen desaturation (9.8% of doses). Other adverse events include hypotension, endotracheal tube reflux or blockage, hypertension, hypercarbia, hypocarbia, vasoconstriction, pallor, and apnea. In a pooled analysis of all controlled studies, the incidence of intracranial hemorrhage (ICH) was not different between the Survanta group and the control group; however, in 2

of the studies (single-dose rescue study and multiple-dose prevention study), the incidence of ICH was significantly higher in patients who received Survanta compared with those in the control group (63.3% vs 30.8%; p=0.001 and 48.8% vs 34.2%; p=0.047, respectively) [4].
Monitoring
Monitor systemic oxygen and carbon dioxide levels with arterial or transcutaneous

measurements frequently during therapy [4].
MECHANISM OF ACTION/PHARMACOKINETICS
Pharmacology
Survanta is a modified natural bovine lung extract containing phospholipids, neutral lipids, fatty acids, and surfactant-associated proteins B and C, to which colfosceril palmitate (dipalmitoylphosphatidylcholine (DPPC)), palmitic acid, and tripalmitin are added. Resulting drug provides 25 mg/mL phospholipids (including 11 to 15.5 mg/mL disaturated phosphatidylcholine), 0.5 to 1.75 mg/mL triglycerides, 1.4 to 3.5 mg/mL fatty acids, and less than 1 mg/mL protein. Survanta is suspended in NS and heat sterilized. Animal metabolism studies show that most of a dose becomes lung-associated within hours of administration, and lipids enter endogenous surfactant pathways of reuse and recycling [4].
ABOUT
Special Considerations/Preparation
Availability: 4- and 8-mL single-use vials (25 mg phospholipids/mL) [4]
Storage: Refrigerate at 2 to 8 degrees C (36 to 46 degrees F) and protect from light.
Inspect Survanta for discoloration; normal color is off-white to light-brown. If settling occurs during storage, swirl vial gently. Do not shake. Vials should be entered only once.
Used vials with residual drug should be discarded.
Unopened vials that have been warmed to room temperature one time may be refrigerated within 24 hours and stored for future use.
Should not be warmed and returned to the refrigerator more than once [4].
Preparation
If a prevention dose is to be given, begin preparation of product prior to infant's birth [1]
After removing unopened vial from the refrigerator, warm at room temperature for at least 20 minutes or warm in hand for at least 8 minutes, do not warm by artificial warming methods [5]
Do not shake vial; swirl gently to redisperse. Some foaming at the surface may occur during handling and is inherent in the nature of the product [5].
Do not filter product [5]
After warming vial, unopened vials can be returned to refrigerator within 24 hours of

warming to store only once, record date and time when vial is removed from the refrigerator.

Vials may not be out of refrigerator for more than 24 hours [5].
Does not require reconstitution or sonication before use [5]

Bevacizumab
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
Long-term benefits and safety and optimal regimens are unknown[1].
Retinopathy of prematurity, Type 1
Most common dose used in studies was 0.625 mg in 0.025 mL per eye via intravitreal
injection for 1 dose [2][3].
Uncontrolled trials evaluated lower doses [4][5][6]; 0.312 mg in 0.025 mL [5] and 0.16 mg
in 0.025 mL [4].
A phase 1 dose de-escalation study, demonstrated improvement by 5 days and no recurrence
requiring additional treatment within 4 weeks for bevacizumab doses of 0.25 mg in 11 of 11
eyes, 0.125 mg for 14 of 14 eyes, 0.063 mg for 21 of 24 eyes, and 0.031 mg for 9 of 9 eyes
of infants with severe ROP, type 1 [6].
Combination bevacizumab 0.25 mg in 0.01 mL with zone 1 sparing laser or deferred laser
treatment was used [7].
Retreatment may be needed after 55 weeks' postmenstrual age [8]. Some infants required retreatment at a mean of 9.8 weeks (6 to 15 weeks) after the initial injection [4]
Premedication/Post-procedure medication
In infants, eyes were prepared with a topical anesthesia (0.5% proparacaine or 0.5%
tetracaine) and ophthalmic antiseptic (5% [9][3][2] or 10% [10] povidone iodine) . After the
procedure ophthalmic antibiotic drops were administered for 7 days [2].
Uses
Retinopathy of Prematurity (ROP)
A systematic review (5 randomized or semi-randomized studies) demonstrated no reduction
in retinal detachment or recurrent ROP in infants treated with intravitreal bevacizumab (n=4
studies) or ranibizumab (n=1 studies) compared with laser therapy; however, refractive
errors were reduced. In a subgroup analysis, the risk of recurrence was lower in type 1, but
higher in type 2 ROP. Intravitreal bevacizumab was well tolerated but long-term systemic
effects are unknown [1]. If bevacizumab is offered, consider only for type 1 ROP treatment in

patients with zone I or posterior zone II disease [8].
In infants with stage 3+ ROP in each eye, intravitreal 0.625 mg bevacizumab significantly reduced the rate of recurrence compared with conventional laser therapy (6% vs 26%; P=0.002) at 54 weeks' postmenstrual age in a randomized trial (N=143 infants). However, a significant treatment effect was observed for zone I but not zone II posterior ROP.
(Bevacizumab Eliminates the Angiogenic Threat of ROP (BEAT-ROP) Trial) [2]. At 2.5 years of age (n=109), a follow-up of the BEAT-ROP trial detected more myopia and very high myopia in laser-treated eyes compared with bevacizumab-treated eyes [11].
In a retrospective study of 241 infants, the ROP recurrence rate was 8.3% with bevacizumab. The recurrence rate was higher in those infants with APROP (31.6%) compared with infants with stage 3+ ROP (6.3%; P less than 0.001) [12]. A follow-up (n=39 eyes) with fluorescein angiograph in infants at 4 years of age detected significant ocularvascular abnormalities in bevacizumab (0.5 mg)-treated eyes compared with laser-treated eyes treated for type 1, zone I ROP [13]

For 2 months after intravitreal bevacizumab (0.625 mg/dose per eye or 0.25 mg/dose per eye), serum vascular endothelial growth factor (VEGF) and insulin-like growth factor-1 concentrations had greater suppression compared with laser surgery in 24 infants. Serum vascular endothelial growth factor concentrations for intravitreal bevacizumab groups (0.5 mg and 1.25 mg) were 50% lower from day 2 to day 60 compared with laser-treated groups (no bevacizumab). There were no significant differences in serum VGEF concentrations between the 2 bevacizumab doses. The clinical significance of these findings is unknown [14].

Pediatric FDA Approved Indications

Safety and effectiveness have not been established in pediatric patients [15].

Administration

Intravitreal Administration

Bevacizumab concentration was 25 mg/mL [2][3]. Diluted concentrations, 3.1 mg/mL to 12.5 mg/mL, have been used with smaller doses [4][5][6].
In pediatric patients a sterile 30-gauge [4][9], 31-gauge [3], or 32-gauge [10] 4-mm needle

injected intravitreally 0.75 mm [10] to 1 mm [4][10][3] or 1.5 mm [9] to 2 mm [4] posterior to the temporal limbus into the vitreous cavity [10].
MEDICATION SAFETY
Contraindications/Precautions
PRECAUTIONS
IV Administration
Cardiovascular: Increased risk for severe (Grade 3 or 4) hypertension; interruption or discontinuation may be necessary [15]
Cardiovascular: Congestive heart failure (CHF) has been reported; discontinue if CHF develops [15]
Gastrointestinal: Gastrointestinal fistulae, including gastrointestinal-vaginal fistula, have been reported and may be accompanied by bowel obstruction requiring surgical interventions. Avoid use in patients with ovarian cancer who have recto-sigmoid involvement by pelvic examination or bowel involvement on CT scan [15]
Hematologic: Thrombotic microangiopathy has been reported [15]
Hematologic: Serious and sometimes fatal arterial thrombotic events (ie, cerebral infarction, angina, transient ischemic attack, myocardial infarction) have been reported, with an increased risk in patients with a history of arterial thromboembolism or diabetes. The highest incidence was reported in patients with glioblastoma. Discontinue use if severe event is suspected [15]
Hematologic: Venous thromboembolic events have been reported; discontinuation required if life-threatening (grade 4) thromboembolism or pulmonary embolism occur [15]
Infusion reactions: Infusion reactions (ie, hypertension, hypertensive crisis with neurological signs and symptoms, wheezing, oxygen desaturation, hypersensitivity reaction (grade 3), chest pain, headache, rigors, and diaphoresis) have been reported; if severe reaction occurs, stop infusion and institute appropriate therapy [15]

Neurologic: Posterior reversible encephalopathy syndrome (PRES) has been reported, occurring from 16 hours up to 1 year after treatment initiation. MRI is required to confirm diagnosis; discontinue use in patients developing PRES [15]
Non-gastrointestinal fistulae: Non-gastrointestinal fistulae (ie, tracheoesophageal,

bronchopleural, biliary, vaginal, renal, bladder), which may be serious and/or fatal, have been reported; discontinuation required for fistula formation involving internal organs, tracheoesophageal fistula or any grade 4 fistula [15]
Renal: Nephrotic syndrome, sometimes fatal, has been reported; discontinue use [15]
Renal: Proteinuria has been reported; interruption of therapy may be necessary [15]
Reproductive: Ovarian failure has been reported [15]
Respiratory: Serious and/or fatal pulmonary hemorrhage has been reported [15]
Adverse Effects
Cardiovascular: Hypotension was reported in a male preterm infant twin 1 day after intravitreal bevacizumab for retinopathy of prematurity. At 9 weeks, intravitreal injection of bevacizumab 0.625 mg/0.025 mL was administered in each eye under IV ketamine (0.3 mg) and local atropine (0.25%). Feeding intolerance, hypotension (42/24 mmHg), and oxygen desaturation (arterial oxygen saturation, 80%) were observed 22 hours after bevacizumab administration and continued the following day. Shortness of breath with apnea and lethargy were also noted. Intubation for mechanical ventilation, treatment with DOPamine, and prophylactic antibiotics were instituted. Blood pressure normalized on day 3 and his general condition improved. On day 6, DOPamine and antibiotics were discontinued. He was successfully extubated on day 7 and arterial oxygen saturation was normal. The sibling received bevacizumab with no episodes of hypotension [18]
Musculoskeletal: Non-mandibular osteonecrosis has been reported in patients younger than 18 years who received IV bevacizumab [15].
Neurologic: In a retrospective study (n=125), the adjusted odds ratio was 3.1 (95% CI, 1.2 to 8.4) for severe neurodevelopmental disability in intravitreal bevacizumab-treated compared with laser-treated preterm infants at 18 months corrected age after adjusting for gestational age, gender, maternal education, Score for Neonatal Acute Physiology-II score, bronchopulmonary dysplasia, sepsis, and severe brain injury [19].
Ophthalmic: More high myopia was seen in eyes treated with bevacizumab (14.6%) than those treated with ranibizumab (0%; p=0.03) at 1 year of age in a retrospective study (n=37 infants) [20].
Black Box Warning
IV Administration
Gastrointestinal Perforations: The incidence of gastrointestinal perforation, some fatal, in

patients receiving bevacizumab ranged from 0.3 to 3%. Discontinue bevacizumab in patients who develop gastrointestinal perforation.
Surgery and Wound Healing Complications: The incidence of wound healing and surgical complications, including serious and fatal complications, is increased in patients receiving bevacizumab. Discontinue bevacizumab in patients who develop wound healing

complications that require medical intervention. Withhold bevacizumab at least 28 days prior to elective surgery. Do not administer bevacizumab for at least 28 days after surgery and until the wound is fully healed.
Hemorrhages: Severe or fatal hemorrhage, including hemoptysis, gastrointestinal bleeding, hematemesis, central nervous systems (CNS) hemorrhage, epistaxis, and vaginal bleeding occur up to 5-fold more frequently in patients receiving bevacizumab. Do not administer bevacizumab to patients with a recent history of hemoptysis. Discontinue in patients who develop Grade 3 to 4 hemorrhage [15]
Solution Compatibility
NS
Solution Incompatibility
D5W
Monitoring
The duration for follow-up is unknown but will require longer follow-up compared with laser treatment [12][8] due to delayed or incomplete vascularization, significant rates of recurrence and need for retreatment, and potential for developmentally abnormal or atypical retinal vascular features [8].
In a retrospective case series recurrent ROP occurred a mean of 51.2 weeks (range, 45.7 to 64.9 weeks) adjusted age after intravitreal bevacizumab in 20 infants [12]. Additionally retinal detachment had occurred in 2 treated patients at the age of 2.5 years [16] and 3 years [17].
MECHANISM OF ACTION/PHARMACOKINETICS
Pharmacology
Mechanism of action
Bevacizumab, a recombinant humanized monoclonal immunoglobulin-1 antibody, binds to vascular endothelial growth factor (VEGF) and inhibits the interaction of VEGF to Flt1 and KDR receptors on the surface of endothelial cells. In the process, it prevents the proliferation of endothelial cells and formation of new blood vessels [15].

Pharmacokinetics
Intravitreal Administration in infants
Serum concentrations
0.5 mg (0.25 mg/dose per eye): 0 on day 0, 72.9 ng/mL on day 2, 424 ng/mL on day 14,
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172.5 ng/mL on day 42, and 78.7 ng/mL on day 60 [14]
1.25 mg (0.625 mg/dose per eye): 0 on day 0, 203.4 ng/mL on day 2, 1002 ng/mL on
day 14, 444.4 ng/mL on day 42, and 305.6 ng/mL on day 60 [14]
Half-life: 21 days in 17 infants after intravitreal administration [14].
IV Administration in adults
Clearance: 0.23 L/day [15].
Distribution: 2.9 L [15].
Half-life: 20 days (range, 11 to 50 days) [15]
ABOUT
Special Considerations/Preparation
Availability: 100 mg/4 mL (25 mg/mL) and 400 mg/16 mL (25 mg/mL) sterile solution for
IV infusion [15]
Storage: Store in the original carton and under refrigerated conditions between 2 and 8
degrees C (36 and 46 degrees F). Protect from light. Do not freeze or shake [15].
Stability (Bevacizumab for intravitreal injection is not commercially available and
bevacizumab IV solution is frequently repackaged for this use.)
Over a 6 month period, the stability of bevacizumab 25 mg/mL IV solution in polycarbonate
and polypropylene syringes (0.13 mL/syringe) was compared with bevacizumab in glass vials
during storage at a constant temperature of 2 to 8 degrees C. There was no significant
difference in the quality of vascular endothelial growth factor (VEGF) binding and protein
physical stability of bevacizumab in the syringes compared with the glass vials [21].
The stability of bevacizumab 25 mg/mL IV solution repackaged as 1.25 mg/0.05 mL and
2.5 mg/0.1 mL using 1 mL plastic, latex-free, tuberculin syringes was evaluated when
stored under refrigeration at 4 degrees C for 1 week, 3 weeks, 3 months, and 6 months, and
when frozen at -10 degrees C. Stability was evaluated based on binding activity to vascular
endothelial growth factor (VEGF-165). The refrigerated syringes lost approximately 1.6% and
0% binding activity at 1 and 3 weeks, and lost 8.8% and 15.9% binding activity at 3 and 6
months. The frozen syringes lost 12% binding activity at 6 months. Pierced vials lost 9.6%

and 12.7% binding activity at 3 and 6 months when stored under refrigeration [22].

Bumetanide
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
0.005 to 0.05 mg/kg/dose IV slow push, IM, or orally. Doses up to 0.1 mg/kg have been used in neonates; however, there are no pharmacodynamic data showing doses greater than 0.05 mg/kg provide additional benefit [1][2][3].
Preterm infants less than 34 weeks gestation in the first 2 months of life: every 24 hours.
Afterward: every 12 hours.
Preterm infants 34 weeks or more gestation and term infants in the first month of life: every 24 hours.
Afterward: every 12 hours.
Infants with lung disease and normal renal function should be started on a low dose. Infants with congestive heart failure or abnormal renal function will need a higher dose.
In a dose-range evaluation of bumetanide pharmacodynamics in critically ill neonates and infants, single IV doses ranging from 0.005 to 0.1 mg/kg (increases in increments of 0.005 mg/kg) were given over 1 to 2 minutes. All doses were associated with at least a 2-fold increase in urine output and electrolyte excretion rates. The dose range corresponding to the maximal effect was 0.035 to 0.04 mg/kg. There were no pharmacodynamic advantages (urine output and electrolyte excretion rate) to doses greater than 0.05 mg/kg [1]. Although doses of 0.05 and 0.1 mg/kg have been studied in neonates, only pharmacokinetic endpoints were determined, and no pharmacodynamic endpoints were reported [2]. In a retrospective study in preterm infants with oliguric renal failure and inadequate response to furosemide, bumetanide was effective in significantly increasing urine output in 29 of 35 infants. The mean bumetanide dose and duration of therapy were 0.03 +/- 0.016 mg/kg every 12 to 24 hours and 5.9 days, respectively. Urine output increased from 0.6 +/- 0.6 mL/kg/hour to 3 +/- 2.1 mL/kg/hour [3].
Uses
Heart Failure or Edema: Diuretic used in patients with renal insufficiency, congestive heart

failure, or significant edema that is refractory to furosemide.
In neonates with pulmonary hypertension, supportive care with diuretics may be used cautiously for signs of right-sided heart failure [5].
Administration
Intravenous: Give undiluted over 1 to 2 minutes [1].
Oral: The intravenous formulation, diluted in sterile water and given orally, has been used

successfully in infants with congenital heart disease [4].
MEDICATION SAFETY
Contraindications/Precautions
Contraindicated:[6].
Anuria
Hepatic coma until the condition is improved or corrected
Severe electrolyte depletion until the condition is improved or corrected
Precautions:
Concomitant use: Use with lithium, probenecid, indomethacin, aminoglycosides, and drugs with ototoxic or nephrotoxic potential is not recommended [6].
Endocrine and metabolic: Hypokalemia may occur; therefore, use caution in patients on low-salt diets, receiving digitalis and diuretics for congestive heart failure, with hepatic cirrhosis and ascites, in states of aldosterone excess with normal renal function, potassiumlosing nephropathy, certain diarrheal states, or other states where hypokalemia may add risks to the patient (eg, history of ventricular arrhythmias); monitoring and possible addition of potassium supplementation or potassium-sparing diuretics recommended [6].
Endocrine and metabolic: Hypocalcemia, hypomagnesemia, and hyperuricemia may occur; monitoring recommended [6].
Hematologic: Thrombocytopenia has been reported; monitoring recommended [6].
Hepatic: Sudden electrolyte alterations in patients with hepatic cirrhosis and ascites may precipitate hepatic encephalopathy and coma; initiation should be done on an inpatient basis with small doses and careful monitoring [6].
Immunologic: Patients with a sulfonamide allergy may show hypersensitivity to bumetanide [6].
Neurologic: Kernicterus could occur in critically ill or jaundiced neonates at risk for kernicterus; bumetanide displaces bilirubin [6].

Otic: Ototoxicity may occur, with an increased risk with IV therapy, frequent and high doses, and impaired renal function [6].
Renal: Reversible elevations in BUN and creatinine may occur, particularly in patients with dehydration and renal insufficiency [6].
Renal: Progressive renal disease with a marked increase in BUN or creatinine or development of oliguria; discontinue [6].
Adverse Effects
Water and electrolyte imbalances occur frequently, especially hyponatremia, hypokalemia, and hypochloremic alkalosis. Potentially ototoxic, but less so than furosemide. May displace bilirubin from albumin binding sites when given in high doses or for prolonged periods.
Black Box Warning

Bumetanide is a potent diuretic which, if given in excessive amounts, can lead to profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required, and dose and dosage schedule have to be adjusted to the individual patient's needs [6].
Solution Compatibility
D5W and NS.
Terminal Injection Site Compatibility
Aztreonam, cefepime, furosemide, lorazepam, milrinone, morphine, piperacillin/tazobactam, and propofol.
Terminal Injection Site Incompatibility
Dobutamine and midazolam.
Monitoring
Serum electrolytes and urine output. Assess patients receiving digoxin concurrently for potassium depletion. Follow weight changes.
MECHANISM OF ACTION/PHARMACOKINETICS
Pharmacology
Bumetanide is a loop diuretic with a similar mechanism of action to furosemide. Inhibits chloride reabsorption in the ascending limb of Henle's loop and inhibits tubular sodium transport, causing major loss of sodium and chloride. Increases urinary losses of potassium, calcium, and bicarbonate. Urine sodium losses are lower with bumetanide than furosemide, but urine calcium losses are higher. Decreases CSF production by weak carbonic anhydrase inhibition. Decreases pulmonary transvascular fluid filtration. Increases renal blood flow and prostaglandin secretion. Highly protein bound (greater than 97%). Data from adults indicate

excellent oral bioavailability and significant hepatic metabolism (40%) via the cytochrome
CYP pathway. Serum half-life varies from 4 to 19 hours in neonates, determined by
gestational age, postnatal age, and disease state.

ABOUT
Special Considerations/Preparation
Supplied as 2-, 4-, and 10-mL vials (0.25-mg/mL solution). Contains 1% (10 mg/mL) benzyl
alcohol; pH adjusted to 7.
A 0.125-mg/mL dilution may be made by adding 3 mL of 0.25-mg/mL injectable solution to 3
mL preservative-free normal saline for injection. Refrigerated dilution is stable for 24 hours.
Discolors when exposed to light.
There is no oral dosing formulation available for neonates. The intravenous formulation,
diluted in sterile water and given orally, has been used successfully in infants with congenital
heart disease [4].

Bupivacaine
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
The dose varies with anesthetic procedure, the area to be anesthetized, the vascularity of the
tissues, the number of neuronal segments to be blocked, the depth of anesthesia and degree
of muscle relaxation required, the duration of anesthesia desired, individual tolerance, and
the physical condition of the patient. Use the lowest dose and concentration to achieve the
desired result [1][2]. The USES section provides dosage ranges; however, other resources
should be consulted for specific techniques and procedures.
Dose Adjustments
Cardiac Disease: Dose reduction recommended [3][4][1][5][6].
Debilitated and Acutely Ill: Dose reduction recommended [3][4][1][5][6].
Liver Disease: Dose reduction recommended [3][4][1][5][2][6].
Risk Factors for Seizures: When bupivacaine is administered by continuous infusion,
reduce the rate in neonates who are at risk for seizures. Risk factors include increased

uptake into the circulation (eg, pulmonary arteriovenous malformation) or lowered seizure threshold (eg, history of febrile convulsions during the postoperative period, hypomagnesemia, or hyponatremia due to free water overload) [7].

Uses

Epidural anesthesia: Epidural anesthesia, whether by caudal or lumbar route, is effective in the neonate [9]. Typical doses of bupivacaine 0.125% to 0.25% are 1.25 mg/kg to 2.5 mg/kg for caudal epidural anesthesia [10], 2 mg/kg up to a maximum of 2.5 mg/kg for epidural anesthesia (other than caudal route) [10][11][7], and 0.2 mg/kg/hr up to a maximum of 0.25 mg/kg/hr for continuous epidural infusion [10][11][12][7] for a maximum duration of 24 to 36 hours [12]. Data are lacking in premature infants. Although, one study used 3.125 mg/kg of 0.5% bupivacaine by the caudal route as an adjunct to general anesthesia in 20 premature infants (0 to 60 days; 520 to 2750 grams). No neonate experienced elevated heart rate or blood pressure at the time of incision [13]. In a retrospective analysis of 750 children (2 days to 16 years of age), bupivacaine 0.25% provided longer postoperative pain relief (up to 5 hours) than lidocaine 0.5% or 1.5% when administered caudally [14].

Peripheral nerve block: For neonatal circumcision a dorsal nerve block with a local anesthetic is recommended [10]. A penile nerve block is appropriate for urethral dilation and hypospadias repair [9]. Solutions containing epinephrine should NOT be used near end-artery areas (eg, digits, nose, external ear, penis) or areas of compromised blood supply [15][3][5] [6]. Efficacy data are lacking in neonates; however, in 2 pharmacokinetic studies bupivacaine nerve blocks were used in neonates without associated toxic concentrations or observed adverse events [16][17]. Doses of bupivacaine were 2 mg/kg for interpleural nerve block in 8 very low birthweight infants (700 g to 1022 g) [16] and 1.5 mg/kg for intercostal block in 11 full-term neonates (1 to 27 days of age) [17].

Spinal anesthesia: The use of spinal anesthesia is common in neonates, even preterm infants. In comparison to adults, the dose is greater in neonates [9]. Dose range is 0.5 to 1 mg/kg [9][18][19] with usual doses of 0.6 mg/kg of 0.75% hyperbaric bupivacaine in 8.25%

dextrose [9][19] and 0.8 mg/kg of 0.5% isobaric bupivacaine [9]. The duration of effective spinal blockade (lack of hip flexion) was 84+/-16 minutes in 11 infants (range: 0.1 to 7 months of age; 2.8 to 9.3 kg) who received 0.75% bupivacaine 0.6 mg/kg in 8.25% dextrose solution with 0.02 mL of 1:1000 epinephrine [19]. Efficacy data are lacking in premature infants.

Pediatric FDA Approved Indications

Indicated for the production of local or regional anesthesia or analgesia for surgical procedures, dental and oral surgery procedures, and diagnostic and therapeutic procedures.

Use is not recommended in pediatric patients younger than 12 years [3][4][1][5][2][6].

Marcaine Spinal: Indicated for production of subarachnoid block (spinal anesthesia). Use in patients younger than 18 years is not recommended [20].

Administration

Bupivacaine is NOT recommended for intravenous regional anesthesia (Bier Block) [1][5][2][6].

Epidural anesthesia: Use only single-dose ampules and single-dose vials for caudal or epidural anesthesia as multiple dose vials contain a preservative. Administer slowly in 3- to 5-mL incremental doses with sufficient time between doses to detect signs/symptoms of unintentional intravascular or intrathecal injection. Perform syringe aspirations before and during each supplemental injection in continuous (intermittent) catheter techniques.

Administer a test dose, which contains epinephrine, and monitor the effects prior to the full dose and with all subsequent doses when a catheter is in place [3][4][1][5][2][6]. The use of a local anesthetic in the test dose is probably unwarranted and may lead to toxicity [8].

Avoid rapid injection of large volumes of anesthetic solutions. When possible, use fractional (incremental) doses [3][4][1][5][2][6].

Local infiltration and peripheral nerve blocks: Check aspiration for blood or cerebrospinal fluid (when applicable) prior to injecting any local anesthetic, both initial and subsequent doses. Avoid rapid injection of large volumes of anesthetic solutions. When possible, use fractional (incremental) doses [3][4][1][5][2][6].

MEDICATION SAFETY

Contraindications/Precautions

CONTRAINDICATIONS

Arrhythmias (eg, complete heart block) which severely restrict cardiac output (spinal injection) [25]

Hypersensitivity to bupivacaine, to other amide-type anesthetics, or to any component of the product [24]
Local infection at the site of proposed lumbar puncture (spinal injection) [25]
Obstetrical paracervical block anesthesia [24]
Septicemia (spinal injection) [25]
Severe hemorrhage (spinal injection) [25]

Severe hypotension (spinal injection) [25]
Shock (spinal injection) [25]
PRECAUTIONS
Administration: Avoid intravascular injection; use proper technique (spinal injection) [25]
Administration: Do not use solutions containing antimicrobial preservatives (eg, multipledose vials) for epidural or caudal anesthesia [3][26]
Administration: Risk of significant increase in plasma concentrations with repeated local administration [3][26]
Administration: Head and neck area administration has been associated with events that occur with systemic toxicity (convulsion, confusion, respiratory depression and/or respiratory arrest, and cardiovascular stimulation or depression); monitoring recommended [3][26]
Administration: Upper airway obstruction, requiring intubation; pulmonary edema; and tachydysrhythmia may occur with inadvertent vagal blockade in patients undergoing glossopharyngeal nerve block with bupivacaine for pain relief after tonsillectomy [27]. Vocal cord paralysis is a potential complication when bupivacaine is infiltrated in the peritonsillar region [28].
Cardiovascular: Cardiac arrest and death have been reported when used for IV regional anesthesia (Bier Block); not recommended [3][26]
Cardiovascular: Cardiac arrest, death, and other dose-related toxicity and acute emergencies may occur; proper medical management required (spinal injection) [25]
Cardiovascular: Serious dose-related arrhythmias may occur with use of bupivacaine in combination with vasoconstrictors such as epinephrine during or after use of potent inhalation anesthetics [25][3][26]
Cardiovascular: Use caution in patients with a history of cardiac rhythm disturbances, shock, heart block, or hypotension [25][3][26]
Cardiovascular: Risk of reduced ability to compensate for functional changes associated with AV conduction prolongation in patients with cardiovascular impairment [3][26]

Cardiovascular: Blood-flow restriction in end-artery areas (eg, digits, nose, external ear, penis) or areas of compromised blood supply may occur when bupivacaine is used in combination with vasoconstrictors; increased risk in patients with a history of hypertensive vascular disease due to an exaggerated vasoconstrictor response; ischemic injury or necrosis may occur [25][3][26]
Concomitant Use: Concomitant use of monoamine oxidase inhibitors (MAOIs) or tricyclic antidepressants should be avoided; if concomitant use is required, administer with extreme caution; may increase risk of severe prolonged hypertension when bupivacaine is in combination with epinephrine or other vasopressors [25][3][26]
Concomitant Use: Concomitant use of ergot-type oxytocic agents should be avoided when bupivacaine is in combination with epinephrine or other vasopressors [25][3][26]
Concomitant use: Mixing or the prior or concurrent use of any other local anesthetic is not recommended (spinal injection) [25]
Endocrine and Metabolic: Familial malignant hyperthermia may be triggered by anesthetics [25][3][26]
Hematologic: Methemoglobinemia has been reported with use of local anesthetics; increased risk in patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites and other drugs associated with methemoglobinemia; if use is required in at-risk patients monitoring is recommended; medical management and discontinuation of therapy is required [22].
Hepatic: Increased risk of developing toxic plasma concentrations in patients with severe hepatic disease, especially with repeat doses [25][3][26]
Immunologic: Some bupivacaine with epinephrine solutions contain sodium metabisulfite; patients with sulfite sensitivity may experience allergic-type reactions including anaphylaxis

[3][26]
Musculoskeletal: Chondrolysis has been reported with postoperative intra-articular infusions of local anesthetics (unapproved use) [25][3][26]

Renal: Impairment of renal function may increase risk of toxic reactions; monitoring recommended [25]
Reproductive: Spinal anesthetics should not used during uterine contractions (spinal injection) [25]
Respiratory: Acidosis, death, and other dose-related toxicity and acute emergencies may occur; proper medical management required (spinal injection) [25]
Special populations: Debilitated and acutely ill patients may have lower tolerance to elevated blood levels; dose adjustment recommended [3]

Adverse Effects

As with other amide-type local anesthetics, adverse effects are related to excessive concentrations due to overdosage, inadvertent intravascular injection, or slow metabolism of bupivacaine. These adverse events are serious, typically dose-related, and generally affect the central nervous and cardiovascular system. Central nervous system reactions include restlessness, anxiety, dizziness, tinnitus, blurred vision, tremors, convulsions, drowsiness leading to unconsciousness and respiratory depression, nausea, vomiting, chills, and miosis.
Cardiovascular reactions include depression of myocardium, decreased cardiac output, heartblock, hypotension, bradycardia, ventricular arrhythmias (ventricular tachycardia and ventricular fibrillation), and cardiac arrest [3][4][20][1][5][2][6].
Rare allergic reactions may occur. Risks with epidural and spinal anesthesia or nerve blocks near the vertebral column include underventilation or apnea with inadvertent subarachnoid injection; and hypotension secondary to loss of sympathetic tone and respiratory paralysis or underventilation when motor blockade extends cephaladly. Other risks of epidural and spinal anesthesia include urinary retention, fecal and urinary incontinence, loss of perineal sensation, persistent anesthesia, paraesthesia, weakness, paralysis of the lower extremities and loss of sphincter control, headache, backache, septic meningitis, meningismus, and cranial nerve palsies due to traction on nerves from loss of cerebrospinal fluid. Risk of other routes of anesthesia include persistent anesthesia, paresthesia, weakness, paralysis, all of which may have slow, incomplete, or no recovery [3][4][20][2][6].
In pharmacokinetic studies, no adverse events were reported in 11 neonates following intercostal nerve block with bupivacaine [17], 8 very low birthweight infants following interpleural nerve block with bupivacaine [16], or 20 newborns (including 18 premature

neonates) administered spinal anesthesia with bupivacaine [18].

Black Box Warning

The 0.75% concentration of bupivacaine injection is not recommended for obstetrical anesthesia. Cardiac arrest with difficult resuscitation or death during use of bupivacaine for epidural anesthesia in obstetrical patients has been reported. In most cases, this has followed use of the 0.75% concentration. Cardiac arrest has occurred after convulsions resulting from systemic toxicity, presumably following unintentional intravascular injection.

The 0.75% concentration should be reserved for surgical procedures where a high degree of

muscle relaxation and prolonged effect are necessary [24].

Solution Compatibility

D5W, NS.

Compatibility information refers to physical compatibility and is derived from Trissels 2 Clinical Pharmaceutics Database. The determination of compatibility is based on concentrations for administration recommended herein. Drug compatibility is dependent on multiple factors (eg, drug concentrations, diluents, storage conditions). This list should not be viewed as all-inclusive and should not replace sound clinical judgment. The user is referred to Trissels 2 for more complete details.

Monitoring

Carefully monitor cardiovascular (including circulation) and respiratory vital signs and neurological status continuously during and after each injection, including during retrobulbar, dental, and stellate ganglion blocks [4][20][1][5][2][6]. Continuously monitor for level of pain control, using an appropriate pain assessment tool [10][21].

Monitor for signs and symptoms of methemoglobinemia [22].

In general, monitoring bupivacaine concentrations is not warranted; however, when there is a concern for accumulation then it may be appropriate. Consider monitoring concentrations when a local anesthesia is administered by continuous infusion at doses greater than 0.5 mg/kg/hr [23].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Bupivacaine is a local anesthetic agent. It acts by blocking the conduction and generation of

nerve impulses, probably by increasing the threshold that produces electrical excitation in the nerve, by reducing the rate of rise of the action potential, and by slowing the nerve impulse propagation. Systemic absorption depends on total dose and concentration, route of administration, vascularity of administration site, and presence or absence of epinephrine in the anesthetic solution. Onset of action is rapid. Compared with other local anesthetics, the duration of bupivacaine is longer. Analgesia persists beyond the return of sensation. Protein binding: 95%. Distributed to some extent to all body tissue, with the highest concentrations in highly perfused organs. After regional block, time to peak is 30 to 45 minutes, followed by a decline to insignificant levels during the next 3 to 6 hours. Metabolized primarily in the liver via conjugation with glucuronic acid. Mainly excreted through kidney; 6% excreted unchanged in the urine. Half-life is 2.7 hours and 8.1 hours in adults and neonates, respectively [3][20][1]. The bupivacaine concentrations considered toxic are 2 to 4 mg/mL [10].

Unbound bupivacaine did not accumulate in neonates and young infants (postmenstrual age, 40 to 59 weeks) administered single epidural injection (n=6; 1.5 mg/kg of 0.25%) and continuous epidural infusion (n=5; 0.2 mg/kg/hr starting 2 hours after single-injection). The median Cmax of unbound bupivacaine was 0.024 mg/L (0.013 to 0.12 mg/L) after a single injection and 0.052 mg/L (0.015 to 0.08 mg/L) after a continuous infusion; the corresponding values for total bupivacaine were 0.55 mg/L (0.37 to 1.61 mg/L) and 0.88 mg/L (0.58 to 1.91 mg/L), respectively [11]. Free bupivacaine concentrations were not elevated in 20 newborns (including 18 premature neonates) administered spinal anesthesia with 0.5% isobaric bupivacaine 1 mg/kg with or without epinephrine 1:200,000. Total and free bupivacaine concentrations were 0.31+/-0.17 mcg/mL and 0.047+/-0.032 mcg/mL, respectively, for the without epinephrine group and 0.25+/-0.09 mcg/mL and 0.062+/-0.025 mcg/mL, respectively, for the with epinephrine group [18]. The volume of distribution, half-life, clearance, and peak concentration were 4.67 L/kg, 453 minutes, 7.9 mL/kg/min, and 0.52 mcg/mL, respectively, in 8 very low birthweight infants (700 g to 1022 g) after interpleural

nerve block with bupivacaine 2 mg/kg [16]. In comparison with 11 full-term neonates (1 to 27 days of age) administered intercostal block with 1.5 mg/kg bupivacaine 0.25% , the values were 2.56 L/kg, 132 minutes, 16.93 mL/kg/min, and 0.82 mcg/mL, respectively [17].

ABOUT

Special Considerations/Preparation

Marcaine: Available as 0.25% (2.5 mg/mL), 0.5% (5 mg/mL), and 0.75% (7.5 mg/mL) of bupivacaine in 10-mL and 30-mL single-dose vials (0.25%, 0.5%, and 0.75% strengths) without methylparaben and 50-mL multidose vials (0.25% and 0.5% strengths) containing methylparaben as a preservative. May be autoclaved at 15-pound pressure, 121 degrees C (250 degrees F) for 15 minutes [4].

Marcaine with epinephrine 1:200,000: Available as 0.25% (2.5 mg/mL) of bupivacaine in 10-mL and 30-mL single-dose vials and a 50-mL multidose vial and as 0.5% (5 mg/mL) of bupivacaine in 3-mL single-dose ampules, 10-mL and 30-mL single-dose vials, and a 50-mL multidose vial. Each mL also contains 0.0091 mg of epinephrine and 0.5 mg of sodium metabisulfite. Multidose vials contain methylparaben as a preservative. Do not autoclave. Protect from light [3].

Marcaine Spinal: Available as 2-mL single-dose ampules containing 15 mg of bupivacaine and 165 mg of dextrose. May be autoclaved once at 15-pound pressure, 121 degrees C (250 degrees F) for 15 minutes. Does not contain preservatives [20].

Sensorcaine: Available as 0.25% and 0.5% of bupivacaine in 50-mL multidose vials. Each mL contains 1 mg methylparaben (preservative). May be autoclaved [1].

Sensorcaine- methylparaben free (MPF): Available as 0.25%, 0.5%, and 0.75% of preservative-free bupivacaine in 10-mL and 30-mL single-dose vials and 30-mL ampules. May be autoclaved [2].

Sensorcaine with epinephrine 1:200,000: Available as 0.25% and 0.5% of bupivacaine in 50-mL multidose vials. Each mL contains 0.005 mg epinephrine, 0.5 mg sodium metabisulfite, and 1 mg methylparaben (preservative). Do not autoclave. Protect from light [5].

Sensorcaine-MPF with epinephrine 1:200,000: Available as 0.25% (10-mL and 30-mL single-dose vials), 0.5% (10-mL and 30-mL single-dose vials), and 0.75% (30-mL singledose vial) of preservative-free bupivacaine. Each mL contains 0.005 mg epinephrine and 0.5 mg sodium metabisulfite. Do not autoclave. Protect from light [6].

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Buprenorphine
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
Neonatal abstinence syndrome: Initial dose, 15.9
mcg/kg/day sublingually in 3 divided
doses, Maximum 60 mcg/kg/day and Maximum number of up-
titrations = 6..
Titrate dose up in 25% increments. Taper in 10%
decrements until the dose is 10% of the
initial dose, then discontinue [1][2][3][4].
Uses
Neonatal abstinence syndrome (NAS): Buprenorphine
would be a reasonable choice for
NAS if the neonate was exposed prenatally to
buprenorphine [5].
Sublingual buprenorphine was associated with the
largest reduction in length of treatment
and length of stay for NAS in a network meta-analysis
of 18 randomized controlled trials
(n=1072) of buprenorphine, clonidine, diluted tincture
of opium and clonidine, diluted
tincture of opium, morphine, methadone, and
phenobarbital. Morphine was the least
effective opioid [6]. The findings should be
interpreted with caution due to significant study
limitations [6][7]
Compared with Methadone or Morphine: There was a 3-day
reduction in the length of
treatment with sublingual buprenorphine compared with
conventional opioids (either
morphine or methadone) in an observational trial of
360 infants (34 weeks or longer
gestation) with NAS. Opioid treatment duration was 7.4
days (6.3 to 8.5 days) in the
buprenorphine group compared with 10.4 days (9.3 to
11.5 days; p less than 0.001) in the
conventional opioid group and the length of stay was
12.4 days (11.3 to 13.6 days) and 15.2
days (14.1 to 16.4 days; p less than 0.001),
respectively. These reductions were consistent
across the different types of intrauterine opioid
exposure (short-acting opioids, methadone,
buprenorphine, or combination of types). The initial
dosage of buprenorphine was 4.5
mcg/kg/dose sublingual every 8 hours; with
titrations/tapering of 1.5 mcg/kg/dose. Clonidine

and/or phenobarbital were optional adjunct agents [8].
Compared with Methadone: A shorter duration of opioid treatment (9.4 vs 14 days) and
shorter length of inpatient stay (16.3 vs 20.7 days) with a sublingual buprenorphine protocol
compared with oral methadone protocol was demonstrated in a retrospective analysis of 201
infants (34 weeks' gestation or older) with NAS. Infants exposed in utero to methadone were
excluded [9].
Compared with Morphine: Sublingual buprenorphine reduced the duration of treatment
for neonatal abstinence syndrome compared with oral morphine (15 days vs 28 days; p less
than 0.001) in a double-blind, double-dummy, single-center study (n=63). Preterm infants
and infants exposed to benzodiazepines in utero were excluded. Median length of hospital
stay was 21 vs 33 days (p less than 0.001) and use of supplemental phenobarbital was 15%
vs 23% (p=0.36) for buprenorphine and morphine, respectively. Rates of adverse events
were not different between the 2 groups [1].

Administration
After administration sublingually, place a pacifier in the infant's mouth. For a volume of the
dose greater than 0.5 mL, give in 2 administrations separated by at least 2 minutes [1].
MEDICATION SAFETY
Contraindications/Precautions
Contraindicated with significant respiratory depression, acute or severe bronchial asthma
(in an unmonitored setting or in the absence of resuscitative equipment), or known or
suspected gastrointestinal obstruction (including paralytic ileus) [11].
Addiction potential: Opioid-type physical dependence may occur [12]
Alcoholism: Use cautiously in patients with acute alcoholism and delirium tremens [11]
Cardiovascular: QTc prolongation has been reported [11]
Cardiovascular:: Avoid use in patients with a history of long QT Syndrome, or an
immediate family member with the syndrome [11]
Cardiovascular: Severe orthostatic hypotension and syncope in ambulatory patients may
occur, especially in patients with compromised ability to maintain blood pressure [11][13]
[12], and in patients with reduced blood volume, or with concurrent administration of CNS
depressants (eg, general anesthetics, phenothiazines) [11]

Cardiovascular: Avoid use in patients with circulatory shock [11].
Concomitant Use: Avoid use with Class 1A antiarrhythmic medications (eg, quinidine, procainamide, disopyramide) or Class 3 antiarrhythmic medications (eg, sotalol, amiodarone, dofetilide), or other medications that prolong the QT interval [11].
Concomitant Use: Patients requiring acute pain management or anesthesia are at risk. use non-opioid analgesia when possible; if opioid needed treat with high-affinity full opioid analgesia under supervision of physician with particular attention to respiratory function. Higher doses may be required. Use extreme care when using opioids as part of anesthesia [13].
Dermatologic: Use implant with caution in patients with history of keloid formation or connective tissue disease (eg, scleroderma) [13].
Endocrine and metabolic: Use with caution in patients with myxedema, hypothyroidism, or adrenal cortical insufficiency [11][13][12].
Endocrine and metabolic: Adrenal insufficiency may occur with opioids. If suspected, perform diagnostic testing. If confirmed wean patient off of opioid if appropriate, treat with corticosteroids, and continue to assess adrenal function [11][13][14]
Gastrointestinal: Use may obscure diagnosis or clinical course in patients with acute abdominal conditions [13][12].
Gastrointestinal: Severe constipation may occur [11]
Hepatic: Sphincter of Oddi spasm may occur with morphine use [11]
Hepatic: Use caution with severe hepatic impairment [11]
Hepatic: Use cautiously in patients with biliary dysfunction [11]
Hepatic: Cytolytic hepatitis, hepatitis with jaundice, and hepatotoxicity, sometimes fatal, has been reported, with an increased risk with pre-existing liver enzyme abnormalities, comorbid hepatitis B or C virus, concomitant hepatotoxic drugs, or IV drug abuse [13]
Hepatic: Avoid use with preexisting moderate to severe hepatic impairment and discontinuation may be necessary if this occurs during treatment (subdermal implants) [13]
Hepatic: Increased intracholedochal pressure has been reported. Use cautiously in patients with biliary dysfunction [12]

Immunologic: Anaphylactic shock, bronchospasm, and angioneurotic edema has been reported [13][12]
Immunologic: Hypersensitivity reactions (eg, pruritus, rashes, hives) have been reported [13] including acute and chronic reactions [11]
Immunologic: Infection may occur at site of implant insertion or removal. Increased risk with excessive palpation after insertion and improper removal [13]
Immunologic: Use implant with caution in patients with history of recurrent MRSA infections [13].
Musculoskeletal: Use cautiously with kyphoscoliosis [11]
Musculoskeletal: Use implant with caution in patients with kyphoscoliosis [13].
Neurologic: Elevation of cerebrospinal fluid (CSF) pressure may occur and interfere with evaluation of patients with head injuries, intracranial lesions, or other conditions that increase CSF pressure [12]
Neurologic: Increased intracranial pressure may occur in susceptible patients (eg, brain tumors or head injury) due to decreased respiratory drive and carbon dioxide retention [11]
Neurologic: Avoid use with impaired consciousness or coma [11].
Neurologic: Use implant with caution in patients with CNS depression or coma [13][12]
Neurologic: New or worsening seizures may occur [11]
Neurologic: Potentially life-threatening serotonin syndrome may occur, particularly with concomitant use of serotonergic drugs [11][14].
Psychologic: Use with caution in patients with toxic psychoses, acute alcoholism, or delirium tremens [13][12].
Psychologic: Use with caution in patients with toxic psychoses [11]
Renal: Use with caution in prostate hypertrophy or urethral stricture [11][13][12]
Renal: Use caution with severe renal impairment [11].
Reproductive: Long-term use of opioids may be associated with decreased sex hormone levels and symptoms such as reduced interest in sex, impotence, or infertility. Laboratory evaluation may be warranted [14].
Respiratory: Increased risk for further respiratory depression, particularly during treatment initiation and titration in patients with chronic pulmonary disease or otherwise impaired respiration [13][12]
Respiratory: Life-threatening respiratory depression may occur, especially with concomitant use of benzodiazepines or other CNS depressants [11][13][12] and particularly in the elderly, cachectic, or debilitated patients, those with chronic obstructive pulmonary disease or cor

pulmonale, and patients with substantially decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression [11].
Respiratory: Sleep-related breathing disorders including central sleep apnea and sleeprelated hypoxemia may occur and risk increases in a dose-dependent fashion; dose reduction may be necessary [15].
Special populations: Mental or physical impairment may occur, especially when beginning treatment or adjusting dosage. Avoid driving or operating dangerous machinery [12].
Special populations: Fatal respiratory depression may occur in children who are accidentally exposed to buprenorphine. Keep expelled implants away from children [13][12].
Special populations: Use implant with caution in debilitated patients [13].
Withdrawal: Abrupt withdrawal may result in severe withdrawal symptoms and should be avoided [13][12].
Adverse Effects
No buprenorphine-related adverse effects were reported in 2 open-label trials (n=50) [3][4].

Black Box Warning
There are serious risks, including profound sedation, respiratory depression, coma, and/or death, associated with combined use of opioids and benzodiazepines, other drugs that depress the CNS, or alcohol. Concomitant use should be reserved for patients with no alternative treatment. If necessary, use the lowest initial dose and titrate based on clinical response. Monitor patients closely for sedation and respiratory depression. Screen patients for risk of substance-use disorders [10].
Solution Compatibility
D5W, D5NS, NS, LR
Terminal Injection Site Compatibility
Buprenorphine 0.04 mg/mL: Acyclovir sodium (7 mg/mL), allopurinol (3 mg/mL), aminocaproic acid (20 mg/mL), amiodarone hydrochloride (3 mg/mL), amphotericin B lipid complex (1 mg/mL), amphotericin B liposome (1 mg/mL), anidulafungin (0.5 mg/mL), argatroban (1 mg/mL), atenolol (0.5 mg/mL), azithromycin (2 mg/mL), aztreonam (40 mg/mL), bivalirudin (5 mg/mL), capreomycin sulfate (10 mg/mL), cefepime hydrochloride (20 mg/mL), cisatracurium besylate (0.1 mg/mL), cytarabine (25 mg/mL), daptomycin (10

mg/mL), dexmedetomidine HCl (4 mcg/mL), diltiazem HCl (5 mg/mL), dolasetron mesylate (2 mg/mL), ertapenem sodium (20 mg/mL), fenoldopam mesylate (80 mcg/mL), filgrastim (30 mcg/mL), foscarnet sodium (24 mg/mL), fosphenytoin sodium (20 mg/mL), gatifloxacin (2 mg/mL), granisetron HCl (50 mcg/mL), hetastarch 6% (Hextend), lepirudin (0.4 mg/mL), leucovorin calcium (2 mg/mL), levofloxacin (5 mg/mL), linezolid (2 mg/mL), lorazepam (0.5 mg/mL), methotrexate sodium (15 mg/mL), metronidazole (5 mg/mL), milrinone lactate (0.2 mg/mL), mivacurium chloride (0.5 mg/mL), mycophenolate mofetil HCl (6 mg/mL), nesiritide (6 mcg/mL), nicardipine HCl (0.1 mg/mL), octreotide acetate (5 mcg/mL), palonosetron HCl (50 mcg/mL), pamidronate disodium (0.3 mg/mL), pancuronium bromide (0.1 mg/mL), pemetrexed disodium (20 mg/mL), piperacillin sodium-tazobactam sodium (40 mg/mL and 5 mg/mL), potassium acetate (0.2 mEq/mL), propofol (10 mg/mL), quinupristin-dalfopristin (5 mg/mL), remifentanil HCl (0.25 mg/mL), rocuronium bromide (1 mg/mL), sodium acetate (0.04 mEq/mL), tacrolimus (20 mcg/mL), teniposide (0.1 mg/mL), tigecycline (1 mg/mL), tirofiban HCl (0.1 mg/mL), vecuronium bromide (1 mg/mL), voriconazole (4 mg/mL), zoledronic acid (40 mcg/mL)

Buprenorphine 0.15 mg/mL: Alfentanil hydrochloride (0.25 mg/mL), amikacin sulfate (20 mg/mL), ascorbic acid injection (250 mg/mL), atracurium besylate (5 mg/mL), atropine sulfate (0.5 mg/mL), benztropine mesylate (0.5 mg/mL), bretylium tosylate (40 mg/mL), bumetanide (0.125 mg/mL), butorphanol tartrate (1 mg/mL), calcium chloride (50 mg/mL), calcium gluconate (50 mg/mL), cefamandole nafate (333 mg/mL), cefazolin sodium (220 mg/mL), cefoperazone (80 mg/mL), cefotaxime (285 mg/mL), cefotetan disodium (400 mg/mL), cefoxitin (450 mg/mL), ceftazidime (400 mg/mL), ceftizoxime (400 mg/mL), ceftriaxone sodium (165 mg/mL), cefuroxime (125 mg/mL), chloramphenicol sodium

succinate (333 mg/mL), chlorpromazine HCl (4 mg/mL), cimetidine HCl (24 mg/mL), clindamycin phosphate (48 mg/mL), cyanocobalamin (0.5 mg/mL), cyclosporine (2 mg/mL), dexamethasone sodium phosphate (12 mg/mL), digoxin (0.125 mg/mL), diphenhydramine HCl (25 mg/mL), dobutamine HCl (6.25 mg/mL), dopamine HCl (12.8 mg/mL), doxycycline

hyclate (4 mg/mL), enalaprilat (0.625 mg/mL), ephedrine sulfate (12.5 mg/mL), epinephrine hydrochloride (0.5 mg/mL), epoetin alfa (5000 units/mL), erythromycin lactobionate (20 mg/mL), esmolol HCl (40 mg/mL), famotidine (5 mg/mL), fentanyl citrate (25 mcg/mL), fluconazole (2 mg/mL), gentamicin sulfate (6.4 mg/mL), glycopyrrolate (0.1 mg/mL), heparin sodium (160 units/mL), hydrocortisone sodium succinate (62.5 mg/mL), hydroxyzine HCl (25 mg/mL), imipenem-cilastatin sodium (5 mg/mL), inamrinone lactate (2.5 mg/mL), regular insulin (50 units/mL), isoproterenol HCl (80 mcg/mL), ketorolac tromethamine (15 mg/mL), labetalol HCl (2.5 mg/mL), lidocaine HCl (10 mg/mL), magnesium sulfate (250 mg/mL), mannitol (150 mg/mL), meperidine HCl (50 mg/mL), metaraminol bitartrate (4 mg/mL), methyldopate HCl (25 mg/mL), methylprednisolone sodium succinate (125 mg/mL), metoclopramide hydrochloride (2.5 mg/mL), metoprolol tartrate (0.5 mg/mL), midazolam HCl (2.5 mg/mL), minocycline hydrochloride (0.8 mg/mL), morphine sulfate (4 mg/mL), multiple vitamins injection (0.08 mL/mL), nafcillin sodium (250 mg/mL), nalbuphine HCl (10 mg/mL), naloxone HCl (16 mcg/mL), netilmicin sulfate (50 mg/mL), nitroglycerin (1.6 mg/mL), nitroprusside sodium (0.8 mg/mL), norepinephrine bitartrate (0.5 mg/mL), ondansetron HCl (1 mg/mL), oxacillin sodium (160 mg/mL), oxytocin (0.08 units/mL), papaverine HCl (15 mg/mL), penicillin G potassium (500,000 units/mL), penicillin G sodium (500,000 units/mL), pentamidine isethionate (24 mg/mL), pentazocine lactate (15 mg/mL), phentolamine mesylate (5 mg/mL), phenylephrine HCl (4 mg/mL), phytonadione (5 mg/mL), piperacillin sodium (320 mg/mL), polymyxin B sulfate (0.667 mg/mL), potassium chloride (1 mEq/mL), procainamide HCl (250 mg/mL), prochlorperazine edisylate (2.5 mg/mL), promethazine HCl (25 mg/mL), propranolol HCl (0.5 mg/mL), protamine sulfate (5 mg/mL), pyridoxine HCl (50 mg/mL), quinidine gluconate (40 mg/mL), ranitidine HCl (2 mg/mL), streptokinase (80,000 units/mL), succinylcholine chloride (8 mg/mL), sufentanil citrate (25 mcg/mL), theophylline (4 mg/mL), thiamine HCl (50 mg/mL), ticarcillin disodium (345 mg/mL), ticarcillin disodiumclavulanate potassium (195 mg/mL), tobramycin sulfate (6.4 mg/mL), tolazoline HCl (12.5 mg/mL), urokinase (50,000 units/mL), vancomycin HCl (20 mg/mL), vasopressin (4 units/mL), verapamil HCl (1.25 mg/mL)

Buprenorphine 0.3 mg/mL: Acetaminophen (10 mg/mL)

Terminal Injection Site Incompatibility

Aminophylline (12.5 mg/mL), amphotericin B cholesteryl (0.83 mg/mL), ampicillin sodium (80 mg/mL), azathioprine sodium (13.33 mg/mL), dantrolene sodium (0.8 mg/mL), diazepam (2.5 mg/mL), diazoxide (7.5 mg/mL), indomethacin sodium trihydrate (1 mg/mL), lansoprazole (0.55 mg/mL), pantoprazole sodium (0.4 mg/mL), pentobarbital sodium (25 mg/mL), phenobarbital sodium (65 mg/mL), phenytoin sodium (25 mg/mL), sodium bicarbonate (0.5 mEq/mL), sulfamethoxazole-trimethoprim (20 mg/mL and 4 mg/mL)

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of action: Buprenorphine hydrochloride, a narcotic analgesic, is a partial muopioid receptor agonist and an antagonist at the kappa-opioid receptor. Lower propensity for physical dependence and longer duration of action compared with morphine [16].

Pharmacokinetics - Pharmacodynamics: Higher average concentrations (Cavg) of buprenorphine were associated with shorter time to neonatal abstinence stabilization in a study of 28 neonates (37 weeks or more gestation; mean birth weight, 3.1 kg) exposed primarily to methadone in utero. No respiratory depression was observed. A dose of 15 mcg/kg/dose SL every 8 hours was predicted to achieve a target buprenorphine Cavg of 0.8 ng/mL; for some neonates 10 mcg/kg/dose may be sufficient and others 20 mcg/kg/dose may be necessary [17].

Plasma concentrations of buprenorphine ranged from less than 0.1 ng/mL (35.6% of samples) to 0.6 ng/mL with high intra-subject variability in 13 term infants administered buprenorphine (13.2 to 39 mcg/kg/day) sublingually. There were 3 out of 202 samples that were outliers. An infant receiving the starting dose of 13.2 mcg/kg/day had a level of (3.69 ng/mL). The outlier values of, 1.8 ng/mL, and 0.85 ng/mL occurred in 1 patient receiving the maximum protocol specified dose of 39 mcg/kg/day [4].

Bioavailability: Sublingual, neonates: 7% in a retrospective population pharmacokinetic analysis of 24 neonates with neonatal abstinence syndrome. Median gestational age in the neonates was 39.2 weeks (range, 36.6 to 41.2 weeks) and median weight was 2.9 kg (range, 2.2 to 4.1 kg) [18].

Protein binding: approximately 96% protein bound (primarily alpha and beta globulin)

[16].
Vd: Sublingual: 142 L in 28 neonates (37 weeks or more gestation; mean birth weight, 3.1 kg) [17]
Metabolism: N-dealkylation, mediated primarily to CYP3A4, to norbuprenorphine as well as glucuronidation. Norbuprenorphine can undergo further glucuronidation [16].
Clearance: Sublingual: 3.5 L/hr/kg in a neonate (postnatal age, 5.4 days; weighing a median of 2.9 kg) [18]; 203 L/hr in 28 neonates (37 weeks or more gestation; mean birth weight, 3.1 kg) [17]
Elimination half-life: predicted half-life was 11 hours for sublingual buprenorphine in a retrospective population pharmacokinetic analysis of 24 neonates with neonatal abstinence syndrome and 5 adults (for model development). Median gestational age in the neonates was 39.2 weeks (range, 36.6 to 41.2 weeks) and median weight was 2.9 kg (range, 2.2 to 4.1 kg). Phenobarbital did not affect the clearance of buprenorphine. [18]. 31 to 35 hours [16].
ABOUT
Special Considerations/Preparation
Sublingual route
A 0.075 mg/mL (75 mcg/mL) buprenorphine solution was compounded by mixing buprenorphine for injection in 100% ethanol USP (30% total volume) and simple syrup USP (85 gm sucrose/100 mL). The solution is stable for 30 days at room temperature when stored in glass bottles and 7 days at room temperature when stored in syringes [19][3].

Caffeine Citrate
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
Apnea of Prematurity
Loading dose: 20 to 25 mg/kg of caffeine citrate IV over 30 minutes or orally.
Maintenance dose: 5 to 10 mg/kg per dose of caffeine citrate IV slow push or orally every 24 hours [1][2].
Maintenance dose should be started 24 hours after the loading dose.

May consider an additional loading dose and higher maintenance doses if able to monitor serum concentrations.
(Please note that emphasis has changed to caffeine citrate due to commercially available product. This product (Cafcit) may be administered both intravenously and orally).
The ratio of caffeine citrate to caffeine base is 2:1 (eg, 20 mg of caffeine citrate = 10 mg caffeine base).
Dose Adjustment
Hepatic Impairment: Dose adjustment is recommended [3].
Renal Impairment: Dose adjustment is recommended [3].
Uses
Apnea: Pharmacological treatment with caffeine is the standard of care for apnea of prematurity [1].
The rate of bronchopulmonary dysplasia in neonates with apnea of prematurity was reduced with caffeine, started within the first 10 days of life, in a randomized, placebo-controlled trial (n=1917). Caffeine was started to prevent apnea, treat apnea, or to facilitate the removal of an endotracheal tube [2]. A follow-up of the study at 18 months corrected age demonstrated that the risk of death or disability (cerebral palsy, cognitive delay, severe hearing loss, and bilateral blindness) was reduced with caffeine [4]. At a 5-year follow-up, there was no difference in disability or death between the caffeine and placebo group [5]. At an 11-year follow-up, the combined rate of academic, motor, and behavioral impairment did not differ between the caffeine and placebo group. There was a reduced risk of motor impairment with caffeine compared with placebo (adjusted OR 0.66 (95% CI, 0.48 to 0.9)) [6]. A secondary analysis (n=675) of a retrospective, multicenter cohort study demonstrated an association of less frequent early acute kidney injury in preterm neonates with caffeine administered by 7 days of life; 11.2% vs 31.6% with and without caffeine, respectively (adjusted odds ratio 0.2 (95% CI, 0.11 to 0.34)) [7].
High-dose (caffeine citrate 40 mg/kg/day loading dose, 20 mg/kg/day maintenance): A significant reduction in extubation failure (22% vs 47%), the frequency of apnea (9 vs 16), and days of documented apnea (2.5 days vs 5 days) were observed with high-dose oral caffeine citrate compared with standard dose (20 mg/kg/day loading dose, 10 mg/kg/day maintenance) in a randomized, double-blind study in 120 preterm (less than 32

weeks gestation; 10 days or younger) with apnea of prematurity. Tachycardia was significantly more frequent (23% vs 8%) in the high-dose vs low-dose group [8].

Initiation:The optimal time to start treatment with caffeine is unknown. A reasonable approach is to start caffeine when apnea develops in infants greater than 28 weeks' gestation who do not require positive pressure support. Earlier (younger than 3 days) prophylactic caffeine in infants who require mechanical ventilation compared with later (3 days or older) has been studied but the safety and efficacy need further study [1].

Caffeine administered within the first 24 hours of life was associated with less mechanical ventilation (71.3% vs 83.2%) and a shorter duration of mechanical ventilation (mean 5 vs 10.8 days) than later caffeine initiation (median of 4 days) in an analysis of an observational study (n=286). Lower rates of patent ductus arteriosus and intraventricular hemorrhage (IVH) were associated with early versus late initiation; however, higher grades of IVH were not reduced. Premature infants (32 weeks' gestational age or less) with respiratory distress syndrome and treated with surfactant were included [9].

Duration: The optimal duration of treatment with caffeine is unknown. Consider a trial off of caffeine in infants who have been free of clinically significant apnea/bradycardia events after 5 to 7 days off positive pressure or at 33 to 34 weeks postmenstrual age, which ever comes first [1]. Extending caffeine treatment beyond when it is normally discontinued (apnea resolution) reduced the number and severity of intermittent hypoxia episodes in infants; however, the long-term benefits and risks to extended treatment are unknown. The postmenstrual age (PMA) at randomization to caffeine or placebo was 34 to 37 weeks (n=95) and continuous pulse oximeter data were collected up until 39 weeks PMA [10]. More studies are needed before implementing extended caffeine treatment beyond apnea resolution [1].

Mechanical Ventilation Weaning: The age at first successful extubation did not differ between early caffeine use (median 24 days of age; interquartile range (IQR), 10 to 41 days) and placebo group (median 20 days of age; IQR, 9 to 43 days; p=0.703) in preterm infants born at 23 to 30 weeks of gestation requiring mechanical ventilation in the first 5 postnatal

days in a randomized, double-blind, placebo-controlled trial (n=83). Additionally, no differences were detected in secondary outcomes (duration of mechanical ventilation and oxygen supplementation, bronchopulmonary dysplasia, or death). The trial was terminated early due to a trend of higher mortality; 22% for caffeine and 12% (p=0.22) for placebo. The mean ages were approximately 3 hours at intubation and 2 days at randomization. The dosage for caffeine citrate was 20 mg/kg followed by 5 mg/kg/day [11].

Pediatric FDA-approved Use

Indicated for the short-term treatment of apnea of prematurity in infants between 28 to younger than 33 weeks of gestational age [3].

The use of caffeine for sudden infant death syndrome prophylaxis or prior to extubation in mechanically-ventilated infants has not been established [3].

Administration

Administer the IV loading dose over 30 minutes and the maintenance dose over 10 minutes [3]

MEDICATION SAFETY

Contraindications/Precautions

PRECAUTIONS

Cardiovascular: Use with caution in infants with cardiovascular disease; caffeine may increase heart rate, left ventricular output, and stroke volume [3].

Concomitant Use: With theophylline is not recommended [3].

Endocrine: Hypoglycemia and hyperglycemia has been reported; monitoring recommended [3].

Hepatic: Use with caution in infants with hepatic impairment; monitoring and dose adjustment recommended [3].

Neurologic: Seizures have been reported; use with caution in infants with seizure disorders [3].

Renal: Use with caution in infants with renal impairment; monitoring and dose adjustment recommended [3].

Adverse Effects

Adverse effects are usually mild, and include restlessness, vomiting, and functional cardiac symptoms. There has been a suggested association with NEC, but causality has never been proven. Loading doses of 25 mg/kg caffeine (50 mg/kg caffeine citrate) have been reported

to decrease cerebral and intestinal blood flow velocity.
Solution Compatibility
D5W and D50W.
Terminal Injection Site Compatibility
Alprostadil, amikacin, aminophylline, calcium gluconate, cefotaxime, cimetidine, clindamycin, dexamethasone, dobutamine, dopamine, doxapram, epinephrine, fentanyl, gentamicin, heparin (concentration less than or equal to 1 unit/mL), isoproterenol, lidocaine, metoclopramide, morphine, nitroprusside, pancuronium, penicillin G, phenobarbital, sodium bicarbonate, and vancomycin.
Terminal Injection Site Incompatibility
Acyclovir, furosemide, ibuprofen lysine, lorazepam, nitroglycerin, and oxacillin.
Monitoring
Laboratory Monitoring
Concentration

Measuring serum concentrations is probably not necessary [1].
Baseline caffeine levels are recommended in neonates previously treated with theophylline and neonates born to mothers who consumed caffeine prior to delivery [3].
Monitor serum concentrations in the presence of renal or hepatic impairment [3].
If monitoring of serum drug concentration is performed, measure the trough level on approximately day 5 of therapy. Therapeutic trough serum concentration is 5 to 25 mcg/mL. Concentrations greater than 40 to 50 mcg/mL are toxic.
Assess for agitation. Monitor heart rate; consider withholding dose if greater than 180 beats per minute.
Other Laboratory Values
Periodically monitor serum glucose [3].
Physical Findings
Watch for signs and symptoms of necrotizing enterocolitis [3].
MECHANISM OF ACTION/PHARMACOKINETICS
Pharmacology
The pharmacological effects of caffeine are mediated by its antagonism of the actions of adenosine at cell surface receptors. It is rapidly distributed in the brain, with CNS levels approximating plasma levels. Caffeine increases the respiratory center output, chemoreceptor sensitivity to CO2, smooth muscle relaxation, and cardiac output. Oxygen consumption may be increased and weight gain may be reduced. Renal effects include diuresis and increased

urinary calcium excretion.
Orally administered caffeine citrate is rapidly and completely absorbed. There is almost no first-pass metabolism. In neonates, approximately 86% is excreted unchanged in the urine, with the remainder metabolized via the CYP1A2 enzyme system.
The serum half-life of caffeine ranges from 40 to 230 hours, decreasing with advancing postmenstrual age until 60 weeks PMA. Half-life is prolonged in infants with cholestatic hepatitis.
In a pharmacokinetic modelling study of simulated caffeine concentrations, dose adjustments were recommended to maintain a concentration range of 15 to 20 mg/mL to account for the developing kidney of the newborn. Options for maintenance dose were a dose titration (e.g. 1 mg/kg/day increase every 1 to 2 weeks) or a fixed maintenance dose (e.g. 10 mg/kg/day) [12].
In a pharmacokinetic study (n=50), the mean half-life was 87+/-25 hours in preterm infants at 35+/-1 weeks postmenstrual age. Mean serum caffeine concentrations were 13.3 mg/L at 24 hours and 4.3 mg/L at 168 hours after stopping caffeine. Caffeine doses were 5 mg/kg/day orally for the majority of infants (86%), with the remainder on 6 to 8 mg/kg/day [13]
ABOUT
Special Considerations/Preparation

Both Cafcit Oral Solution and Cafcit Injection for intravenous administration are preservative free and available in 3-mL single use vials. Each mL of Cafcit contains 20 mg of caffeine citrate (equivalent to 10 mg caffeine base). Store at room temperature.
Extemporaneous compounds
Injectable solution 20 mg/mL caffeine citrate
Dissolve 10 g of caffeine citrate powder in 250 mL of sterile water for injection USP.
Transfer the solution to a 500-mL empty evacuated container (EEC). Add sufficient sterile water for injection for a total volume of 500 mL.
Filter the solution through a 0.22 micron filter set into an empty 500-mL EEC, then transfer the filtered solution into sterile, empty 10-mL vials. Autoclave the vials at 121 degrees Centigrade for 15 minutes and allow to cool.
Quarantine the product until sterility and pyrogen testing are completed. Stable for 90 days under refrigeration [14].

Oral solution 20 mg/mL caffeine citrate
Dissolve 10 g of caffeine citrate powder in 250 mL of sterile water for irrigation USP. Add a 2:1 mixture of simple syrup and cherry syrup to make a total volume of 500 mL. Stable for 90 days under refrigeration [14].
Oral solution 10 mg/mL caffeine base (Note: 10 mg caffeine base = 20 mg of caffeine citrate)
Alternatively, an oral solution may be prepared by dissolving 2.5 g of caffeine anhydrous powder in 250 mL of water, yielding a final concentration of 10 mg/mL caffeine base. Solution is stable for 4 weeks refrigerated. Crystals form when stored at low temperature but dissolve at room temperature without loss of potency. Do not freeze.

Calcium - Oral
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
Hypocalcemia, non-acute: 20 to 80 mg/kg/day elemental calcium orally in 2 to 4 divided doses scheduled around oral feedings.
Calcium gluconate 10% IV formulation (9.3 mg/mL elemental calcium): 2 to 8 mL/kg/day.
Calcium carbonate 250 mg/mL suspension (100 mg/mL elemental calcium): 0.2 to 0.8 mL/kg/day.
Calcium glubionate syrup (23 mg/mL elemental calcium): 1 to 3.5 mL/kg/day.
Rickets
Preterm neonates: Supplementation with 20 mg/kg/day of elemental calcium and 10 to 20 mg/kg/day of elemental phosphorus. Increase as tolerated, to a maximum 70 to 80 mg/kg/day of elemental calcium and 40 to 50 mg/kg/day of elemental phosphorus in preterm infants enterally fed [1]. Administer in 2 to 4 divided doses.
Calcium gluconate 10% IV formulation (9.3 mg/mL elemental calcium): 2 to 8 mL/kg/day.
Calcium carbonate 250 mg/mL suspension (100 mg/mL elemental calcium): 0.2 to 0.8 mL/kg/day.
Calcium glubionate syrup (23 mg/mL elemental calcium): 1 to 3.5 mL/kg/day.
Uses
Hypocalcemia, non-acute in babies able to tolerate oral medications.
Rickets: In enterally fed preterm infants with radiologic evidence of rickets, maximize

nutrient intake by increasing human milk fortifier and/or volume of preterm formula. If maximization cannot be tolerated, then supplementation with elemental calcium and phosphorus is recommended. Vitamin D status should be evaluated and target 25-hydroxyvitamin D concentrations of greater than 20 ng/mL (50 nmol/L). The recommended intakes for enterally fed, very low birth weight infants are 150 to 220 mg/kg/day for calcium and 75 to 140 mg/kg/day for phosphorus [1].

MEDICATION SAFETY

Adverse Effects

Oral calcium preparations are hypertonic, especially calcium glubionate syrup. Gastric irritation and diarrhea occur often. Use with caution in infants who are at risk for necrotizing

enterocolitis.

Monitoring

Periodically measure serum calcium concentrations. Assess GI tolerance. Assess serum phosphorus and vitamin D levels when indicated.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Absorption of calcium administered orally is approximately 50%. Absorption takes place throughout the small intestine, and is primarily regulated by 1,25-dihydroxy Vitamin D. Calcium carbonate significantly interferes with the absorption of levothyroxine. The osmolarity of calcium glubionate syrup is 2500 mOsm/L, and of calcium gluconate is 700 mOsm/L.

ABOUT

Special Considerations/Preparation

Calcium carbonate (Roxane) is available as a 250 mg/mL suspension (equivalent to 100 mg/mL elemental calcium) in 5-mL unit dose cups. Calcium glubionate syrup 360 mg/mL (1.8 g/5 mL) (Rugby/Watson) yields 23 mg/mL elemental calcium (1.16 mEq/mL) and is available in 473 mL bottles. Osmolarity is 2500 mOsm/L.

Calcium Chloride

NeoFax Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Cardiac Resuscitation (documented hypocalcemia, hyperkalemia,
hypermagnesemia): 20 mg/kg/dose calcium chloride 10% (0.2 mL/kg calcium chloride
10%) slow IV push/IO Maximum single dose 2 g[1]. Dose recommendation based on
Pediatric Advanced Life Support guidelines.
Early Hypocalcemia, Symptomatic (eg, seizures)
Doses are extrapolated from the calcium gluconate dose based on the elemental calcium as
well as from the calcium chloride package insert. Calcium gluconate is recommended as
calcium chloride may cause metabolic acidosis. [2][3][4][5][6]Doses for calcium chloride are
provided for circumstances when calcium gluconate is unavailable and IV route is necessary.
Acute treatment: 20 to 70 mg/kg/dose calcium chloride 10% (0.2 to 0.7 mL/kg/dose
calcium chloride 10%) IV .
Maintenance treatment: 75 to 300 mg/kg/day calcium chloride 10% (0.75 to 3 mL/kg/day
calcium chloride 10%). Administer by continuous IV infusion. Treat for 3 to 5 days.
Exchange transfusion: 33 mg calcium chloride 10% per 100 mL citrated blood exchanged
(equals 0.33 mL per 100 mL blood exchanged). Infuse IV over 10 to 30 minutes.
Uses
Acute treatment of neonatal symptomatic hypocalcemia [5][6]. Treatment and
prevention of hypocalcemia, usually defined as a serum ionized calcium concentration less
than approximately 4 mg/dL (or total serum calcium less than approximately 7 to 8 mg/dL)
[6]. Calcium gluconate given at the same elemental calcium dose may be preferred as
calcium chloride may cause a metabolic acidosis [5][6].
Cardiac resuscitation: Use only in cases of documented hypocalcemia, hyperkalemia,
hypermagnesemia, or calcium channel blocker toxicity. Routine use of calcium in cardiac
resuscitation is not recommended [1][7][9]. The American Heart Association (AHA) did not
review calcium use in the 2015 Neonatal Resuscitation guidelines; therefore, the 2010 AHA
guidelines still apply [10].
FDA approve use: Treatment of hypocalcemia when IV route is necessary (eg, neonatal
tetany and tetany due to parathyroid deficiency, vitamin D deficiency and alkalosis) and for
prevention of hypocalcemic during exchange transfusions. As adjunctive therapy in the
treatment of acute symptoms in lead colic. Treatment of magnesium sulfate overdose. In
severe hyperkalemia, to combat deleterious effects on ECG function, pending correction of

the potassium level in the extracellular fluid. In cardiac resuscitation, particularly after open heart surgery, when epinephrine fails [2].

Administration
Cardiac resuscitation: Administer by slow IV push for cardiac arrest [1]; infuse over 30 to 60 minutes for other indications [7]. May dilute in compatible solution for intermittent infusion or continuous infusion. Infuse through a large vein [2]; central line is preferred.
Do not exceed rate of injection of 1 mL/minute (Calcium chloride 10% solution) [2].
Do not administer into the cardiac muscle [2].
Hypocalcemic seizures: Infuse IV over 10 to 60 minutes while monitoring for bradycardia [5][7][6]. Stop infusion if heart rate is less than 100 beats per minute.
Do not give intra-arterially [6]. Warm solution to body temperature. Infuse through a large vein [2], preferably a central line [8].
MEDICATION SAFETY
Contraindications/Precautions
Contraindicated in patients with ventricular fibrillation [11]. Coadministration of ceftriaxone sodium injection with calcium-containing IV solutions (including continuous calciumcontaining infusions such as parenteral nutrition) is also contraindicated due to the risk of precipitation of ceftriaxone-calcium [12]. Rapid administration is associated with bradycardia or cardiac arrest [13].
Adverse Effects
Precipitate in the infusion line with crystalline deposits in the lungs and kidneys has been reported in some deceased neonates who were coadministered ceftriaxone IV and calciumcontaining fluids, sometimes in the same infusion line. At least one neonatal fatality has been reported following coadministration at different times and with separate infusion lines, though no crystalline deposits were found at autopsy in this neonate. These reports have been confined to neonates [12]. Cutaneous necrosis or calcium deposition occurs with extravasation. Bolus infusions by UAC have been associated with intestinal bleeding and lower-extremity tissue necrosis.
Solution Compatibility
D5W, D10W, and NS.
Terminal Injection Site Compatibility
Amikacin, amiodarone, chloramphenicol, dobutamine, dopamine, epinephrine, esmolol,

hydrocortisone, isoproterenol, lidocaine, micafungin, milrinone, morphine, penicillin G,

pentobarbital, phenobarbital, prostaglandin E1, and sodium nitroprusside.
Terminal Injection Site Incompatibility
Amphotericin B, ceftriaxone, sodium bicarbonate, and phosphate and magnesium salts when mixed directly.
Monitoring
If possible, measure ionized calcium directly. Avoid hypercalcemia during treatment. Correct hypomagnesemia if present. Observe IV infusion site closely for extravasation. Observe IV tubing for precipitates. Monitor continuously for bradycardia when giving bolus doses[5][7][6] .
MECHANISM OF ACTION/PHARMACOKINETICS
Pharmacology
Calcium chloride may be more bioavailable than calcium gluconate, but it also is more likely to cause metabolic acidosis. Administration by continuous infusion is more efficacious than intermittent bolus dosing due to less renal calcium loss. Ionized calcium is the physiologically active fraction, accounting for approximately 50% of total blood calcium. The remainder is bound to albumin (40%) or complexed (10%) with citrate, phosphate, and bicarbonate. Early hypocalcemia is common in asphyxiated infants, premature infants, and infants of diabetic mothers. Significant decreases in ionized calcium may occur during acute alkalosis and following exchange transfusions with citrated blood. Clinical signs suggestive of hypocalcemia in neonates include muscle twitching, jitteriness, generalized seizures, and QTc above 0.4 second.
ABOUT
Special Considerations/Preparation
Calcium chloride 10% injection yields 27 mg/mL elemental calcium (1.36 mEq/mL). Osmolarity is 2040 mOsm/L. Injectable calcium salts should be stored at room temperature and are stable indefinitely [11].

Calcium Gluconate
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION

Dose
Early Hypocalcemia, Symptomatic (eg, seizures)
Initial treatment: 100 to 200 mg/kg/dose calcium gluconate 10% (1 to 2 mL/kg/dose) [1][2][3][4][5].
Maintenance treatment: 200 to 800 mg/kg/day calcium gluconate 10% (2 to 8 mL/kg/day) [1][2][3].
Administer by continuous IV infusion. Treat for 3 to 5 days [2].
If tolerating oral feeds and after initial correction, may administer the IV formulation orally (200 to 800 mg/kgday)[1] in divided doses with feedings.
Daily Requirement
Preterm neonates: 2 to 4 mEq/kg/day IV of calcium [6].
Full-term neonates: 0.5 to 4 mEq/kg/day IV of calcium [6].
Exchange transfusion: 100 mg calcium gluconate 10% per 100 mL citrated blood exchanged (equals 1 mL per 100 mL blood exchanged).
Infuse IV over 10 minutes.
Uses
Acute treatment of neonatal symptomatic hypocalcemia[3][5]. Treatment and prevention of hypocalcemia, usually defined as a serum ionized calcium concentration less than approximately 4 mg/dL (or total serum calcium less than approximately 7 to 8 mg/dL) [5]. Calcium gluconate given at the same elemental calcium dose may be preferred as calcium chloride may cause a metabolic acidosis [3][5].
Treatment of asymptomatic infants is controversial.
Administration
Administer over 10 to 60 minutes while monitoring heart rate [1][7][3]. Temporarily stop infusion if bradycardia develops. Avoid intra-arterial infusions of high calcium concentrations.
Use caution with the use of an umbilical venous catheter with the tip close to or in the heart [1].
Administer into a large vein through a small needle to avoid hypercalcemia, extravasation, and necrosis [8][3].
Not for IM or subQ use[8].
Administer by slow IV push for cardiac arrest[7]. May dilute in compatible solution for intermittent or continuous infusion. Infusion through central line is preferred.

MEDICATION SAFETY
Contraindications/Precautions

Calcium salts are contraindicated in patients with ventricular fibrillation or hypercalcemia (or when calcium levels are above normal). Coadministration of ceftriaxone sodium injection with calcium-containing IV solutions (including continuous calcium-containing infusions such as parenteral nutrition) is also contraindicated due to the risk of precipitation of ceftriaxonecalcium [9].
Product contains aluminum that may be toxic with prolonged IV administration and in patients with impaired kidney function. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which contain aluminum. Studies showed that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5 mcg/kg/day accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration.
Rapid administration is associated with vasodilation, hypotension, bradycardia, syncope, cardiac arrhythmias, and cardiac arrest[9].
Adverse Effects
Precipitate in the infusion line with crystalline deposits in the lungs and kidneys has been reported in some deceased neonates who were coadministered ceftriaxone IV and calciumcontaining fluids, sometimes in the same infusion line. At least one neonatal fatality has been reported following coadministration at different times and with separate infusion lines, though no crystalline deposits were found at autopsy in this neonate. These reports have been confined to neonates [9].
Solution Compatibility
D5W, D10W, and NS.
Terminal Injection Site Compatibility
Amikacin, aminophylline, amiodarone, ampicillin, aztreonam, caffeine citrate, cefazolin, cefepime, chloramphenicol, dobutamine, enalaprilat, epinephrine, famotidine, furosemide, heparin, hydrocortisone, lidocaine, linezolid, micafungin, midazolam, milrinone, netilmicin, nicardipine, penicillin G, phenobarbital, piperacillin-tazobactam, potassium chloride, propofol, remifentanil, tobramycin, and vancomycin.
Terminal Injection Site Incompatibility

Amphotericin B, ceftriaxone, fluconazole, indomethacin, meropenem, methylprednisolone,

metoclopramide, and phosphate and magnesium salts when mixed directly.
Monitoring
If possible, measure ionized calcium directly. Avoid hypercalcemia during treatment. Correct hypomagnesemia if present. Observe IV infusion site closely for extravasation. Observe IV tubing for precipitates. Monitor continuously for bradycardia when giving bolus doses. Assess for GI intolerance when treating orally.
MECHANISM OF ACTION/PHARMACOKINETICS
Pharmacology
Ionized calcium is the physiologically active fraction, accounting for approximately 50% of total blood calcium. The remainder is bound to albumin (40%) or complexed (10%) with citrate, phosphate, and bicarbonate. Early hypocalcemia is common in asphyxiated infants, premature infants, and infants of diabetic mothers. Significant decreases in ionized calcium may occur during acute alkalosis and following exchange transfusions with citrated blood. Clinical signs suggestive of hypocalcemia in neonates include muscle twitching, jitteriness, generalized seizures, and QTc above 0.4 second. Calcium chloride may be more bioavailable than calcium gluconate, but it also is more likely to cause metabolic acidosis. Administration by continuous infusion is more efficacious than intermittent bolus dosing due to less renal calcium loss.
ABOUT
Special Considerations/Preparation
Calcium gluconate 10% injection yields 9.3 mg/mL elemental calcium (0.46 mEq/mL). Osmolarity is 700 mOsm/L. Injectable calcium salts should be stored at room temperature and are stable indefinitely.

Calfactant
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
Initial dose: 3 mL/kg/dose (containing 35 mg phospholipids/mL) intratracheally; may be repeated if needed every 12 hours up to a total of 3 doses. For prophylactic therapy in premature infants less than 29 weeks of gestational age at significant risk for respiratory distress syndrome, Infasurf should be given as soon as possible, preferably within 30 minutes after birth [1]. For rescue therapy, administer as soon as possible, preferably within

2 hours after birth [2].
In the Infasurf versus Survanta treatment trial, repeat doses were administered as early as 6 hours after the previous dose for a total of up to 4 doses if the infant was still intubated and required at least 30% inspired oxygen to maintain a PaO2 of 80 torr or less [1].

Uses

Respiratory distress syndrome (RDS): Routine continuous positive airway pressure (CPAP) is considered superior to prophylactic surfactant therapy. It is strongly recommended that CPAP immediately after birth with subsequent selective surfactant administration be considered as an alternative to routine intubation with prophylactic or early surfactant administration in preterm infants. Severe RDS in preterm infants born younger than 30 weeks gestation who need mechanical ventilation should be administered surfactant after initial stabilization. Consider the use of rescue surfactant for infants with hypoxic respiratory failure attributable to secondary surfactant deficiency, such as meconium aspiration syndrome or sepsis/pneumonia[2]. Animal-derived surfactants (beractant, calfactant, and poractant alfa) had comparable outcomes for air leak syndromes, death, and bronchopulmonary dysplasia in a retrospective study (n=51,282; median birth weight of 1435 g; median gestation age of 30 weeks (27 to 33 weeks)) [4].

Late Administration: Calfactant administered at 7 to 14 days of age in infants (28 weeks of gestational age or younger) who required mechanical ventilation and were receiving inhaled nitric oxide did not improve survival without bronchopulmonary dysplasia (BPD) at 36 weeks' or 40 weeks' postmenstrual age or improve the severity of BPD, in a randomized, masked, multicenter trial (n=511). Infants were randomized to either calfactant every 24 to 72 hours up to 5 doses, if the infants still required intubation, or sham. Due to unlikely benefit the trial was terminated early [5]. At 1-year corrected age follow-up (n=450), home respiratory support was reduced with late surfactant compared with inhaled nitric oxide alone. However, no improvement was noted on composite outcome of pulmonary morbidity (PM) (measured by use of medications, hospitalization, and home respiratory support) or persistent PM [6].

Neonatal FDA-Approved Indications

Infasurf is indicated for the prevention of respiratory distress syndrome (RDS) in premature infants less than 29 weeks of gestational age at significant risk for RDS. Treatment should be

given as soon as possible, preferably within 30 minutes after birth [1][7][8].

Infasurf is indicated for infants less than 72 hours of age with RDS (confirmed by clinical and radiological findings) and requiring endotracheal intubation [1][7][9].

Administration

For intratracheal administration only [3].

Warming of suspension is not necessary [3]

Calfactant intratracheal suspension may be administered by either of the following 2 methods [3]:

1) Administration by instilling the suspension through a side-port adapter into the endotracheal tube. Two attendants are needed to facilitate dosing; one to instill the calfactant, the other to monitor the patient and assist in positioning. The dose (3 mL/kg) should be administered in 2 aliquots of 1.5 mL/kg each. After each aliquot is instilled, the neonate should be positioned with either the right or the left side dependent. Administration is made while ventilation is continued over 20 to 30 breaths for each aliquot, with small bursts timed only during the inspiratory cycles. A pause followed by evaluation of the respiratory status and repositioning should separate the two aliquots.

2) Administration by instilling the suspension through a 5 French feeding tube inserted into the endotracheal tube. The total dose is instilled in 4 equal aliquots with the catheter removed between each instillation and mechanical ventilation resumed for 0.5 to 2 minutes. For even distribution of calfactant, each of the aliquots should be administered with the neonate in 1 of 4 positions; prone, supine, right, and left lateral.

MEDICATION SAFETY

Contraindications/Precautions

Transient episodes of reflux of surfactant into the endotracheal tube, cyanosis, bradycardia, and airway obstruction have been reported during administration. A higher rate of intraventricular hemorrhage and periventricular leukomalacia was observed in Infasurf-treated infants compared with Exosurf-treated infants in clinical trials [1].

Adverse Effects

Most common adverse reactions observed in clinical trials were cyanosis (65%), airway

obstruction (39%), bradycardia (34%), reflux of surfactant into the endotracheal tube (21%), requirement for manual ventilation (16%), and reintubation (3%). Reactions were usually transient and not associated with severe complications or mortality [1].

Monitoring

Monitor closely for appropriate oxygen therapy and ventilatory support [1].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Pulmonary lung surfactants are essential for effective ventilation by modifying alveolar surface tension thereby stabilizing the alveoli. Infasurf is a sterile, non-pyrogenic natural surfactant extracted from calf lungs containing phospholipids, neutral lipids, fatty acids, and surfactant-associated proteins B and C. Preservative free. Each mL of Infasurf contains 35 mg of total phospholipids (26 mg of phosphatidylcholine of which 16 mg is disaturated phosphatidylcholine) and 0.65 mg of proteins including 0.26 mg of SP-B [1].

ABOUT

Special Considerations/Preparation

Available in 3-mL and 6-mL single-use vials. Refrigerate at 2 to 8 degrees C (36 to 46 degrees F) and protect from light. The 3 mL vial must be stored upright. Inspect Infasurf for discoloration; normal color is off-white, and visible flecks and foaming at the surface are normal. Suspension settles during storage; gently swirl vial in order to uniformly suspend. Do not shake. Used vials with residual drug should be discarded. Unopened vials that have been warmed to room temperature one time may be refrigerated within 24 hours and stored for future use. Should not be warmed and returned to the refrigerator more than once [1].

Captopril

NeoFax Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Initial dose: 0.01 mg/kg/dose orally every 12 hours. Incrementally increase dose [1][2].

Adjust dose and interval based on response.

Dosage: 0.1 to 0.4 mg/kg/dose orally every 6 hours [2][3] to 24 hours [3] has been suggested for hypertension. In neonates with heart failure, 0.4 to 1.6 mg/kg/day orally divided every 8 hours was recommended [4]; based on a retrospective study for congenital heart disease 1 to maximum 1.5 mg/kg/day orally divided every 8 hours was suggested [5].

A significant decrease in creatinine clearance in preterm and term neonates with cardiovascular disease warrants extreme care in term neonates treated with captopril and questions the use of captopril in preterm neonates in a retrospective review (n=206) [6].

Uses

Heart failure: Afterload reduction in patients with congestive heart failure.

Hypertension: Treatment of moderate to severe hypertension.

Administration

Administer 1 hour before feeding; food decreases absorption.

MEDICATION SAFETY

Contraindications/Precautions

The use of captopril is contraindicated in patients with bilateral renovascular disease or with unilateral renal artery stenosis in a solitary kidney, as the loss of adequate renal perfusion could precipitate acute renal failure.

Adverse Effects

Neonates are more sensitive to the effects of captopril than are older infants and children. Significant decreases in cerebral and renal blood flow have occurred in premature infants with chronic hypertension who received higher doses (0.15 to 0.30 mg/kg per dose) than

those recommended above. These episodes occurred unpredictably during chronic therapy, and some were associated with neurologic (seizures, apnea, lethargy) and renal (oliguria) complications. Hyperkalemia occurs primarily in patients receiving potassium-sparing diuretics or potassium supplements [7].

The CrCl significantly decreased in preterm and term neonates with cardiovascular disease after initiation of ACEIs (captopril or enalapril) in a retrospective review (n=206). The body surface area was less than 0.33 m2 for all neonates [6].

Monitoring

Frequent assessment of blood pressure, particularly after the first dose.

Periodic assessment of renal function
Periodic measurement of serum potassium.
MECHANISM OF ACTION/PHARMACOKINETICS
Pharmacology
Mechanism of action: Captopril is an angiotensin-converting enzyme (ACE) inhibitor that blocks the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor. It thereby decreases plasma and tissue concentrations of angiotensin II and aldosterone, and increases plasma and tissue renin activity. Captopril also prevents the breakdown of bradykinin, a potent vasodilator. Vascular resistance is reduced without reflex tachycardia. Beneficial effects are thought to be caused by a combination of afterload reduction and long-term inhibition of salt and water retention.
Bioavailability is good in neonates, although food will decrease absorption.
Onset of action is 15 minutes after a dose, with peak effects seen in 30 to 90 minutes.
Duration of action is usually 2 to 6 hours, but may be significantly longer (greater than 24 hours).
ABOUT
Special Considerations/Preparation
Available in 12.5-mg, 25-mg, 50-mg, and 100-mg tablets.
Extemporaneous Oral Compounds
Captopril 1 mg/mL oral solution was stable for 56 days at 4 degrees C and 28 days at 22 degrees C. Two captopril 50-mg tablets were dissolved in 50 mL of water in a graduate. One ascorbic acid 500-mg tablet was added and allowed to dissolve. Sufficient distilled water was added for a final volume of 100 mL. Shake well. Do not filter [8].
Captopril 1 mg/mL oral solution was stable for 56 days at 4 degrees C and 14 days at 22

degrees C. Two captopril 50-mg tablets were dissolved in 50 mL of water in a graduate.
Sodium ascorbate injection 500 mg was added and mixed well. Sufficient distilled water was added for a final volume of 100 mL. Shake well. Do not filter [8].
Captopril 0.03 mg/mL oral suspension was stable for 14 days at room temperature or 56 days when refrigerated. Captopril 6.25 mg (one-half of a scored 12.5-mg tablet) was dissolved in 10 mL of sterile water, 1000 mg of sodium ascorbate for injection (4 mL of 250-mg/mL solution) was added to decrease oxidation, then sufficient water was added to make

a final volume of 200 mL. The final concentration was 0.03 mg/mL captopril and 5 mg/mL sodium ascorbate. Some undissolved excipients remained visible [9].

Aqueous captopril solutions have been reported to degrade rapidly, and stability in different solutions is highly variable and dependent on many factors (pH, type of vehicle, drug concentration, addition of preservative). There have been conflicting results in various studies over the years. The data below represents some of the studies of various extemporaneously prepared captopril oral solutions [10][11][9].

Captopril 1 mg/mL oral solution made with tablets and undiluted syrup was stable for 30 days refrigerated (5 degrees C). In this study, different formulations of captopril solutions were made using either tablets or powder with different vehicles used (sterile water, syrup, methylcellulose); edetate disodium was added to some of the formulations. Better stability was noted when captopril tablets were used compared with powder, with undiluted versus diluted syrup as the vehicle, and when edetate disodium was added as the preservative [11].

To overcome potential stability problems, powder papers and compounded capsules have been utilized to extemporaneously prepare captopril solutions just prior to administration [12][13].

Carglumic Acid

NeoFax Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Acute or Chronic Hyperammonemia due to N-acetylglutamate synthase (NAGS) deficiency; Adjunct: Initial, 100 to 250 mg/kg/day divided into 2 to 4 doses per day concomitantly with other ammonia lowering agents. Titrate dose to maintain within normal plasma ammonia levels for age. Normal plasma ammonia levels usually attained by day 3. Therapy is continuous and life-long [1][2].

Based on retrospective case series (n=22), maintenance doses were typically less than 100 mg/kg/day [1].

Uses

Treatment of hyperammonemia due to various metabolic disorders [2][3]. Based upon use in newborns from case reports, carglumic acid, when administered in addition to standard

therapy, acutely reduces plasma ammonia levels in patients with branched-chain organic acidemias, such as methylmalonic aciduria (MMA), propionic aciduria (PA), and isovaleric acidemia (IVA) . In these metabolic disorders, synthesis of N-acetylglutamate is inhibited due to the build up of the respective branched-chain organic acid; once standard therapy has corrected the acidemia, hyperammonemia is also resolved [4]. Doses used in these cases ranged from 70 to 200 mg/kg/day, administered as a single dose [4] or over a 48-hour period [3].

FDA Approved Indications

Indicated as adjunctive therapy for the treatment of acute hyperammonemia due to deficiency of the hepatic enzyme N-acetylglutamate synthase (NAGS) from the time of birth.

Also indicated as maintenance therapy for chronic hyperammonemia due to NAGS deficiency [1].

Administration

Do NOT administer tablets whole or crushed. Dissolve one 200-mg tablet in 2.5-mL of water for a concentration of 80 mg/mL for oral or nasogastric (NG) tube administration. For oral administration, measure dose using an oral syringe, discard the unused portion, administer immediately, then refill the oral syringe with 1 to 2 mL of water and administer immediately to ensure complete delivery of dose. For NG tube administration, measure dose using an oral syringe, discard the unused portion, administer immediately, and flush NG tube with small volume of water. Do not use other liquids or food for preparation or administration.

Administer prior to feedings [1].

MEDICATION SAFETY

Contraindications/Precautions

Prolonged exposure to increased plasma ammonia levels can rapidly result in brain injury or death; monitoring recommended [1].

During initial treatment, complete protein restriction is recommended for 24 to 48 hours; supplement calories to avoid catabolism and nitrogen turnover [1].

Adverse Effects

Adverse reaction which occurred in 13% or more patients from a retrospective case series include abdominal pain, anemia, diarrhea, ear infection, headache, infection, nasopharyngitis, pyrexia, tonsillitis, and vomiting [1][2].

Monitoring

Monitor plasma ammonia levels, neurological status, and clinical response [1].
MECHANISM OF ACTION/PHARMACOKINETICS
Pharmacology
Carglumic acid is a synthetic analogue of N-acetylglutamate (NAG), a product of Nacetylglutamate synthase (NAGS). NAG is an essential activator of carbamoyl phosphate
synthetase 1 (CPS 1), which is the first enzyme in the urea cycle. Carglumic acid acts as a
replacement for NAG in patients with NAGS deficiency, thereby activating CPS 1. Following
administration, plasma ammonia levels are reduced within 24 hours. Tmax occurs in 2 to 4
hours. Drug partially metabolized by intestinal flora, likely to carbon dioxide, which is
eliminated through the lungs. Unchanged drug is excreted in the feces (60%) and urine
(9%). Mean terminal half-life is 5.6 hours [1].
ABOUT
Special Considerations/Preparation
Available as a 200-mg tablet. Store sealed bottle in refrigerator prior to opening for the first
time; do not refrigerate after opening. Discard product 1 month after first opening [1].

Caspofungin
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
Aspergillus or Candida Infection, Suspected or Documented:
25 mg/m2/dose IV every 24 hours [1]. This dose has not been evaluated in clinical studies.
Duration of therapy for candidemia, without metastatic complications, is 2 weeks after
documented clearance of Candida from the bloodstream and resolution of symptoms [2].
Uses
Aspergillus or Candida Infection:
Treatment of patients with refractory Candidemia, intra-abdominal abscesses, peritonitis and
pleural space infections, and those patients intolerant of amphotericin B. Treatment of
invasive Aspergillosis in patients who are refractory to or intolerant of other therapies.
There are case reports, but not controlled clinical trials, treating endocarditis, osteomyelitis,

and meningitis due to Candida.
Neonatal Candidiasis, Including CNS Infection[2]
Invasive candidiasis, candidemia, or very low-birth weight infants with asymptomatic candiduria .
Amphotericin B deoxycholate is recommended.
Fluconazole IV or oral is an alternative for those who have not been receiving prophylaxis with fluconazole.
Lipid formulation amphotericin B agent is an alternative; however, use with caution, especially in the presence of urinary tract involvement.
Echinocandins (caspofungin, anidulafungin, or micafungin) should be limited to salvage therapy or scenarios of resistance or toxicity to amphotericin B deoxycholate or fluconazole.
Central nervous system infections
Amphotericin B deoxycholate is recommended.
Liposomal amphotericin B agent is an alternative.
Salvage therapy with flucytosine may be added in those patients who have not responded to initial therapy.
Fluconazole may be used as step-down therapy for fluconazole-susceptible isolates in those patients who respond to initial therapy.
Neonatal intensive care unit (with greater than 10% rate of invasive candidiasis)
Prophylaxis with IV or oral fluconazole for 6 weeks is recommended for neonates with birth weights of less than 1000 g

Prophylaxis with oral nystatin is an alternative in neonates with birth weights of less than 1500 g when fluconazole is unavailable or fluconazole resistance is present
Comparison to Amphotericin B: There was no difference in clinical response between echinocandins and amphotericin B (OR 1.38; 95% CI, 0.68 to 2.8) for the treatment of suspected or confirmed invasive candidiasis in a meta-analysis (n=5; 354 neonates and children). Antifungals included were micafungin, caspofungin, amphotericin B deoxycholate, and liposomal amphotericin B. Subanalysis demonstrated no difference in other comparisons including mycological response, mortality, recurrence of candida infection, type of echinocandin, different risk groups (high-risk, low-risk, or neutropenic groups), and type of use (targeted or empirical). Discontinuation due to adverse effects were higher with

amphotericin B than the echinocandins (OR 0.3; 95% CI, 0.12 to 0.76) [5].
Pediatric FDA Approved Indications
The following indications are FDA approved for pediatric patients 3 months and older [6]:
Empirical therapy for presumed fungal infections in febrile, neutropenic patients.
Treatment of candidemia and the following Candida infections: intraabdominal abscesses, peritonitis and pleural space infections.
Treatment of esophageal candidiasis.
Treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies.
Administration
Administer by slow IV infusion over approximately 1 hour at a concentration not to exceed 0.5 mg/mL.[3] The recommended concentration is 0.5 mg/mL [4]. Do not dilute in dextrose-containing solutions.
MEDICATION SAFETY
Contraindications/Precautions
Concomitant Use: Increased risk of hepatotoxicity when used with cyclosporine [6].
Dermatologic: Stevens-Johnson syndrome and toxic epiderma necrolysis, sometimes fatal, have been reported; discontinue at first sign or symptom [7]
Hepatic: Hepatic abnormalities, including abnormal liver function tests and hepatic failure, have been reported; monitoring recommended [6].
Hepatic: Dose adjustment may be required for hepatic impairment [6].
Immunologic: Anaphylaxis and other hypersensitivity reactions have been reported; discontinue use if occurs [7].
Immunologic: Histamine-mediated adverse reactions (eg, rash, facial swelling, angioedema, pruritus, sensation of warmth, bronchospasm) have been reported; discontinuation may be necessary [7].

Adverse Effects
Adverse effects reported in neonates (small number of patients): thrombophlebitis, hypercalcemia, hypokalemia, elevated liver enzymes, and isolated direct hyperbilirubinemia.
In pediatric studies, the primary adverse effects were fever, hypokalemia, diarrhea, increased liver enzymes, rash, hypotension and chills.
Solution Compatibility
NS, NS, NS, LR.
Solution Incompatibility
All solutions containing dextrose.

Terminal Injection Site Compatibility
Azithromycin, aztreonam, dobutamine, dopamine, famotidine, fluconazole, insulin, linezolid, meropenem, metronidazole, morphine, potassium chloride, and vancomycin.
Terminal Injection Site Incompatibility
Acyclovir, cefazolin, ceftriaxone, clindamycin, furosemide, heparin, and piperacillin/tazobactam.
Monitoring
Assess IV site for signs of irritation. Periodic measurement of serum potassium, calcium, and hepatic transaminases.
For candidemia, monitor blood cultures daily or every other day until Candida is cleared [2].
MECHANISM OF ACTION/PHARMACOKINETICS
Pharmacology
Caspofungin is the first of a new class of antifungal agents (echinocandins) that inhibit the synthesis of ?-(1,3)-D-glucan, an integral component of the fungal cell wall. It is fungicidal

against Candida species, but fungistatic against Aspergillus. The echinocandins are excreted primarily by the liver, presumably metabolized through an O-methyltransferase. They are not metabolized through the CYP enzyme system and therefore have significantly fewer drugdrug interactions than the azoles. Dexamethasone, phenytoin, carbamazepine, nevirapine, and rifampin all induce caspofungin drug clearance, lowering serum concentrations.
In a pharmacokinetic study in infants less than 3 months (n=18) with esophageal/oropharyngeal candidiasis or invasive candidiasis, a dose of 25 mg/m2 appeared to provide similar drug exposure compared with adults receiving 50 mg/dose. The majority of infants were born premature (approximately 70%) and 12 of 18 infants were 4 weeks postnatal age or younger [8].
ABOUT
Special Considerations/Preparation
Cancidas is supplied as a white to off-white powder cake in single-use vials, containing either 50 or 70 mg. To prepare the 50-mg (5 mg/mL) or 70-mg (7 mg/mL) Cancidas vial:
1) Equilibrate the refrigerated vial to room temperature. 2) Aseptically add 10.8 mL Normal Saline or Sterile Water for Injection to the vial. The powder cake will dissolve completely with gentle mixing. This reconstituted solution can be stored at room temperature for up to one

hour. Visually inspect the reconstituted solution for particulate matter or discoloration. Do not use if the solution is cloudy or has precipitated. Single-use vials: discard remaining unused solution. 3) Remove desired volume of drug based on calculated dose and further dilute in compatible solution (NS, NS, NS, LR) to a final concentration not to exceed 0.5 mg/mL.
The infusion solution can be stored for up to 24 hours at room temperature or up to 48 hours refrigerated. Do not use diluents containing dextrose.

CeFAZolin
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
25 mg/kg/dose IV or IM.
Antibiotic Dosing Chart:
Renal function and drug elimination are most strongly correlated with Postmenstrual Age (PMA; equivalent to Gestational Age plus Postnatal Age). PMA is the primary determinant of dosing interval, with Postnatal Age as the secondary qualifier.
Dosing Interval Chart
PMA (weeks)
PostNatal (days)
Interval (hours)
?29 0 to 28
>28
12
8
30 to 36 0 to 14
>14
12
8
37 to 44 0 to 7
>7
12
8
?45 ALL 6
Uses
Use in neonates is generally limited to perioperative infection prophylaxis and treatment of urinary tract and soft tissue infections caused by susceptible organisms, e.g. penicillinresistant Staph. aureus, Klebsiella, and Proteus.
Infective endocarditis: The following recommendations are based on a consensus of

experts [3]. The full pediatric guidelines can be found here:
https://doi.org/10.1161/CIR.0000000000000298
Organism Directed Therapy
Organism First-Choice Alternative Choice
Streptococci
Highly susceptible to penicillin G (MBC 0.1 mcg/mL or less); includes most viridans streptococci, groups A, B, C, G nonenterococcal, group D streptococci (S bovis, S equinus)
Penicillin G or
CefTRIAXone
Vancomycin or
First-generation cephalosporin or
CefTRIAXone
Relatively resistant to penicillin (MBC 0.2 mcg/mL or more); less-susceptible viridans streptococci or
enterococci
Penicillin G or
Ampicillin +
Gentamicin (for first 2 weeks, or entire course for enterococci)
Vancomycin +
Gentamicin for enterococci
Ampicillin +
CefTRIAXone (for aminoglycoside (AMG)-resistant enterococci or

AMG-intolerant patient)
CefTRIAXone +
gentamicin (not for enterococcal endocarditis)
Resistant to penicillin Consult an infectious disease specialist.

Staphylococci (S aureus or coagulase-negative staphylococci)
Penicillin G susceptible (1 mcg/mL or less) (rare)
Penicillin G Oxacillin or
Nafcillin or
First-generation cephalosporin or
Vancomycin
Penicillin G resistant (0.1 mcg/mL)
Oxacillin or
Nafcillin
with or without
Gentamicin

Vancomycin (for those
highly allergic to betalactam
antibiotics) or
First-generation
cephalosporin
Oxacillin (MRSA) resistant (4 mcg/mL)
Vancomycin Daptomycin for rightsided
endocarditis, maybe
for left-sided
Vancomycin resistant or intolerant Daptomycin Unknown
When prosthetic material present add riFAMpin
+ gentamicin (for first 2 weeks) for all
staphylococci
Gram-negative enteric bacilli
CefTAZidime or
Cefepime or
Cefotaxime or
CefTRIAXone
Plus gentamicin (or
tobramycin or
amikacin, depending
on susceptibility)
Broad-spectrum penicillin
Plus gentamicin (or
tobramycin or amikacin)
HACEK group
CefTRIAXone or
Cefotaxime or
Ampicillin-sulbactam
Ampicillin (when
susceptible)
Plus aminoglycoside
KEY: AMG = aminoglycosides; HACEK = Haemophilus
species, Aggregatibacter species,
Cardiobacterium hominis, Eikenella corrodens, and
Kingella species; MBC = minimum bactericidal
concentration, MRSA = methicillin-resistant
Staphylococcus aureus (includes resistance to
oxacillin,
nafcillin, and cephalosporins)
Baltimore, 2015
Sepsis, Prophylaxis; Catheter Removal: Reductions (11% vs 0%; p=0.021) in cultureconfirmed
sepsis were demonstrated in a prospective randomized controlled study in 88
preterm infants administered cefazolin 1 hour prior to and 12 hours after removal of a PICC
line compared with no antibiotic use[4]. However, this study was criticized for methodology
shortcomings that limit its applicability [5]. Sepsis rates were 10.3% with removal of a PICC
without antibiotics 48 hours prior to removal compared with 1.5% (p=0.002) in neonates on
cefazolin/gentamicin at the time of removal of the PICC in a retrospective study (n=345) [6].
Administration

May be given by IV direct (bolus) injection, IV infusion, or IM injection [1][2].
For IV bolus injection, inject slowly over 3 to 5 minutes at a concentration of 100 mg/mL. For IV intermittent or continuous infusion, dilute reconstituted solution to a concentration of 5 to 20 mg/mL [1][2].
For IM injection, use a concentration of 225 mg/mL. Maximum 330 mg/mL[1][2].
MEDICATION SAFETY
Adverse Effects
Adverse effects are rare, but include phlebitis and eosinophilia.
Solution Compatibility
D5W, D10W, and NS.
Terminal Injection Site Compatibility
Acyclovir, alprostadil, amikacin, aztreonam, calcium gluconate, clindamycin, enalaprilat, esmolol, famotidine, fluconazole, heparin, insulin, lidocaine, linezolid, magnesium sulfate, midazolam, milrinone, morphine, metronidazole, multivitamins, nicardipine, pancuronium bromide, propofol, prostaglandin E1, ranitidine, remifentanil, and vecuronium.
Terminal Injection Site Incompatibility
Amiodarone, caspofungin, cimetidine, and vancomycin.
Monitoring
Serum concentrations are not routinely monitored.
MECHANISM OF ACTION/PHARMACOKINETICS
Pharmacology

First generation cephalosporin that is bactericidal against many gram-positive and a few gram-negative organisms. Inactivated by ?-lactamase producing organisms. Poor CNS penetration. Renally excreted as unchanged drug. Half-life in neonates is 3 to 5 hours.
ABOUT
Special Considerations/Preparation
Availability: Powder for injection in 500-mg and 1000-mg vials.
Reconstitution: 2 mL of sterile water for injection in 500 mg vial for 225 mg/mL concentration and 2.5 mL of sterile water for injection in 1000 mg vial for a 330 mg/mL concentration. Reconstituted solution stable for 24 hours at room temperature or 10 days in refrigerator [1].
Dilutions: Further dilute reconstituted solution in 5 mL of sterile for injection for a bolus

injection or dilute in 50 to 100 mL of a compatible solution for intermittent or continuous infusion. Solution stable for 24 hours at room temperature or 10 days in refrigerator [1].

Cefepime
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
Term and preterm infants greater than 28 days of age: 50 mg/kg/dose IV every 12 hours.
Term and preterm infants 28 days of age and younger: 30 mg/kg/dose IV every 12 hours.
Meningitis and severe infections due to Pseudomonas aeruginosa or Enterobacter spp: 50 mg/kg/dose IV every 12 hours.
Uses
Treatment of serious infections caused by susceptible gram-negative organisms (eg, E coli, H influenzae, Enterobacter, Klebsiella,Morganella, Neisseria, Serratia, and Proteus species), especially Pseudomonas aeruginosa that are resistant to 3rd generation cephalosporins.
Treatment of serious infections caused by susceptible Gram-positive organisms (eg, Strep pneumoniae, Strep. pyogenes, Strep. agalactiae, and Staph. aureus).
A positive clinical response was observed in 26 of the 32 (81.3%) evaluable neonates treated with cefepime (mean dose 36 mg/kg/dose IV every 12 hours) in a retrospective, singlecenter study (n=74; mean postmenstrual age at initiation, 33 weeks). Concomitant antibiotics were used during all courses; most common infections were late-onset sepsis (42%), early-onset sepsis (17.6%), and multiple indications (16.2%) [3].
Infective endocarditis: The following recommendations are based on a consensus of experts [4]. The full pediatric guidelines can be found here: https://doi.org/10.1161/CIR.0000000000000298
Initial Empirical Therapy or Culture-Negative Endocarditis*
Unknown Organism First-Choice Alternative Choice
Native valve (community acquired) Ampicillin/sulbactam + gentamicin with or without vancomycin
For prosthetic valve involvement, add rifAMPin

Vancomycin
"Late" prosthetic valve infection + gentamicin
(more than 1 year after surgery)
Nosocomial endocarditis associated with
vascular cannulae
Vancomycin
+ gentamicin
(with or without rifAMPin if prosthetic
material present)
+ cefepime or cefTAZidime
Unknown
"Early" prosthetic valve endocarditis
(1 year or less after surgery)

* Culture-negative endocarditis (CNE): generally,
attempt to culture the infecting organism for at
least 48 hours. Severely ill children need immediate
treatment. Consider infectious disease
consultation for CNE
Baltimore, 2015
Organism Directed Therapy
Organism First-Choice Alternative Choice
Streptococci
Highly susceptible to penicillin G (MBC 0.1 mcg/mL
or less); includes most viridans streptococci,
groups A, B, C, G nonenterococcal, group D
streptococci (S bovis, S equinus)
Penicillin G or
CefTRIAXone
Vancomycin or
First-generation
cephalosporin or
CefTRIAXone
Relatively resistant to penicillin (MBC 0.2 mcg/mL
or more); less-susceptible viridans streptococci
or
enterococci
Penicillin G or
Ampicillin +
Gentamicin (for first
2 weeks, or entire
course for
enterococci)
Vancomycin +
Gentamicin for
enterococci
Ampicillin +
CefTRIAXone (for
aminoglycoside (AMG)-
resistant enterococci or
AMG-intolerant patient)
CefTRIAXone +
gentamicin (not for
enterococcal endocarditis)

Resistant to penicillin Consult an infectious disease specialist.

Staphylococci (S aureus or coagulase-negative staphylococci)
Penicillin G susceptible (1 mcg/mL or less) (rare)
Penicillin G Oxacillin or
Nafcillin or
First-generation cephalosporin or
Vancomycin
Penicillin G resistant (0.1 mcg/mL)
Oxacillin or
Nafcillin
with or without
Gentamicin
Vancomycin (for those highly allergic to betalactam antibiotics) or
First-generation cephalosporin
Oxacillin (MRSA) resistant (4 mcg/mL)
Vancomycin Daptomycin for rightsided endocarditis, maybe for left-sided
Vancomycin resistant or intolerant Daptomycin Unknown
When prosthetic material present add riFAMpin + gentamicin (for first 2 weeks) for all staphylococci
Gram-negative enteric bacilli
CefTAZidime or
Cefepime or
Cefotaxime or
CefTRIAXone
Plus gentamicin (or tobramycin or amikacin, depending on susceptibility)
Broad-spectrum penicillin
Plus gentamicin (or tobramycin or amikacin)
HACEK group CefTRIAXone or Ampicillin (when

Cefotaxime or
Ampicillin-sulbactam susceptible)
Plus aminoglycoside
KEY: AMG = aminoglycosides; HACEK = Haemophilus species, Aggregatibacter species, Cardiobacterium hominis, Eikenella corrodens, and Kingella species; MBC = minimum bactericidal concentration, MRSA = methicillin-resistant Staphylococcus aureus (includes resistance to oxacillin,

nafcillin, and cephalosporins)
Baltimore, 2015
Administration
Give as an IV infusion in a compatible solution over 30 minutes at a concentration of 1 to [1]
100 mg/mL. A large healthcare system selected 40 mg/mL and 100 mg/mL (IV push) as
standard concentrations for cefepime [2].
May be given by IM injection at a concentration of 280 mg/mL [1]. To reduce pain at IM
injection site, cefepime may be mixed with 1%
lidocaine without epinephrine.
MEDICATION SAFETY
Adverse Effects
Safety has been documented to be the same as commonly used second- and thirdgeneration
cephalosporins. Reported adverse effects are uncommon, but include rash,
diarrhea, elevated hepatic transaminases,
eosinophilia, and positive Coomb's test.
In a retrospective, single-center study of 74 neonates (mean postmenstrual age at initiation
was 33 weeks) treated with cefepime (mean dose 36 mg/kg/dose IV every 12 hours), acute
kidney injury (16.2%), hypophosphatemia (12.2%), seizures (0.03%), and hyponatremia
(0.01%) were reported. Concomitant nephrotoxic agents (i.e., vancomycin and gentamicin)
were used in all neonates [3].
Solution Compatibility
D5W, D10W, D5LR, D5NS, and NS.
Terminal Injection Site Compatibility
Amikacin, ampicillin, aztreonam, bumetanide, calcium gluconate, clindamycin,
dexamethasone, fluconazole, furosemide, gentamicin, heparin, hydrocortisone succinate,
imipenem/cilastatin, lorazepam, methylprednisolone, metronidazole, milrinone, piperacillintazobactam,
potassium chloride, ranitidine, remifentanil, sodium bicarbonate,
ticarcillin/clavulanate,
trimethoprim/sulfamethoxazole, and zidovudine.

Terminal Injection Site Incompatibility
Acyclovir, aminophylline, amphotericin B, cimetidine, diazepam, dobutamine, dopamine,
enalaprilat, erythromycin lactobionate, famotidine, ganciclovir, magnesium sulfate,
metoclopramide, midazolam, morphine, nicardipine, phenytoin, tobramycin, and vancomycin.
Monitoring
Measuring serum concentration is not usually necessary.
MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology
Cefepime is a fourth-generation cephalosporin with treatment efficacy equivalent to thirdgeneration cephalosporins. Potential advantages include: more rapid penetration through the
cell wall of Gram-negative pathogens; enhanced stability to hydrolysis by ?-lactamases; and enhanced affinity for penicillin-binding proteins. The drug distributes widely in body tissues
and fluids (i.e. CSF, bile, bronchial secretions, lung tissue, ascitic fluid, middle ear). Protein
binding is low (approximately 20%), and it is primarily excreted unchanged in the urine.
Serum half-life in infants older than 2 months of age is approximately 2 hours.
ABOUT
Special Considerations/Preparation
Available as powder for injection in 500-mg, 1-g, and 2-g vials. For IM use, reconstitute 500-
mg or 1-g vial with 1.3 mL or 2.4 mL of compatible diluent (sterile water for injection, NS, D5
W, lidocaine 0.5% or 1%, or sterile bacteriostatic water for injection) respectively, to a
concentration of 280 mg/mL. For IV use, reconstitute 500-mg vial with 5 mL and 1-g vial
with 10 mL of compatible diluent to a concentration of 100 mg/mL. Reconstitute 2-g vial with
10 mL of compatible diluent to a concentration of 160 mg/mL. Further dilute reconstituted
solution in compatible infusion solution to a concentration of 1 to 40 mg/mL. Reconstituted
solution and solution for infusion are stable for 24 hours at room temperature and 7 days
refrigerated [1].

Cefotaxime
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
Disseminated Gonococcal Infections and Gonococcal Scalp Abscesses: 25
mg/kg/dose IV or IM every 12 hours for 7 days, with a duration of 10 to 14 days if meningitis
is documented [1].
Meningitis:
0 to 7 days of age: 100 to 150 mg/kg/day IV divided every 8 to 12 hours. Consider smaller
doses and longer intervals for very low-birth weight neonates (less than 2 kg) [2].
8 days or older: 150 to 200 mg/kg/day IV divided every 6 to 8 hours. Consider smaller
doses and longer intervals for very low-birth weight neonates (less than 2 kg) [2].

Sepsis: The following recommendations were based on developmental pharmacokineticpharmacodynamic analysis (n=100) to achieve time above MIC (2 mg/L for postnatal age younger than 7 days and 4 mg/L for postnatal age 7 days or older) of 75% [3]:

Gestational Age (weeks)	Postnatal Age (days)	Regimen
All weeks	younger than 7 days	50 mg/kg/dose IV every 12 hours
Less than 32 weeks	7 days or older	50 mg/kg/dose IV every 8 hours
32 weeks or more	7 days or older	50 mg/kg/dose IV every 6 hours

Leroux, 2016

Usual dose for bone and joint, genitourinary, intra-abdominal, lower respiratory tract, or skin and skin structure infection [4]

7 days or younger and any weight: 50 mg/kg/dose IV/IM every 12 hours [5].

8 days to 28 days and 2 kg or less: 50 mg/kg/dose IV/IM every 8 to 12 hours [5].

8 days to 28 days and more than 2 kg: 50 mg/kg/dose IV/IM every 8 hours [5].

Uses

Disseminated gonococcal infections and gonococcal scalp abscesses The recommended regimen is ceftriaxone or cefotaxime [1].

Infective endocarditis: The following recommendations are based on a consensus of experts [7]. The full pediatric guidelines can be found here: https://doi.org/10.1161/CIR.0000000000000298

Organism	Directed Therapy	
Organism	First-Choice	Alternative Choice
Streptococci		
Highly susceptible to penicillin G (MBC 0.1 mcg/mL or less); includes most viridans streptococci, groups A, B, C, G nonenterococcal, group D streptococci (S bovis, S equinus)	Penicillin G or CefTRIAXone	Vancomycin or First-generation cephalosporin or CefTRIAXone
Relatively resistant to penicillin (MBC 0.2 mcg/mL or more); less-susceptible viridans streptococci or enterococci	Penicillin G or Ampicillin + Gentamicin (for first 2 weeks, or entire	

course for
enterococci)
Vancomycin +
Gentamicin for
enterococci
Ampicillin +
CefTRIAXone (for
aminoglycoside (AMG)-
resistant enterococci or
AMG-intolerant patient)
CefTRIAXone +
gentamicin (not for
enterococcal endocarditis)
Resistant to penicillin Consult an infectious
disease specialist.

Staphylococci (S aureus or coagulase-negative
staphylococci)
Penicillin G susceptible (1 mcg/mL or less) (rare)
Penicillin G Oxacillin or
Nafcillin or
First-generation
cephalosporin or
Vancomycin
Penicillin G resistant (0.1 mcg/mL)
Oxacillin or
Nafcillin
with or without
Gentamicin
Vancomycin (for those
highly allergic to betalactam
antibiotics) or
First-generation
cephalosporin
Oxacillin (MRSA) resistant (4 mcg/mL)
Vancomycin Daptomycin for rightsided
endocarditis, maybe
for left-sided
Vancomycin resistant or intolerant Daptomycin Unknown
When prosthetic material present add riFAMpin
+ gentamicin (for first 2 weeks) for all
staphylococci
Gram-negative enteric bacilli
CefTAZidime or
Cefepime or
Cefotaxime or
CefTRIAXone
Plus gentamicin (or
tobramycin or
amikacin, depending
on susceptibility)
Broad-spectrum penicillin
Plus gentamicin (or
tobramycin or amikacin)
HACEK group
CefTRIAXone or
Cefotaxime or
Ampicillin-sulbactam

Ampicillin (when
susceptible)
Plus aminoglycoside
KEY: AMG = aminoglycosides; HACEK = Haemophilus
species, Aggregatibacter species,
Cardiobacterium hominis, Eikenella corrodens, and
Kingella species; MBC = minimum bactericidal
concentration, MRSA = methicillin-resistant
Staphylococcus aureus (includes resistance to
oxacillin,
nafcillin, and cephalosporins)
Baltimore, 2015
Meningitis: Empiric agents for the treatment of
meningitis in neonates are ampicillin,
gentamicin, and cefotaxime [8]. Reassess therapy based
on culture and sensitivity results

[2].
Sepsis caused by susceptible gram-negative organisms
(e.g. E coli, H influenzae,and
Klebsiella). Optimal treatment for suspected, early-
onset sepsis is broad-spectrum
antimicrobial coverage using a combination of
ampicillin and an aminoglycoside (usually
gentamicin); once a pathogen is identified, therapy
should be narrowed unless synergism is
required [9].
Duration:
Procalcitonin values in addition to perinatal risk
factors, signs and symptoms, and laboratory
values may aid in the determination to discontinue
antibiotic therapy in neonates with
suspected early-onset sepsis. The duration of
antibiotic therapy was reduced by 9.9 hours
with a procalcitonin-guided algorithm compared with
standard care in a multicenter
randomized control trial of 1710 neonates born after
34 weeks of gestational age with
possible or unlikely sepsis. Re-infection and
mortality was not different between the groups
(risk difference 0.1% (95% CI, -5.2% to 5.3%)) [10].
Pediatric FDA Approved Indications
Lower respiratory tract infections (including
pneumonia) caused by Streptococcus
pneumoniae, S pyogenes and other streptococci
(excluding enterococci), Staphylococcus
aureus (penicillinase and non-penicillinase
producing), Escherichia coli, Klebsiella species,
Haemophilus. influenzae (including ampicillin
resistant strains), H parainfluenzae, Proteus
mirabilis, Serratia marcescens, Enterobacter species,
indole positive Proteus and
Pseudomonas species (including P aeruginosa) [4].

Genitourinary infections (urinary tract infections) caused by Enterococcus species, S epidermidis, S aureus (penicillinase and non-penicillinase producing), Citrobacter species, Enterobacter species, E coli, Klebsiella species, P mirabilis, P vulgaris, P stuartii, M. morganii, P rettgerr, S marcescens, and Pseudomonas species (including P. aeruginosa). Also uncomplicated gonorrhea (cervical/urethral and rectal) caused by N. gonorrhoeae, including penicillinase-producing strains [4].
Bacteremia/sepsis caused by E coli, Klebsiella species, and S marcescens, S aureus, and Streptococcus species (including S pneumoniae) [4].
Skin and skin structure infections caused by S aureus (penicillinase and non-penicillinase producing), S epidermidis, S pyogenes and other streptococci, Enterococcus species, Acinetobacter species, E. coli, Citrobacter species (including C freundii), Enterobacter species, Klebsiella species, P. mirabilis, P vulgaris, M. morganii, P rettgerr, Pseudomonas species, S marcescens, Bacteroides species, and anaerobic cocci (including Peptostreptococcus species and Peptococcus species) [4].
Intra-abdominal infections caused by Streptococcus species, E. coli, Klebsiella species, Bacteroides species, anaerobic cocci (including Peptostreptococcus species and Peptococcus species), P mirabilis, and Clostridium species [4].
Cefotaxime plus metronidazole is considered an appropriate combination antibiotic regimen for pediatric patients with a complicated extra-biliary intra-abdominal infection [11].
Bone and/or joint infections caused by S aureus (penicillinase and non-penicillinase producing), Streptococcus species (including S pyogenes), Pseudomonas species (including P aeruginosa), and P mirabilis [4].
Central nervous system infections (eg, meningitis and ventriculitis) caused by N meningitidis,

H influenzae, S pneumoniae, K pneumoniae, and E coli [4].

Administration

May be given by IM injection, IV push (over 3 to 5 minutes), or intermittent IV infusion.
For IV push, a concentration of 50 to 100 mg/mL may be used. For intermittent IV infusion, dilute to a concentration of 10 to 40 mg/mL and infuse over 10 to 30 minutes [6].

MEDICATION SAFETY

Contraindications/Precautions

Extravasation, including extensive perivascular, may occur causing tissue damage
requiring surgical intervention [4]
Use cautiously in patients with a history of gastrointestinal disease, especially colitis [4]
Clostridium difficile-associated diarrhea, ranging from mild diarrhea to fatal colitis, has
been reported. Discontinuation may be required [4]
Leukopenia, neutropenia, or granulocytopenia and in rare cases bone marrow
failure, pancytopenia, or agranulocytosis may occur [4]
Increased risk of allergic reaction including serious reactions requiring medical intervention
in patients with previous hypersensitivity to penicillins, other drugs, or other demonstrated
allergy [4]
Drug-resistant bacteria may develop if used in the absence of bacterial infection [4]
Use caution in the presence of renal insufficiency. Dose reductions are recommended with
CrCL less than 20 mL/min/1.73 m(2) [4]
Rapid bolus injection via a central venous catheter has resulted in life-threatening
arrhythmias [4]
A false-positive reaction for urine glucose may occur with copper reduction test. Enzymebased
tests for glycosuria are recommended [4]
Adverse Effects
Side effects are rare but include rash, phlebitis, diarrhea, leukopenia, granulocytopenia, and
eosinophilia.
In a prospective cohort study (n=4579), third generation cephalosporins started by day 3 of
life in extremely low birth weight infants (less than 1000 g) were associated with a
significantly increased risk of candidiasis compared with other antibiotics [12].
Solution Compatibility
D5W, D10W, and NS.

Terminal Injection Site Compatibility
Acyclovir, alprostadil, amikacin, aztreonam, caffeine citrate, cimetidine, clindamycin,
famotidine, gentamicin, heparin, lorazepam, magnesium sulfate, metronidazole, midazolam,
milrinone, morphine, oxacillin, penicillin g, potassium chloride, propofol, and remifentanil.
Terminal Injection Site Incompatibility
Azithromycin, fluconazole, protamine sulfate, sodium bicarbonate, and vancomycin.
Monitoring
Measuring serum concentration is not usually necessary. Periodic CBC.

MECHANISM OF ACTION/PHARMACOKINETICS
Pharmacology
Mechanism of action: Cefotaxime is one of many third-generation cephalosporin
antibiotics. The mechanism of action appears to be by bacterial cell wall disruption.
Pharmacokinetics
Metabolized in the liver to an active compound, desacetylcefotaxime. The drug distributes
widely (i.e. CSF, bile, bronchial secretions, lung tissue, ascitic fluid, middle ear). Excreted
renally as unchanged drug (20% to 36%) and active metabolite (15% to 25%) [6].
Vd: 0.64 L/kg in 100 infants with a median postnatal age of 9 days (0 to 69 days), median
gestational age of 31.5 weeks (23 to 42 weeks), postmenstrual age of 33 weeks (25 to 44
weeks), and birth weight of 1,415 g (512 g to 3,990 g) [3].
CL: 0.12 L/kg/hr (0.04 to 0.26 L/kg/hr) in 100 infants with a median postnatal age of 9 days
(0 to 69 days), median gestational age of 31.5 weeks (23 to 42 weeks), postmenstrual age of
33 weeks (25 to 44 weeks), and birth weight of 1,415 g (512 g to 3,990 g) [3].
Half-life: 3.63 hours (1.67 to 10.35 hours) in 100 infants with a median postnatal age of 9
days (0 to 69 days), median gestational age of 31.5 weeks (23 to 42 weeks), postmenstrual
age of 33 weeks (25 to 44 weeks), and birth weight of 1,415 g (512 g to 3,990 g) [3].
ABOUT
Special Considerations/Preparation

Available as powder for injection in 500-mg, 1-g, and 2-g vials.
Reconstitution
For IM use: Dilute the 500-mg, 1-g, and 2-g vials with 2, 3, and 5 mL of sterile water for
injection or bacteriostatic water for injection, respectively, for concentrations of 230, 300,
and 330 mg/mL, respectively.
For IV use: Dilute the 500-mg, 1-g, and 2-g vials with 10 mL of sterile water for injection to
yield concentrations of 50, 95, and 180 mg/mL, respectively.
Storage: Reconstituted solution for IV use is stable for 24 hours at room temperature and 7
days refrigerated. [6].

CefOXitin
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
90 to 100 mg/kg/day IV divided every 8 hours [1][2][3].
Uses
Use in neonates is generally limited to treatment of skin, intra-abdominal and urinary tract infections caused by susceptible bacteria - anaerobes (e.g. Bacteroides fragilis), gram positives (e.g. Staphylococcus aureus, Streptococcus pneumoniae, and other streptococci except enterococcus) and gram negatives (e.g. Haemophilus influenzae, Klebsiella species, E. coli, Proteus vulgaris, and Neisseria gonorrhoeae).
Administration
Give as an intermittent IV infusion at a concentration of 10 to 40 mg/mL over 15 to 60 minutes [4];[5][1][6].
MEDICATION SAFETY
Adverse Effects
Adverse effects are rare. Transient eosinophilia and elevation of hepatic transaminases have been reported in less than 3% of treated patients. Severe overdose can cause tachypnea, pallor, hypotonia, and metabolic acidosis.
Solution Compatibility
D5W, D10W, and NS.
Terminal Injection Site Compatibility

Acyclovir, amikacin, aztreonam, cimetidine, clindamycin, dopamine, famotidine, fluconazole, gentamicin, heparin, insulin, lidocaine, linezolid, magnesium sulfate, metronidazole, morphine, multivitamins, oxacillin, penicillin g, potassium chloride, propofol, ranitidine, remifentanil, sodium bicarbonate, and tobramycin.
Terminal Injection Site Incompatibility
Erythromycin lactobionate, sodium bicarbonate, and vancomycin.
Monitoring
Serum concentrations are not routinely monitored.
MECHANISM OF ACTION/PHARMACOKINETICS
Pharmacology
Broad spectrum bactericidal second generation cephalosporin that has enhanced activity against anaerobic bacteria. Inhibits bacterial cell wall synthesis by binding to one or more penicillin-binding proteins. Not inactivated by ?-lactamase. Poor CNS penetration. Highly

protein bound. Renally excreted as unchanged drug (85 to 90%). Half-life in term neonates
is approximately 1.4 hours, and 2.3 hours in preterm neonates --considerably longer than
children (0.6 hours) and adults (0.8 hours).
ABOUT
Special Considerations/Preparation
Available as powder for injection in 1-g and 2-g vials.
IV administration: Reconstitute 1-g vial with 9.5 mL sterile water for injection to a
concentration of 100 mg/mL. A 40 mg/mL dilution may be made by adding 4 mL of
reconstituted solution to 6 mL sterile water for injection, or D5W. Stable for 18 hours at room temperature or 7 days refrigerated.

CefTAZidime
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
Usual dose: 30 mg/kg/dose IV infusion or IM.
To reduce pain at IM injection site, cefTAZidime may be mixed with 1% lidocaine without
epinephrine.
Antibiotic Dosing Chart:
Renal function and drug elimination are most strongly correlated with Postmenstrual Age
(PMA; equivalent to Gestational Age plus Postnatal Age). PMA is the primary determinant of
dosing interval, with Postnatal Age as the secondary qualifier.
Dosing Interval Chart
PMA
(weeks)
PostNatal
(days)
Interval
(hours)
?29 0 to 28
>28
12
8
30 to 36 0 to 14
>14
12
8
37 to 44 0 to 7
>7
12
8
?45 ALL 8
Meningitis

0 to 7 days of age: 100 to 150 mg/kg/day IV divided every 8 to 12 hours. Smaller doses and longer intervals may needed for very low-birth weight neonates (less than 2000 g) [1].
8 to 28 days of age: 150 mg/kg/day IV divided every 8 hours. Smaller doses and longer intervals may needed for very low-birth weight neonates (less than 2000 g) [1].
Uses
Treatment of neonatal meningitis and sepsis caused by susceptible gram-negative organisms (e.g. E coli, H influenzae, Neisseria, Klebsiella, and Proteus species), especially Pseudomonas aeruginosa. Resistance among strains ofSerratia and Enterobacteriaceae is increasing.
Infective endocarditis: The following recommendations are based on a consensus of experts [4]. The full pediatric guidelines can be found here: https://doi.org/10.1161/CIR.0000000000000298
Initial Empirical Therapy or Culture-Negative Endocarditis*
Unknown Organism First-Choice Alternative Choice
Native valve (community acquired) Ampicillin/sulbactam + gentamicin
Vancomycin
"Late" prosthetic valve infection + gentamicin

with or without vancomycin
For prosthetic valve involvement, add rifAMPin
(more than 1 year after surgery)
Nosocomial endocarditis associated with vascular cannulae
Vancomycin
+ gentamicin
(with or without rifAMPin if prosthetic material present)
+ cefepime or cefTAZidime
Unknown
"Early" prosthetic valve endocarditis
(1 year or less after surgery)
* Culture-negative endocarditis (CNE): generally, attempt to culture the infecting organism for at least 48 hours. Severely ill children need immediate treatment. Consider infectious disease consultation for CNE
Baltimore, 2015
Organism Directed Therapy
Organism First-Choice Alternative Choice
Streptococci
Highly susceptible to penicillin G (MBC 0.1 mcg/mL or less); includes most viridans streptococci,

groups A, B, C, G nonenterococcal, group D streptococci (S bovis, S equinus)
Penicillin G or
CefTRIAXone
Vancomycin or
First-generation cephalosporin or
CefTRIAXone
Relatively resistant to penicillin (MBC 0.2 mcg/mL or more); less-susceptible viridans streptococci or enterococci
Penicillin G or
Ampicillin +
Gentamicin (for first 2 weeks, or entire course for enterococci)
Vancomycin +
Gentamicin for enterococci
Ampicillin +
CefTRIAXone (for aminoglycoside (AMG)-resistant enterococci or AMG-intolerant patient)
CefTRIAXone +
gentamicin (not for enterococcal endocarditis)
Resistant to penicillin Consult an infectious disease specialist.

Staphylococci (S aureus or coagulase-negative staphylococci)
Penicillin G susceptible (1 mcg/mL or less) (rare)
Penicillin G Oxacillin or
Nafcillin or
First-generation cephalosporin or
Vancomycin
Penicillin G resistant (0.1 mcg/mL)
Oxacillin or
Nafcillin
with or without
Gentamicin
Vancomycin (for those highly allergic to betalactam antibiotics) or
First-generation cephalosporin
Oxacillin (MRSA) resistant (4 mcg/mL)
Vancomycin Daptomycin for rightsided endocarditis, maybe for left-sided
Vancomycin resistant or intolerant Daptomycin Unknown
When prosthetic material present add riFAMpin + gentamicin (for first 2 weeks) for all staphylococci

Gram-negative enteric bacilli CefTAZidime or
Cefepime or
Cefotaxime or
CefTRIAXone
Plus gentamicin (or
tobramycin or
amikacin, depending
on susceptibility)
Broad-spectrum penicillin
Plus gentamicin (or
tobramycin or amikacin)
HACEK group
CefTRIAXone or
Cefotaxime or
Ampicillin-sulbactam
Ampicillin (when
susceptible)
Plus aminoglycoside
KEY: AMG = aminoglycosides; HACEK = Haemophilus species, Aggregatibacter species, Cardiobacterium hominis, Eikenella corrodens, and Kingella species; MBC = minimum bactericidal concentration, MRSA = methicillin-resistant Staphylococcus aureus (includes resistance to oxacillin, nafcillin, and cephalosporins)
Baltimore, 2015
Administration
Intravenous
IV push over 3 to 5 minutes at a maximum concentration of [2] 100 mg/mL [3] or 200 mg/mL [2].
Intermittent IV infusion over 30 minutes at a concentration of 1 to 40 mg/mL [2] as well as 50 mg/mL [3].
Intramuscular
Deep IM administration into a large muscle mass for less serious infections [2].
MEDICATION SAFETY
Adverse Effects
Reported adverse effects are uncommon but include rash, diarrhea, elevated hepatic transaminases, eosinophilia, and positive Coombs' test.
In a prospective cohort study (n=4579), third generation cephalosporins started by day 3 of life in extremely low birth weight infants (less than 1000 g) were associated with a significantly increased risk of candidiasis compared with other antibiotics [5].
Solution Compatibility
D5W, D10W, and NS.
Terminal Injection Site Compatibility

Acyclovir, amikacin, aminophylline, aztreonam, cimetidine, clindamycin, dobutamine, dopamine, enalaprilat, epinephrine, esmolol, famotidine, furosemide, gentamicin, heparin, ibuprofen lysine, linezolid, metronidazole, milrinone, morphine, potassium chloride, propofol, ranitidine, remifentanil, sodium bicarbonate, tobramycin, and zidovudine.

Terminal Injection Site Incompatibility

Amiodarone, azithromycin, erythromycin lactobionate, fluconazole, midazolam, nicardipine, phenytoin, and vancomycin.

Monitoring

Measuring serum concentration is not usually necessary.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of action: CefTAZidime is a third-generation cephalosporin with activity against Pseudomonas species. It is bactericidal in action, and inhibits enzymes responsible for cellwall synthesis [6].

Distribution: Widely in body tissues and fluids (ie, CSF, bile, bronchial secretions, lung tissue, ascitic fluid, middle ear). Protein binding is low (less than 10%) [6].

Excretion: Unchanged in the urine (80% to 90%) [6].

Half-Life (adults): Serum half-life following IV administration is approximately 1.9 hours. Half-life significantly longer in patients with renal impairment [6].

ABOUT

Special Considerations/Preparation

Available as powder for injection in 500-mg and 1-g, 2-g, and 6-g vials.

Intravenous solution: Reconstitute 500-mg vial with 10 mL of sterile water for injection to make a concentration of 50 mg/mL. Reconstituted solution stable for 12 hours at room temperature, 3 days refrigerated.

Intramuscular solution: Prepared by reconstituting 500-mg vial with 2.2 mL of 1% lidocaine without epinephrine or Sterile Water to a concentration of 200 mg/mL. Solution is stable for 12 hours at room temperature, 3 days refrigerated.

All vials contain sodium carbonate; when reconstituted, carbon dioxide bubbles will form.

Using a vented needle may help reduce spraying and leaking.

CefTRIAXone
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
Sepsis: 50 mg/kg IV every 24 hours.
Meningitis: 100 mg/kg IV loading dose, then 80 mg/kg IV every 24 hours.
Gonococcal Infections
Disseminated Gonococcal Infections and Scalp Abscesses: 25 to 50 mg/kg/day IV/IM
in a single daily dose for 7 days, with a duration of 10 to 14 days if meningitis is documented
[1].
Gonococcal Infection: 25 to 50 mg/kg (maximum 125 mg) IV/IM as a single dose [1].
Uncomplicated Gonococcal Ophthalmia: 25 to 50 mg/kg (maximum 125 mg) IV/IM
as a single dose. (Note: topical antibiotic therapy alone is inadequate and is unnecessary if
systemic treatment is given.) [1]
Uses
Gonococcal Infections
Recommended for the treatment of gonococcal ophthalmia neonatorium,
disseminated gonococcal infection, gonococcal scalp abscess, and presumptive
gonococcal infection in neonates born to mothers with untreated gonorrhea and at a high
risk for infection. A single dose of ceftriaxone is also effective for ophthalmia neonatorum
prophylaxis when erythromycin ointment is not available [1].
Infective endocarditis: The following recommendations are based on a consensus of
experts [3]. The full pediatric guidelines can be found here:
https://doi.org/10.1161/CIR.0000000000000298
Organism Directed Therapy
Organism First-Choice Alternative Choice
Streptococci
Highly susceptible to penicillin G (MBC 0.1 mcg/mL or less); includes most viridans streptococci,
groups A, B, C, G nonenterococcal, group D streptococci (S bovis, S equinus)
Penicillin G or
CefTRIAXone
Vancomycin or
First-generation cephalosporin or
CefTRIAXone

Relatively resistant to penicillin (MBC 0.2 mcg/mL or more); less-susceptible viridans streptococci or enterococci
Penicillin G or Ampicillin + Gentamicin (for first 2 weeks, or entire course for enterococci)
Vancomycin + Gentamicin for enterococci
Ampicillin + CefTRIAXone (for aminoglycoside (AMG)-resistant enterococci or AMG-intolerant patient)
CefTRIAXone +

gentamicin (not for enterococcal endocarditis)
Resistant to penicillin Consult an infectious disease specialist.

Staphylococci (S aureus or coagulase-negative staphylococci)
Penicillin G susceptible (1 mcg/mL or less) (rare)
Penicillin G Oxacillin or Nafcillin or First-generation cephalosporin or Vancomycin
Penicillin G resistant (0.1 mcg/mL)
Oxacillin or Nafcillin with or without Gentamicin
Vancomycin (for those highly allergic to betalactam antibiotics) or First-generation cephalosporin
Oxacillin (MRSA) resistant (4 mcg/mL)
Vancomycin Daptomycin for rightsided endocarditis, maybe for left-sided
Vancomycin resistant or intolerant Daptomycin Unknown
When prosthetic material present add riFAMpin + gentamicin (for first 2 weeks) for all staphylococci
Gram-negative enteric bacilli
CefTAZidime or Cefepime or

Cefotaxime or
CefTRIAXone
Plus gentamicin (or
tobramycin or
amikacin, depending
on susceptibility)
Broad-spectrum penicillin
Plus gentamicin (or
tobramycin or amikacin)
HACEK group
CefTRIAXone or
Cefotaxime or
Ampicillin-sulbactam
Ampicillin (when
susceptible)
Plus aminoglycoside
KEY: AMG = aminoglycosides; HACEK = Haemophilus species, Aggregatibacter species, Cardiobacterium hominis, Eikenella corrodens, and Kingella species; MBC = minimum bactericidal concentration, MRSA = methicillin-resistant Staphylococcus aureus (includes resistance to oxacillin,
nafcillin, and cephalosporins)
Baltimore, 2015
Meningitis
Treatment of neonatal meningitis caused by susceptible gram-negative organisms (e.g. E coli, Pseudomonas, Klebsiella, H influenzae).
CefTRIAXone is contraindicated due to the risk of kernicterus in neonates [4]
Sepsis
Treatment of neonatal sepsis caused by susceptible gram-negative organisms (e.g. E coli, Pseudomonas, Klebsiella, H influenzae).
Optimal treatment for suspected, early-onset sepsis is broad-spectrum antimicrobial coverage using a combination of ampicillin and an aminoglycoside (usually gentamicin); once a pathogen is identified, therapy should be narrowed unless synergism is required.
CefTRIAXone is contraindicated due to the risk of kernicterus in neonates [4].
There was no difference in failure rate between a 7-day vs 10-day duration of empiric

treatment with IV cefTRIAXone and amikacin for culture-proven sepsis in 132 neonates, 1.5 kg or more and gestational age 32 weeks or more, who remitted clinically by day 5 in a randomized study. The follow-up period was 28 days. The median age at presentation was 3 days (2 to 4 days) and 56.8% had early-onset sepsis. The majority of organisms in blood

cultures were Klebsiella spp. (40.9%), Staphylococcus aureus (22.7%), Enterobacter spp. (16.7%), and MRSA (7.6%) [5].

Administration

Intravenous:Administer over 60 minutes at a concentration of 10 to 40 mg/mL (lower concentrations may be used, if necessary). Do not mix with calcium-containing solutions in the same IV line; precipitation may occur [2]. Avoid administration of calcium-containing solutions or products within 48 hours of the last administration of cefTRIAXone.

Intramuscular: To reduce pain at the injection site, reconstitute with 1% lidocaine without epinephrine to a final concentration of 250 mg/mL or 350 mg/mL.

MEDICATION SAFETY

Contraindications/Precautions

Contraindications[2]

Contraindicated in premature neonates.

Contraindicated for use in neonates with hyperbilirubinemia. Displaces bilirubin from albumin binding sites, resulting in higher free bilirubin serum concentrations.

Concurrent administration of cefTRIAXone andIV calcium-containing solutions (including parenteral nutrition) or products in neonates is contraindicated. There have been a small number of fatal cases of cardiorespiratory arrest in young infants, with 6 deaths, associated with concurrent administration of cefTRIAXone and calciumcontaining intravenous solutions. In all cases, the cefTRIAXone dose (150 to 200 mg/kg/day) significantly exceeded the FDA recommended dose and/or was administered IV push. Crystalline material was noted in vascular beds on autopsy (lungs and kidneys) in 4 of the 5 infants for which results were available

Lidocaine added to IV cefTRIAXone solutions is contraindicated.

[2].

Precautions

Serious and occasionally fatal hypersensitivity reactions have occurred [2].

Clostridium difficile associated diarrhea has been reported [2].

Hematologic: Methemoglobinemia has been reported; risk factors are glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites [6].

Hemolytic anemia, resulting in profound morbidity and fatalities, has been reported in

children receiving cefTRIAXone. The majority of cases have occurred in patients with immune deficiencies or sickle cell disease; all patients had previous exposure to cefTRIAXone [7][8] [9].

Prothrombin time alteration in patients with impaired vitamin K synthesis or low vitamin K stores [2]
Presence of both hepatic dysfunction and renal disease[2].
Pediatric patients are at a greater risk of gallbladder pseudolithiasis (ceftriaxone-calcium precipitates) [2].
Pediatric patients are at a greater risk of ceftriaxone-calcium precipitates in the urinary tract, which may present as urolithiasis, and ureteral obstruction and post-renal acute renal failure[2].
biliary stasis and biliary sludge risk factors, such as preceding major therapy, severe illness, and total parenteral nutrition; increased risk of pancreatitis, possibly secondary to biliary obstruction [2]

Adverse Effects

Eosinophilia, thrombocytosis, leukopenia. Increase in bleeding time. Diarrhea. Increase in BUN and serum creatinine. Increase in AST and ALT. Skin rash. Transient gallbladder precipitations occasionally associated with colicky abdominal pain, nausea, and vomiting.
In a prospective cohort study (n=4579), third generation cephalosporins started by day 3 of life in extremely low birth weight infants (less than 1000 g) were associated with a significantly increased risk of candidiasis compared with other antibiotics [10].

Solution Compatibility

D5W, D10W, and NS.

Solution Incompatibility

Any calcium-containing solution.

Terminal Injection Site Compatibility

Acyclovir, amikacin, amiodarone, aztreonam, clindamycin, famotidine, gentamicin, heparin, linezolid, metronidazole, morphine, potassium chloride, propofol, remifentanil, sodium bicarbonate, and zidovudine.

Terminal Injection Site Incompatibility

Aminophylline, azithromycin, calcium chloride, calcium gluconate, caspofungin, fluconazole and vancomycin.

Monitoring
Monitor prothrombin time in high risk patients (eg, chronic hepatic disease and malnutrition).
Frequently monitor coagulation parameters during concomitant vitamin K antagonist therapy.
Monitor for signs and symptoms of gallbladder disease [2].
CBC for eosinophilia, thrombocytosis, leukopenia. Serum electrolytes, BUN, creatinine. AST, ALT, bilirubin. Consider abdominal ultrasonography.
MECHANISM OF ACTION/PHARMACOKINETICS
Pharmacology
cefTRIAXone is one of many third-generation cephalosporin antibiotics. The drug distributes widely (i.e. CSF, bile, bronchial secretions, lung tissue, ascitic fluid, middle ear). It is eliminated unchanged by both biliary (40%) and renal mechanisms. Serum half-life in premature infants is 5 to 16 hours. Dosage adjustment is necessary only for patients with combined hepatic and renal failure.
ABOUT
Special Considerations/Preparation
Intravenous solution: Available as a powder for injection in 250-mg, 500-mg, 1-g, and 2-g vials. Prepared by reconstituting powder with compatible solution (sterile water for injection, D5W, or D10W) to a concentration of 100 mg/mL. Reconstituted solution is stable for 2 days at room temperature, 10 days refrigerated. A dark color may appear after reconstitution; however, potency is retained.
To make 40-mg/mL solution add 6.2 mL to the 250-mg vial.
Intramuscular solution: Prepared by reconstituting 250-mg vial with 0.9 mL of 1% lidocaine without epinephrine to a concentration of 250 mg/mL. Solution is stable for 24 hours at room temperature, 3 days refrigerated.

Chloral hydrate
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
Oral and rectal products are no longer manufactured in the US [1]. Due to long halflife, unpredictable responses, and reported deaths, chloral hydrate is a poor choice as a sedating agent for procedures [2][3].
25 to 75 mg/kg per dose orally or rectally.

Uses
Oral and rectal products are no longer manufactured in the US[1].
Sedative/hypnotic for short-term use only. Chloral hydrate has no analgesic properties;
excitement may occur in patients with pain.
Administration
Oral: Oral preparation should be diluted or administered after a feeding to reduce gastric irritation [4].
Rectal: The oral preparation may be given rectally [5][6].
MEDICATION SAFETY
Contraindications/Precautions
Contraindicated in patients with significant hepatic or renal impairment, and in those with
severe cardiac disease. Oral administration not recommended in patients with esophagitis,
gastritis, or gastric or duodenal ulcers [7][4].
Adverse Effects
Episodes of bradycardia are more frequent for up to 24 hours after a single dose in former
premature infants. Gastric irritation and paradoxical excitement may also occur after a single
dose. Other toxic effects have generally been reported in patients who received either
repeated doses at regular intervals or acute overdoses. These effects may persist for days
and include CNS, respiratory, and myocardial depression; cardiac arrhythmias; and ileus and
bladder atony. Indirect hyperbilirubinemia may occur because trichloroethanol and bilirubin

compete for hepatic conjugation.
Monitoring
Assess level of sedation.
MECHANISM OF ACTION/PHARMACOKINETICS
Pharmacology
Well absorbed from the oral route, with the onset of action in 10 to 15 minutes. Chloral
hydrate is rapidly converted by alcohol dehydrogenase to the active and potentially toxic
metabolite trichloroethanol (TCEt), which is excreted renally after glucuronidation in the liver.
It is also metabolized to trichloroacetic acid (TCA), which is carcinogenic in mice when given
in very high doses. Both TCEt (8 to 64 hours) and TCA (days) have long serum half-lives in
neonates and accumulate with repeated doses.
ABOUT
Special Considerations/Preparation
Oral and rectal products are no longer manufactured in the US[1].

Chloramphenicol
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
In very low-birth weight neonates (less than 2000 g), lower doses and less frequent administration are recommended [1].
0 to 7 days of age: 25 mg/kg/day IV once daily [1].
8 to 28 days: 50 mg/kg/day IV divided every 12 to 24 hours [1].
Uses
A wide-spectrum antimicrobial bacteriostatic agent. May be bactericidal to species such as H influenzae and Neisseria meningitidis .
Anthrax: Chloramphenicol (for 32 weeks or more gestational age) Should only be used when other options are unavailable. Use as part of a triple regimen for systemic anthrax (meningitis or disseminated infection or meningitis cannot be ruled out). Duration: For anthrax, for 2 to 3 weeks or more until stable. Continue antimicrobial course of prophylaxis (usually oral therapy) for up to 60 days[5].
Bacterial meningitis: An alternative agent for bacterial meningitis due to Streptococcus pneumoniae when penicillin MIC is less than 0.1 mcg/mL, Neisseria meningitidis when penicillin MIC is less than 1 mcg/mL, and Haemophilus influenza (?-lactamase negative or positive) [6][1].
Administration
For IV intermittent infusion, dilute to a concentration of 20 to 25 mg/mL in compatible solution and infuse over 15 to 60 minutes [2][3].
In the preparation and administration of injections, the National Institute for Occupational Safety and Health (NIOSH) recommends the use of double gloves and a protective gown.
Prepare in a biological safety cabinet or a compounding aseptic containment isolator; eye/face and respiratory protection may be needed.
Prepare compounds in a closed system drug transfer device. During administration, if there is a potential that the substance could splash or if the patient may resist, use eye/face protection. Administer certain dosage forms via a closed system drug transfer device [4].
MEDICATION SAFETY

Adverse Effects
Reversible bone marrow suppression, irreversible aplastic anemia. Serum concentration greater than 50 mcg/mL has been associated with the "gray baby" syndrome (ie, abdominal distention, pallid cyanosis, vasomotor collapse; may lead to death within hours of onset).
Fungal overgrowth.
Black Box Warning
According to the manufacturer's black box warning, serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) are known to occur. There have been reports of aplastic anemia which later terminated in leukemia.
Blood dyscrasias have occurred after both short-term and prolonged therapy with this drug.
It is essential that adequate blood studies be made during treatment. If blood dyscrasias occur, therapy should be discontinued.
Solution Compatibility
D5W, D10W, and NS.
Terminal Injection Site Compatibility
Acyclovir, amikacin, aminophylline, ampicillin, calcium chloride, calcium gluconate, dopamine, enalaprilat, esmolol, heparin, hydrocortisone succinate, lidocaine, magnesium sulfate, metronidazole, morphine, nafcillin, nicardipine, oxacillin, penicillin G, pentobarbital, potassium chloride, ranitidine, sodium bicarbonate, and vitamin K1.
Terminal Injection Site Incompatibility
Erythromycin lactobionate, fluconazole, metoclopramide, phenytoin, and vancomycin.
Monitoring
Close monitoring of serum concentration is mandatory. Small changes in dose and interval can lead to disproportionately large changes in serum concentration. Therapeutic peak serum concentration: 10 to 25 mcg/mL. Monitor CBC and reticulocyte counts. Assess hepatic and renal function.

MECHANISM OF ACTION/PHARMACOKINETICS
Pharmacology
Both esters (succinate and palmitate) are biologically inactive prodrugs. Hydrolysis to the active compound is erratic in newborns. Metabolized by hepatic glucuronyl transferase.
Hepatically and renally eliminated. Inhibits metabolism of phenobarbital, phenytoin, and other agents.
ABOUT
Special Considerations/Preparation

Chloramphenicol succinate is available as powder for injection in a 1-g vial. Contains 52 mg (2.25 mEq) of sodium per gram. Reconstitute with 10 mL sterile water for injection or D5W to a concentration of 100 mg/mL. For IV intermittent infusion, further dilute to a concentration of 20 to 25 mg/mL in compatible solution.

Chlorothiazide

DOSING/ADMINISTRATION

Dose

Diuresis: 10 to 20 mg/kg/dose orally every 12 hours.

Diabetes insipidus: 5 mg/kg/dose orally every 12 hours [1].

Administer with food (improves absorption).

IV administration not recommended because of a lack of data.

Note: Do not confuse with hydrochlorothiazide.

Uses

Bronchopulmonary dysplasia (BPD): May improve pulmonary function in patients with BPD; typically a thiazide and spironolactone are used together [2]. In oxygen-dependent infants who were on ventilator support over thirty days (n=43), chlorothiazide (40 mg/kg/day orally in 2 divided doses) in combination with spironolactone (4 mg/kg/day orally in 2 divided doses) until supplemental oxygen was discontinued was associated with improved pulmonary function and decreased fractional oxygen requirement, but was not associated with a decrease in duration of oxygen requirement when compared with placebo [3]. Thiazide diuretics may be appropriate for improving lung mechanics in ventilator-dependent preterm infants greater than 3 weeks of age [4][5].

Diabetes insipidus: Thiazide diuretics are recommended to treat central and/or nephrogenic diabetes insipidus [1][6][7][8].

Edema and Hypertension: Diuretic used in treating both mild to moderate edema and mild to moderate hypertension. Effects increased when used in combination with furosemide or spironolactone.

Heart Failure: In neonates with pulmonary hypertension, supportive care with diuretics may be used cautiously for signs of right-sided heart failure [9].

MEDICATION SAFETY

Adverse Effects

Hypokalemia and other electrolyte abnormalities. Hyperglycemia. Hyperuricemia.

Do not use in patients with significant impairment of renal or hepatic function.

Solution Compatibility
D5W and NS.
Terminal Injection Site Compatibility
Alprostadil.
Monitoring
Serum electrolytes, calcium, phosphorus, and glucose; urine output and blood pressure.
MECHANISM OF ACTION/PHARMACOKINETICS
Pharmacology
Limited data in neonates. Variable absorption from GI tract. Onset of action within 1 hour. Elimination half-life depends on GFR, and is approximately 5 hours. Major diuretic effect results from inhibition of sodium reabsorption in the distal nephron. Increases urinary losses of sodium, potassium, magnesium, chloride, bicarbonate, and phosphorus. Decreases renal excretion of calcium. Inhibits pancreatic release of insulin. Displaces bilirubin from albumin binding sites.
ABOUT
Special Considerations/Preparation
Available: 250 mg/5mL suspension for oral use and 500-mg vial as lyophilized powder for injection.
Preparation of IV
Reconstitute 500-mg vial with 18 mL (never less) of sterile water for injection to make a concentration of 28 mg/mL. Use solution immediately after reconstitution; discard unused portion. May further dilute in compatible solution for IV infusion (D5W and NS).

Cimetidine
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
2.5 to 5 mg/kg/dose every 6 to 12 hours orally or IV infusion over 15 to 20 minutes.
Uses
Prevention and treatment of stress ulcers and GI hemorrhage aggravated by gastric acid secretion.
Apnea of prematurity: Reducing gastric acidity or increasing gastric motility for the sole

purpose to reduce apnea episodes is not supported by the literature [3].
Crying and irritability: In otherwise healthy term infants, histamine2 receptor antagonists or proton pump inhibitors should not be used for the treatment of crying and distress [4].
Gastroesophageal Reflux (GER): The risks associated with acid reducing agents outweighs the benefits in preterm infants for GER. Acid blocking agents should not be used and if used in preterm infants, use sparingly [5]. In otherwise healthy term infants, histamine2 receptor antagonists or proton pump inhibitors should not be used for the treatment of visible regurgitation [4].
Gastroesophageal Reflux Disease (GERD): Proton pump inhibitors (PPIs) are the firstline agents for erosive esophagitis in infants and children with GERD. Histamine2 receptor antagonists are the second-line agent if PPIs are not available or are contraindicated. A duration of treatment for 4 to 8 weeks for GERD symptoms is recommended. Regularly reassess the need for long-term acid suppression. If no response after 4 to 8 weeks, then reevaluate for other causes of symptoms. H2RAs and PPIs are not recommended for extraesophageal symptoms (e.g. cough, wheezing, asthma), unless GERD symptoms are present and/or GERD has been diagnosed [4].
A trial use of PPIs as a diagnostic test for GERD is not recommended in infants or in patients presenting with extraesophageal symptoms. However, in children with typical GERD symptoms, a trial of 4 to 8 weeks with a PPI may be used as a diagnostic test [4].
Administration
Intermittent IV infusion: Dilute in D5W or other compatible solution to a final concentration of 6 mg/mL and infuse over 15 to 20 minutes [1].
Oral: Administer doses with meals and at bedtime. Do not administer simultaneously with antacids since antacids may interfere with cimetidine absorption [2].
MEDICATION SAFETY

Contraindications/Precautions
CONTRAINDICATIONS
Contraindicated in patients receiving cisapride due to precipitation of life-threatening arrhythmias. Cardiac arrhythmias and hypotension have been reported following the rapid IV bolus administration of cimetidine [2].

PRECAUTIONS
Infection: Increased risk of infections (necrotizing enterocolitis, pneumonia, upper respiratory tract infections, sepsis, urinary tract infections, and Clostridium difficile infections) in infants and children on H2 blockers or PPIs demonstrated in case-control studies [4][7].
Adverse Effects
Known adverse effects of cimetidine in adults include mental confusion, seizures, thrombocytopenia, neutropenia, nausea, vomiting, diarrhea, gynecomastia, rash, and muscular pain. Cimetidine has been reported to increase the serum level and potentiate toxicity of other drugs such as chlordiazepoxide, diazepam, lidocaine, metronidazole, nifedipine, phenytoin, propranolol, theophylline, warfarin, and certain tricyclic antidepressants [2][8][9].
The use of H2-blockers in preterm infants has been associated with facilitating Candida species colonization [10], and an increased risk for late-onset bacterial and fungal sepsis [11] [10].
In a prospective, multicenter, observational study comparing VLBW neonates receiving raNITIdine (n=91) to those not receiving raNITIdine (n=183), neonates receiving raNITIdine had an increased rate of infection (37.4% versus 9.8%; OR 5.5; 95% CI, 2.9 to 10.4), increased risk for NEC (9.8% versus 1.6%; OR 6.6; 95% CI, 1.7 to 25), and increased mortality (9.9% versus 1.6%) [12].
In a retrospective, case-control study, H2-blocker use in VLBW infants was associated with an increased incidence of NEC (OR 1.7; 95% CI, 1.34 to 2.19) [13].
Solution Compatibility
D5W, D10W, and NS.
Terminal Injection Site Compatibility
Acetazolamide, acyclovir, amikacin, aminophylline, ampicillin, atropine, aztreonam, caffeine citrate, cefotaxime, cefoxitin, ceftazidime, clindamycin, dexamethasone, diazepam, digoxin, enalaprilat, epinephrine, erythromycin lactobionate, esmolol, fentanyl, fluconazole, flumazenil, furosemide, gentamicin, glycopyrrolate, heparin, insulin, isoproterenol, lidocaine, linezolid, lorazepam, meperidine, meropenem, metoclopramide, midazolam, milrinone, morphine, nafcillin, nicardipine, nitroprusside, pancuronium, penicillin G, piperacillin/tazobactam, potassium chloride, propofol, prostaglandin E1 , protamine,

remifentanil, sodium bicarbonate, vancomycin, vecuronium, vitamin K1, and zidovudine.
Terminal Injection Site Incompatibility
Amphotericin B (Immediate precipitation occurs), cefazolin, cefepime, indomethacin, and pentobarbital.
Monitoring
Consider esophageal pH monitoring to assess for efficacy (pH greater than 4) [6]. Observe for impaired consciousness and reduced spontaneous movements.
MECHANISM OF ACTION/PHARMACOKINETICS
Pharmacology
Inhibits gastric acid secretion by histamine H2-receptor antagonism. Peak inhibition occurs in 15 to 60 minutes after both oral and IV administration. Metabolized in the liver via sulfation and hydroxylation to inactive compounds that are 90% renally eliminated. Half-life in neonates is 1.1 to 3.4 hours, and is prolonged in patients with renal or hepatic insufficiency. The sulfoxide metabolite may accumulate in the CNS and cause toxicity. Antacids interfere with absorption; therefore, concomitant administration is not recommended.
ABOUT
Special Considerations/Preparation
Available as a 150-mg/mL injectable solution in 2-mL single-use vials and 8-mL multidose vials. A 15-mg/mL dilution may be made by adding 1 mL of 150 mg/mL concentration to 9 mL of preservative-free normal saline. Dilution stable for 48 hours. Manufacturer's oral solution (60 mg/mL) contains 2.8% alcohol. A 2.4 mg/mL oral dilution may be prepared by adding 1 mL (60 mg) of manufacturer's oral solution to 24 mL of sterile water. Stable for 14 days refrigerated. Also available in 200-, 300-, 400-, and 800-mg tablets.

Clindamycin
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
Usual dose: 5 to 7.5 mg/kg/dose IV infusion or orally. Increase dosing interval in patients with significant liver dysfunction.
Antibiotic Dosing Chart:
Renal function and drug elimination are most strongly correlated with Postmenstrual Age

(PMA; equivalent to Gestational Age plus Postnatal Age). PMA is the primary determinant of dosing interval, with Postnatal Age as the secondary qualifier.

Dosing Interval Chart

PMA (weeks)	PostNatal (days)	Interval (hours)
?29	0 to 28	>28
		12
		8
30 to 36	0 to 14	>14
		12
		8
37 to 44	0 to 7	>7
		12
		8
?45	ALL	6

Anthrax:[1]

32 up to 34 weeks gestational age

0 to 1 week of age: 5 mg/kg/dose IV or orally every 12 hours

1 to 4 weeks of age: 5 mg/kg/dose IV or orally every 8 hours

34 weeks gestational age or older

0 to 1 week of age: 5 mg/kg/dose IV or orally every 8 hours

1 to 4 weeks of age: 5 mg/kg/dose IV or orally every 6 hours

Duration: Duration: For 14 days or longer until stable as combination therapy for systemic anthrax when meningitis is ruled out. For 2 to 3 weeks or more until stable as triple therapy for systemic anthrax (anthrax meningitis or disseminated infection and meningitis cannot be ruled out). For naturally-acquired cutaneous infection, 7 to 10 days. Continue antimicrobial course of prophylaxis (usually oral therapy) for up to 60 days [1].

Uses

Bacteriostatic antibiotic used for the treatment of bacteremia and pulmonary and deep tissue infections caused by anaerobic bacteria and some gram-positive cocci.

Clindamycin should not be used in the treatment of meningitis due to inadequate perfusion into the CSF [4].

Anthrax[1]:
Postexposure prophylaxis for Bacillus anthracis(Oral)
Penicillin-resistant strains or prior to susceptibility testing
Preferred: Ciprofloxacin. Alternatives in order of preference: clindamycin, doxycycline (not for neonates 37 weeks gestation or younger), or levofloxacin.
Penicillin-susceptible strains
Preferred: Amoxicillin. Alternative: penicillin VK.
Cutaneous Anthrax treatment, without systemic involvement (Oral)
All strains, regardless of penicillin susceptibility or if susceptibility is unknown
Preferred: Ciprofloxacin. Alternatives in order of preference: doxycycline (not for neonates 37 weeks gestation or younger), clindamycin, levofloxacin.
Alternatives for penicillin-susceptible strains
Preferred: Amoxicillin. Alternative: penicillin VK.
Systemic Anthrax when meningitis can be ruled out (IV)
Combination IV Therapy
Preferred: Ciprofloxacin. Alternatives in order of preference: meropenem, levofloxacin, imipenem/cilastatin, or vancomycin. If strains are penicillin-susceptible, then penicillin G (preferred) or ampicillin (alternative).
Plus
Preferred: Clindamycin. Alternatives in order of preference: linezolid, doxycycline (not for neonates 37 weeks gestation or younger), or rifampin.
Systemic Anthrax (meningitis or disseminated infection and meningitis cannot be ruled out) (IV)
Triple IV Therapy
Preferred: Ciprofloxacin. Alternatives in order of preference: levofloxacin or moxifloxacin
Plus
Preferred: Meropenem. Alternatives in order of preference: imipenem/cilastatin or doripenem. If strains are penicillin-susceptible, then penicillin G (preferred) or ampicillin (alternative).
Plus
Preferred: Linezolid. Alternatives in order of preference: clindamycin or rifampin or as a last resort, chloramphenicol
Oral follow-up therapy for severe anthrax
Combination Oral Therapy
Preferred: Ciprofloxacin. Alternative: levofloxacin.
If strains are penicillin-susceptible, amoxicillin (preferred) or penicillin VK (alternative).
Plus
Preferred: Clindamycin. Alternatives in order of preference: doxycycline (not for

neonates 37 weeks gestation or younger) or linezolid.
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Administration
Infuse IV over 10 to 60 minutes, not to exceed 30 mg/min, at a concentration not to exceed 18 mg/mL[2]. The recommended standard concentration for neonates is 6 mg/mL [3].
MEDICATION SAFETY
Contraindications/Precautions
Contraindicated in patients with a history of lincomycin allergies [4].
Concomitant use with erythromycin is not recommended [5][4].
Exercise caution in patients with a history of gastrointestinal disease, particularly colitis [5].
Anaphylactic and severe hypersensitivity reactions (eg, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, and Steven-Johnson syndrome), sometimes fatal, have been reported. Discontinue use upon occurrence [5][4].
Use cautiously in patients with a history of atopy [5].
Superinfections may occur, especially yeast overgrowth [5][4].
Not recommended for treatment of meningitis. Clindamycin does not adequately diffuse into CSF [5].
Adverse Effects
Hypersensitivity reactions, and jaundice and liver function test abnormalities have been reported in association with clindamycin therapy.
Should not be used in combination with topical or oral erythromycin-containing products due to possible antagonism.
Black Box Warning
Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clindamycin, and may range in severity from mild to life-threatening. Because clindamycin therapy has been associated with severe colitis which may end fatally, it should be reserved for serious infections where less toxic antimicrobial agents are inappropriate. Diarrhea, colitis, and pseudomembranous colitis have been observed to begin up to several weeks following cessation of therapy with clindamycin. If pseudomembranous colitis is suspected or confirmed, consider discontinuation of clindamycin and initiate appropriate fluid and electrolyte management, protein supplementation, C. difficile antibiotic treatment, and surgical evaluation as clinically indicated.

Solution Compatibility

D5W, D10W, and NS.
Terminal Injection Site Compatibility
Acyclovir, amikacin, amiodarone, ampicillin, aztreonam, caffeine citrate, cefazolin, cefepime, cefotaxime, cefoxitin, ceftazidime, ceftriaxone, cimetidine, enalaprilat, esmolol, gentamicin, heparin, hydrocortisone succinate, linezolid, magnesium sulfate, metoclopramide, metronidazole, midazolam, milrinone, morphine, netilmicin, nicardipine, penicillin G, piperacillin, piperacillin/tazobactam, potassium chloride, propofol, prostaglandin E1, ranitidine, remifentanil, sodium bicarbonate, tobramycin, and zidovudine.
Terminal Injection Site Incompatibility
Aminophylline, azithromycin, barbiturates, caspofungin, fluconazole, and phenytoin.
Monitoring
Assess liver function. Monitor GI status closely. Therapeutic serum concentration ranges from 2 to 10 mcg/mL (bioassay yields variable results).
MECHANISM OF ACTION/PHARMACOKINETICS
Pharmacology
Clindamycin inhibits bacterial protein synthesis and is primarily bacteriostatic at therapeutically attainable concentrations. Widely distributed into most tissues, especially the lung. Poor cerebrospinal fluid penetration. Oral clindamycin is completely absorbed from the gastrointestinal tract. Highly protein bound. Almost complete metabolism in the liver, with excretion via bile and feces. Available data in neonates suggest extremely variable clearance, especially in premature infants. No data are available regarding conversion of ester to active drug.
ABOUT
Special Considerations/Preparation
Oral
Availability: Clindamycin palmitate hydrochloride powder for solution to make a 75 mg/5 mL (15 mg/mL) solution when reconstituted with water.

Do not refrigerate. Stable at room temperature for 2 weeks.
Injection
IV preparation (clindamycin phosphate) is available as a 150 mg/mL solution in 2-mL, 4-mL,

and 6-mL vials containing 9.45 mg/mL benzyl alcohol. It should be diluted using D5W, NS, or LR to a maximum concentration of 18 mg/mL, and infused at a rate no greater than 30 mg/min. Also available in premixed bags (50 mL) without benzyl alcohol containing 300 mg, 600 mg or 900 mg of clindamycin.

CloNIDine

NeoFax Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Neonatal Abstinence Syndrome; Adjunct

35 weeks GA or older: Initial, 0.5 to 1 mcg/kg, followed by 0.5 to 1.25 mcg/kg/dose orally every 4 to 6 hours [1][2][3][4]. Discontinue based on NAS scores and patient stability.

Uses

Neonatal abstinence syndrome, adjunct: CloNIDine has been used as an adjunct to tincture of opium in neonates with intrauterine exposure to heroin or methadone. In a prospective, randomized, double-blind, placebo-controlled trial, infants 35 weeks GA and older receiving tincture of opium with oral cloNIDine experienced fewer treatment failures, a shorter duration of treatment and observation, and required less tincture of opium than infants receiving tincture of opium with placebo. There were no clinically important changes in blood pressure and heart rate in the cloNIDine group [4]. In a prospective, randomized, open-label trial, infants 35 weeks gestational age or older treated with morphine for NAS experienced shorter morphine treatment days (4.6 less days (95% CI, 0.3 to 8.9 days)) and no difference in morphine total dose with adjunctive phenobarbital compared with cloNIDine. However, the total duration of phenobarbital therapy continued for an average of 3.8 months (range 1 8 months) [5].

Sublingual buprenorphine was associated with the largest reduction in length of treatment and length of stay for NAS in a network meta-analysis of 18 randomized controlled trials (number of participants=1072) of buprenorphine, clonidine, diluted tincture of opium and clonidine, diluted tincture of opium, morphine, methadone, and phenobarbital. Morphine was the least effective opioid [6]. The findings should be interpreted with caution due to significant study limitations [6][7].

Neonatal abstinence syndrome (NAS), monotherapy: Overall, cloNIDine monotherapy for NAS appeared to be as effective as morphine in a randomized, double-blind, pilot study of 31 neonates younger than 7 days (gestational age, 35 weeks or more). Rescue drugs were not necessary in any neonate. The initial cloNIDine dose was 0.625 mcg/kg/dose orally every 3 hours with dose titrations up to a maximum of 12 mcg/kg/day [8].

Sedation and analgesia, Adjunct; Mechanical ventilation: There is a lack of evidence to support the use in term and preterm newborn infants. There was no improvement in mortality, duration of mechanical ventilation or intensive care unit stay between the cloNIDine (1 mcg/kg/hr) and placebo group in a study of 112 term infants [9].

Administration

Oral: Some experts recommend using a dilution of the epidural formulation of cloNIDine for use in neonates with NAS due to concerns about extemporaneous compounded oral suspensions and accuracy of dosing [3][4]. The epidural formulation (100 mcg/mL) was diluted in NS to a concentration of 5 mcg/mL and used orally in a randomized controlled trial [4].

MEDICATION SAFETY

Contraindications/Precautions

Epidural Injection

Contraindicated in patients with an injection site infection, patients with a bleeding diathesis, and patients on concurrent anticoagulant therapy. Epidural administration above the C4 dermatome is also contraindicated [10].

Precautions

Abrupt discontinuation may result in symptoms of withdrawal (eg, agitation, headache, tremor, rapid rise of blood pressure); a gradual reduction of dosage is recommended when therapy is discontinued [11].

Adverse Effects

Local anesthetics; adjunct: The use of cloNIDine as an adjunct with local anesthetics for caudal or spinal anesthesia/analgesia has been associated with apnea and respiratory depression in neonates and premature infants [12][13][14][15].

Neonatal abstinence syndrome (NAS): The use of cloNIDine for treatment of NAS has not been associated with clinically important changes in blood pressure or heart rate;

however, close monitoring is imperative [16][4].
Adjunct cloNIDine up to doses of 24 mcg/kg/day in neonates at least 35 weeks' gestation resulted in a heart rate decrease between 7 to 10 beats per minute compared with baseline in a retrospective study (n=64). Systolic blood pressure did not significantly change during cloNIDine treatment with any dose, but diastolic blood pressure was significantly increased 5 mm Hg with doses between 1.5 and 2 mcg/kg/dose every 3 hours. After discontinuation of clonidine the blood pressure (systolic and diastolic) increased (8 and 4 mm Hg, respectively) compared with baseline [16].
Monitoring
Monitor heart rate and blood pressure every 4 hours the first 2 days of therapy and every 12 hours thereafter; monitor blood pressure closely for 48 hours after discontinuing cloNIDine to access for rebound hypertension. Monitor NAS scores every 3 to 4 hours during treatment using a published abstinence assessment tool such as the modified Neonatal Abstinence Scoring System (Finnegan) or the Lipsitz tool [2][4].

MECHANISM OF ACTION/PHARMACOKINETICS
Pharmacology
Mechanism of action: CloNIDine is a centrally acting alpha-2-adrenergic agonist. Stimulation of these alpha-adrenoreceptors in the brain stem results in decreased sympathetic outflow from the CNS and in reductions in peripheral resistance, heart rate, and blood pressure. Its action in ADHD is unknown [11].
Onset and Peak effect: After oral administration, onset of action of hypotension occurs within 30 to 60 minutes with a peak effect within 2 to 4 hours [11].
Tmax: Peak concentrations occur 3 to 5 hours after dosing of immediate-release formulation [11].
Effect of food: Food does not affect the pharmacokinetics [11].
Elimination: Approximately 50% of a dose is metabolized in the liver and approximately 40% to 60% of a dose is eliminated in the urine as unchanged drug [3].
Half-life: Elimination half-life in neonates is 44 to 72 hours [3] and is prolonged in patients with renal impairment [11][17].
Clearance: In neonates, clearance of cloNIDine rapidly increases with postnatal age over the first month of life. Pharmacokinetic modelling showed that by the age of 1 month,

neonates had achieved 70% of adult clearance [18].
Extracorporeal membrane oxygenation (ECMO): Clearance doubles and Vd increases
by 55% for clonidine in infants on ECMO compared to no ECMO. In 22 infants (median age, 1
month; gestational 38.9 weeks) administered clonidine for sedation, the estimated clearance
and Vd were 29.9 L/hr/70 kg and 454 L/70 kg, respectively. The tubing for the ECMO circuit
was polyvinyl chloride. The priming volume was 350 mL for the neonates and 900 mL for the
pediatric patients. The majority (90%) of infants were also on continuous venovenous
hemofiltration. There was no association between the type of ECMO (venovenous or
venoarterial) and parameters (volume or clearance) [19].
ABOUT
Special Considerations/Preparation
Oral
Availability: 0.1-, 0.2- and 0.3-mg immediate-release tablets [11].
Extemporaneous Preparation
CloNIDine 0.01 mg/mL (10 mcg/mL) oral suspension can be prepared by triturating
three 0.1 mg cloNIDine tablets in a glass mortar, then levigating with 1 to 2 mL of Oral Mix
or Oral Mix SF. Transfer to an amber plastic bottle, rinse mortar and pestle with the
vehicle, and add sufficient vehicle for a final volume of 30 mL. The solution stored in amber
glass bottles, plastic bottles, or oral plastic syringes is stable for 91 days at 25C. The
solution is stable in amber glass or plastic bottles at 4 C for 91 days[20]. Also when made
with Ora-Blend, is stable for at least 91 days when stored in clear plastic syringes at either
25C or 4C [21]
CloNIDine 0.01 mg/mL (10 mcg/mL) oral solution was prepared by dissolving 60 mg
of clonidine hydrochloride active substance powder in 5 mL of water for injection and

agitating using a magnetic stirrer. Inorpha (Inresa) 95 mL was added and mixed with
the magnetic stirrer for 5 minutes. Then 1 mL aliquots were transferred to pre-filled (60 mL)
Inorpha amber polyethylene terephthalate bottles for a final concentration of 10 mcg/mL.
Contents were homogenized by 10 repeated inversions. The solution remained stable for 60
days at 5C. The solution also remained stable when pre-stored for 30 days at 5C, then

another 30 days with daily opening. No microbial growth was observed [22].

CloNIDine 0.02 mg/mL (20 mcg/mL) oral solution withOUT preservatives [23]:

Mix 100 mg cloNIDine hydrochloride powder with 100 mL purified water for a 1 mg/mL stock solution

Mix 2 mL of the cloNIDine stock solution with sufficient quantity of simple syrup (64 g sucrose/36 g water) for a final volume of 100 mL

Adjust pH to 4 to 5 with citric acid 5% w/v

Physicochemical stability was noted at 90 days for solutions stored at 5C, 25C, and 40C in unopened or opened (3 times/day) glass amber bottles.

In opened (3 times/day) glass amber bottles: When stored at 5C, 25C, and 40C, the solutions were microbiologically stable for up to 42 days, 7 days and 28 days.

In unopened glass amber bottles: When stored at 5C, 25C, and 40C, the solutions were microbiologically stable for up to 90 days.

Osmolality on day 0 was 1327 mOms/kg-H2O and a range of 1313 to 1376 mOms/kg-H2O on day 90.

CloNIDine 0.02 mg/mL (20 mcg/mL) oral solution with a preservative: [23]

Mix 100 mg cloNIDine hydrochloride powder with 100 mL purified water for a 1 mg/mL stock solution

Stir 150 mg of potassium sorbate with 48 mL of purified water in a beaker

Mix 2 mL of the cloNIDine stock solution to the potassium sorbate solution

Add sufficient quantity of simple syrup (64 g sucrose/36 g water) for a final volume of 100 mL

Adjust pH to 4 to 5 with citric acid 5% w/v

Physicochemical stability was noted at 90 days for solutions stored at 5C in unopened or opened (3 times/day) glass amber bottles. CloNIDine degraded to less than 90% at 10 days at 40C, and within 40 days at 25C.

In opened (3 times/day) glass amber bottles: When stored at 5C, 25C, and 40C, the solutions were microbiologically stable for up to 42 days.

In unopened glass amber bottles: When stored at 5C, 25C, and 40C, the solutions were microbiologically stable for up to 90 days.

Osmolality on day 0 was 1350 mOms/kg-H2O and a range of 1360 to 1483 mOms/kg-H2O on day 90.

CloNIDine 0.02 mg/mL (20 mcg/mL) oral solution can be prepared by triturating six 0.1 mg cloNIDine tablets in a glass mortar, then levigating with 1 to 2 mL of simple syrup NF.

Transfer to an amber plastic bottle and add sufficient simple syrup for a final volume of 30 mL. The solution is stable for 35 days under refrigeration. No negative effect on neonatal feeding osmolality is expected [24].
Although a 100 mcg/mL concentration can be prepared, it's not practical when measuring neonate doses. CloNIDine 0.1 mg/mL (100 mcg/mL) oral suspension can be prepared by grinding thirty (30) 0.2 mg-cloNIDine tablets, adding 2 mL of Purified Water, USP, to make a fine paste, and adding enough Simple Syrup, NF, for a final volume of 60 mL. The suspension is stable for 28 days when refrigerated (4 degrees C) [25].

Epidural Injection
Availability: 100 mcg/mL and 500 mcg/mL epidural injection in 10-mL single-dose vials.
Vials are preservative free. The 500 mcg/mL-strength must be diluted with NS to a final concentration not exceeding 100 mcg/mL prior to use. Do not use with preservativecontaining diluents [10].

Clopidogrel
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
Thrombosis; Prophylaxis
35 weeks of gestation or greater: initial, 0.2 mg/kg orally once daily [1].
In the Platelet Inhibition in Children On cLOpidogrel (PICOLO) trial (n=73; neonates 30 days and younger (n=34) and infants greater than 30 days (n=39)), a clopidogrel dose of 0.2 mg/kg/day given to infants and children (aged 0 to 24 months; 35 weeks of gestation or greater) at risk of arterial thrombosis achieved a similar antiplatelet effect (30% to 50% inhibition of 5 mcmol/L adenosine diphosphate (ADP)-induced platelet aggregation) as a 75 mg/day regimen in adults. A total of 79% of the subjects were taking low-dose aspirin 81 mg or less per day (aspirin mean dose, 8.8 +/- 14 mg/kg/day) [1].
Discontinuation
Clopidogrel should be discontinued 5 days prior to elective surgery if an antiplatelet effect is

not desired [2].
Uses
Thromboprophylaxis: Antiplatelet agent for the prophylaxis of thrombotic events [3][4][1].
Has been used successfully for the prophylaxis of thrombosis in cardiac disease and cardiac conditions associated with a high risk for arterial thrombosis [3][1][4].
Pediatric FDA Approved Indications
Not FDA approved in pediatric patients [2].
Administration
May be given without regard to feedings [2].
MEDICATION SAFETY
Contraindications/Precautions
Contraindications
Contraindicated in patients with active, pathological bleeding (eg, peptic ulcer or intracranial hemorrhage). Bleeding risk is increased with the concomitant use of clopidogrel, NSAIDs or warfarin [2]. In one pediatric clinical study (n=17), significant intracranial hemorrhage was reported in 25% of pediatric patients (n=2/9) when clopidogrel was used

concomitantly with aspirin [7]. In another study (n=46), 1 case each of severe epistaxis and gastrointestinal bleeding was reported in the 2 children receiving concomitant warfarin and clopidogrel therapy [4]. There was 1 report of massive upper GI bleeding in a child on concomitant clopidogrel, low-dose aspirin, and warfarin in another study (n=15) [5].
Thrombotic thrombocytopenic purpura, some cases fatal, has been reported [2].
Precautions
Administration: Nasogastric administration in critically ill patients after cardiopulmonary resuscitation increases risk of impaired clopidogrel bioavailability [8]
Concomitant use: Avoid with omeprazole or esomeprazole [6]: in a subgroup analysis (n=49) of the Platelet Inhibition in Children On cLOpidogrel (PICOLO) trial, clopidogrel plus a proton pump inhibitor reduced platelet inhibition and reduced the numbers of responders [9]
Concomitant use: Etravirine not recommended [10]
Discontinuation: Premature discontinuation may increase risk of cardiovascular events, including [6] stent thrombosis, myocardial infarction, and death, particularly in patients undergoing percutaneous coronary intervention [11]; restart as soon as possible when temporary discontinuation is required [6]

Hematologic: Thrombotic thrombocytopenic purpura, with some cases fatal, has been reported [2]
Hematologic: Bleeding risk is increased with use [6]
Immunologic:Hypersensitivity reactions (including angioedema or hematologic reaction) has been reported, including patients with a history of hypersensitivity or hematologic reaction to other thienopyridines [12]
Surgery: Interrupt use 5 days prior to elective surgery with major risk of bleeding, when possible [6]

Adverse Effects

Bleeding and thrombotic thrombocytopenic purpura are the most common hematological adverse events [2][4]. Anemia, neutropenia, and leukopenia have also been reported [4].

Black Box Warning

The effectiveness of clopidogrel hydrogen sulfate results from its antiplatelet activity, which is dependent on its conversion to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19. Clopidogrel hydrogen sulfate at recommended doses forms less of the active metabolite and so has a reduced effect on platelet activity in patients who are homozygous for nonfunctional alleles of the CYP2C19 gene, (termed CYP2C19 poor metabolizers). Tests are available to identify patients who are CYP2C19 poor metabolizers. Consider use of another platelet P2Y12 inhibitor in patients identified as CYP2C19 poor metabolizers [6].

Monitoring

Measure bleeding time prior to therapy initiation and 3 to 7 days after therapy initiation to assess drug efficacy. Platelet aggregation assay studies may be useful in some patients to

evaluate response [5]. Monitor hematological parameters closely during the first few months of therapy and every 2 to 3 months in patients on long-term therapy [4].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of action: Clopidogrel is a prodrug that is metabolized to the active form (thiol derivative) which inhibits platelet aggregation by selectively and irreversibly binding to the adenosine diphosphate (ADP) P2Y12 receptor on platelets. This binding prevents activation of the ADP-mediated glycoprotein GPIIb/IIIa complex, which is necessary for platelet aggregation [2].

Pharmacodynamics: This action is irreversible for the remainder of the platelet lifespan (7 to 10 days). Dose-dependent inhibition of platelet aggregation can be seen 2 hours after single oral doses. Platelet inhibition reaches steady state at days 3 to 7 after therapy initiation. Platelet aggregation and bleeding time gradually return to baseline values after treatment is discontinued, generally in about 5 days [2].
Bioavailability: at least 50%; food does not affect absorption. Peak concentration achieved 30 to 60 minutes after administration [2].
Metabolism: Extensively metabolized by two main metabolic pathways: one mediated by esterases and leading to hydrolysis into an inactive carboxylic acid derivative (85% of circulating metabolites) and one mediated by multiple cytochrome P450 enzymes (CYP2C19, CYP3A, CYP2B6 and CYP1A2). The active thiol metabolite binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation for the lifespan of the platelets [2].
Elimination: Approximately 50% and 46% is eliminated in the urine and feces, respectively [2].
Half-life: Clopidogrel, 6 hours (75-mg dose in adults); active metabolite, 30 minutes [2].
ABOUT
Special Considerations/Preparation
Available: 75-mg and 300-mg tablets [2].
Extemporaneous Compound (oral suspension): Triturate four 75-mg tablets in a mortar and mix with 30 mL of Ora-Plus and 30 mL of Ora-Sweet for a final concentration of 5 mg/mL. Suspension is stable for 60 days at room temperature or refrigerated.Shake well before use [13].

Colistin
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
Aerosolized/nebulization
Not an approved route and there are no strong data to support dose recommendations. See USES section for more information.
IV
Gram-negative infections: 2.5 to 5 mg/kg/day of colistin base IV or IM in 2 to 4 divided doses, depending on severity of infection. Maximum: 5 mg/kg/day of colistin base

activity in patients with normal renal function [1]. Doses of 5 mg/kg/day colistin base may be inadequate; average concentration was 1.1 mcg/mL after a single IV dose of 5 mg/kg in 7 neonates (median 38 weeks gestation and 13 days postnatal age) in the neonatal intensive care unit [2].

Dosage Adjustment

Renal impairment: There are no data available for pediatric patients with renal impairment; however, the following dose adjustments are based on recommendations for adults with renal impairment [1]:

50 to 79 mL/min: 2.5 to 3.8 mg/kg/day divided into 2 doses per day

30 to 49 mL/min: 2.5 mg/kg once daily or divided into 2 doses per day

10 to 29 mL/min: 1.5 mg/kg every 36 hours

Uses

Optimal dosing for colistin is unknown. However, a review of adult data suggest higher colistin concentrations, which may not be achieved with the manufacturer recommended dosing, and a regimen of colistin combined with other antibiotics may be necessary. The safety of higher doses is unknown [7].

Gram-negative infections, multi-drug resistant: Intermittent IV colistin in combination with at least one other antibiotic, used for the treatment of multi-drug resistant infections, mostly Acinetobacter baumannii and Klebsiella pneumoniae, resulted in a 76% favorable clinical outcome in a retrospective study (n=21 treatment courses in 18 neonates). Microbiological clearance was documented in 17 of the 21 courses. During therapy with colisin, 5 patients with severe sepsis and multi-organ dysfunction died. The dose of colistimethate sodium ranged from 50,000 to 75,000 IU/kg/day in 3 divided doses [1.7 to 2.5 mg/kg/day of colistin base]. Renal impairment developed in 2 neonates, both subsequently died of multi-organ dysfunction [3].

No significant difference in clinical and microbiological outcomes were observed between very low birthweight infants (VLBW, less than 1500 g) and non-VLBW infants with multi-drug resistant gram-negative bacilli infections treated with colistin 5 mg/kg/day IV in 3 divided doses in a retrospective study (n=66). Efficacy (microbiological clearance and survival) was

89.3% for the VLBW group and 86.8% for the non-VLBW group (p greater than 0.99). Serum

magnesium and potassium concentrations were lower (p less than 0.001 for both events), as well as the need for magnesium and potassium supplementation were higher (p less than 0.001 for both events) in the VLBW group compared with non-VLBW group. There was no difference in the rate of acute kidney injury (14.3% vs 2.6%, respectively). Klebsiella pneumoniae was the most commonly treated infection, occurring in 60.7% and 63.2% of the VLBW and non-VLBW groups [4].

Aerosolized colistin either as monotherapy [5] or in combination with other IV antibiotics [6] demonstrated potential for treating full-term and pre-term neonates with Acinetobacter baumannii (13 of the 16 neonates had multidrug-resistant isolates) ventilator-associated pneumonia in 2 retrospective studies. Neither clinical nor laboratory adverse events were reported. The dosage of colistin base was 4 mg/kg/dose aerosolized with an ultrasonic nebulizer for 15 minutes every 12 hours for a median of 9 days (4 to 14 days) in neonates on a ventilator while receiving concurrent IV antibiotics. All of the 16 neonates who received nebulized colistin cleared the A baumannii infection. [6]. Another regimen was colistimethate sodium 1 million international units (33.4 mg colistin base) monotherapy twice daily for an average of 9.1 days (4 to 22 days) [5].

Administration

Intramuscular Route:

Administer by deep IM injection into large muscle mass (eg, gluteal muscles or lateral portion of thigh). The concentration of colistin base is 75 mg/mL [1].

Intravenous Route

Continuous Infusion:

Slowly inject one-half the total daily dose over 3 to 5 minutes at a concentration of 75 mg/mL of colistin base. Add the remaining half of the total daily dose to a compatible solution. Administer by slow IV infusion, starting 1 to 2 hours after the initial dose, over the next 22 to 23 hours. The choice of IV solution and the volume used are dictated by the requirements of fluid and electrolyte management [1].

Intermittent Administration:

Infuse one-half of the total daily dose slowly over 3 to 5 minutes at a concentration of 75 mg/mL colistin base every 12 hours [1]. Doses were added to 5 mL of normal saline and infused over 30 minutes in an observational study of 18 neonates [3].

MEDICATION SAFETY

Contraindications/Precautions

Acute respiratory failure may result when reconstituted colistimethate solution for

inhalation is not used promptly. After reconstitution, colistimethate is hydrolyzed to form active components, including polymyxin E1, which has shown to cause localized inflammation of the airway epithelia and eosinophilic infiltration when administered by inhalation [9]
Bronchospasms may occur with inhalation of colistin; consider premedication with a bronchodilator [10][11].
Clostridium difficile-associated diarrhea (CDAD), including mild diarrhea to fatal colitis, has been reported and may occur more than 2 months after administration. If CDAD is

suspected or confirmed, discontinue any ongoing antibiotic therapy [1]
Concomitant use of sodium cephalothin should be avoided [1]
Increased risk of neuromuscular blockade leading to apnea in patients with renal impairment. Dosage adjustment should be reduced in proportion to the extent of the impairment [1]
Respiratory arrest has been reported after IM administration [1]
Reversible and dose-dependent nephrotoxicity may occur [1]
Transient neurological disturbances (eg, circumoral paresthesia or numbness, tingling or formication of the extremities, generalized pruritus, vertigo, dizziness, and slurring of speech), may occur and dosage adjustments may be necessary [1]
Adverse Effects
The most commonly reported adverse effects are gastrointestinal upset, slurred speech, dizziness, tingling of the extremities or tongue, itching, urticaria, rash, fever, respiratory distress, apnea, and nephrotoxicity [1].
Serum creatinine increased more than 0.5 mg/dL above baseline in 2 out of 18 neonates administered IV colistin [3].
Neither clinical nor laboratory adverse events were reported with aerosolized colistin in 8 neonates. Serum creatinine and blood urea nitrogen remained within normal limits 72 hours after completion of colistin therapy [5][6].
Solution Compatibility
NS, D5NS, D5 0.45%NS, D5W
Terminal Injection Site Compatibility
Aminophylline, atropine sulfate, calcium chloride, calcium gluconate, chloramphenicol sodium succinate, chlorothiazide sodium, chlorpheniramine maleate, chlorpromazine hydrochloride,

clarithromycin, cloxacillin sodium, cyclophosphamide, dexamethasone sodium phosphate, digoxin, edetate calcium disodium, epinephrine hydrochloride, ergonovine maleate, erythromycin lactobionate, furosemide, gallamine triethiodide, gentamicin sulfate, heparin sodium, hydralazine hydrochloride, hydrocortisone sodium succinate, isoproterenol hydrochloride, kanamycin sulfate, lidocaine hydrochloride, lincomycin hydrochloride, mechlorethamine hydrochloride, mephentermine sulfate, metaraminol bitartrate, methohexital sodium, methyldopate hydrochloride, nalorphine hydrobromide, norepinephrine bitartrate, oxytocin, penicillin G potassium, penicillin G sodium, phenobarbital sodium, phentolamine mesylate, polymyxin B sulfate, potassium chloride, procainamide hydrochloride, prochlorperazine mesylate, promazine hydrochloride, promethazine hydrochloride, propranolol hydrochloride, streptomycin sulfate, succinylcholine chloride, trimetaphan camsylate, tubocurarine chloride.

Monitoring

Closely monitor for toxicity in pediatric patients [1]. Monitor urine output, BUN, and serum creatinine[8].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Microbiology

Colistimethate sodium is a surface active agent that is used to penetrate and disrupt the cell membrane of bacteria. It has demonstrated bactericidal activity against most strains of aerobic gram-negative microorganisms (Enterobacter aerogenes, Escherichia coli, Klebsiella pneumonia, and Pseudomonas aeruginosa) both in vitro and in clinical infections [1].

Pharmacokinetics

Higher serum levels were obtained at 10 minutes following IV administration compared with IM administration [1].

Half-life was 2 to 3 hours after administration (either IM or IV) in both the adult and pediatric populations, including premature infants [1]. The half-life was 2.6 hours in neonates (0 to 7 days) and 2.3 hours in infants 7 days or older [12].

Urine levels ranged, on average, from 270 mcg/mL at 2 hours to 15 mcg/mL at 8 hours following IV administration and 200 mcg/mL to 25 mcg/mL over a similar time period with IM administration [1].

IV Administration Within 6 hours of IV colistin base 5 mg/kg, the colistin concentration was less than 2 mcg/mL in all 7 neonates (median 38 weeks gestation and 13 days postnatal age) after a single IV colistin base dose of 5 mg/kg/day [2].

Nebulization Administration: After a single-dose of ultrasonic-nebulized colistin base 4 mg/kg in 6 neonates (median gestational age 39 weeks (32 to 39) and postnatal age 7 days (3 to 7)) with ventilator-associated pneumonia, 50% of tracheal aspirate concentrations of colistin were below 2 mcg/mL 24 hours after administration. The ratio of colistin plasma concentrations-to-tracheal aspirate was 0.038 (3.8%) [13][14].

The following were the pharmacokinetic parameters for colistin in the tracheal aspirate and plasma via nebulization and in the plasma via IV administration:

Single-Dose, Colistin Pharmacokinetics in Neonates

Parameters (mean (range))	Nebulization 4 mg/kg (n=6)*	IV 5 mg/kg (n=7)**
Tracheal Aspirate	Plasma	Plasma
Cmax	24 mcg/mL (15.6 to 34.6 mcg/mL)	0.59 mcg/mL (0.32 to 1.1 mcg/mL)	3 mcg/mL
Tmax	1.8 hours (0.5 to 6 hours)	1.9 hours	1.3 hours
AUC (0 to 24)	147.6 mcg x hr/mL	2.34 mcg x hr/mL	21.1 mcg x hr/mL
AUC (0 to infinity)	183.8 mcg x hr/mL	7.57 mcg x hr/mL	25.3 mcg x hr/mL
Clearance of formed colistin	0.027 L/hr/kg	1.01 L/hr/kg	0.6 L/hr/kg
Half-life	9.8 hours	10.2 hours	9+/-6.5 hours
Vd of formed colistin	0.46 L/kg	11.7 L/kg	7.7+/-9.3 L/kg

KEY: Cmax = maximum colistin concentration, Tmax = time to maximum colistin concentration, AUC = area under the concentration time curve, Vd = apparent volume of distribution

*Nakwan, 2015

** Nakwan, 2016

Pharmacodynamics

The ratio of AUC/MIC of colistin base is the most predictive of antibacterial activity [7].
ABOUT
Special Considerations/Preparation
Each vial containing colistimethate sodium (pentasodium colistin-methanesulfonate) is equivalent to 150 mg of colistin base activity [1].
Colistin base 1 mg is equivalent to 2.4 mg of colistimethate sodium. Colistimethate sodium is 12,500 international units/mg and colistin base is 30,000 international units/mg [15].
Store vials at controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F), with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F) [1].
Intravenous:
Reconstitute 150 mg (colistin base) vial with 2 mL sterile water for injection for a resulting concentration of 75 mg/mL colistin base; swirl gently to avoid frothing [1].
Once diluted with sterile water for injection, store solution up to 7 days, between 20 and 25 degrees C (68 and 77 degrees F) or refrigerated between 2 and 8 degrees C (36 and 46 degrees F) [1].
Colistimethate for continuous infusion should be mixed with NS, D5NS, D5W, D5-0.45%NaCl, D5-0.225%NaCl, LR, or 10% invert sugar solution and used within 24 hours [1].
Inhalation: Use immediately after mixed. Do not use after 24 hours. In solution, colistimethate undergoes spontaneous hydrolysis to form its 2 active components polymyxin E1 (colistin A), which is toxic to the lungs, and polymyxin E2 (colistin B). Use after 24 hours can result in increased colistin concentration and the potential for increased lung toxicity [9].

Cosyntropin
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
Adrenocortical Insufficiency; Diagnosis
2 years or younger: 0.125 mg IV or IM (manufacturer dose) [1];alternatively, may use 0.015 mg/kg IV for infants [2].
Low-dose, 0.001 mg (1 mcg) IV may be considered in the setting of short supply [2].
Uses
Pediatric FDA Approved Indications
As a diagnostic agent in the screening of patients presumed to have adrenocortical insufficiency [1].

Administration
IV: Dilute dose in 2 to 5 mL sodium chloride and administer over 2 minutes [1]. To minimize loss of drug in tubing when using a low dose (1 mcg), consider using a 2.5 cm plastic tube rather than long IV plastic tubing and follow the dose with 5 mL normal saline flush[3].
IV Infusion: Dilute dose in glucose or sodium chloride and infuse over 4 to 8 hours [1].
MEDICATION SAFETY
Contraindications/Precautions
Contraindication
Previous adverse reaction to cosyntropin [1]
Precautions
Immunologic: Acute hypersensitivity reaction, including anaphylaxis, is possible [1].
Adverse Effects
Bradycardia, tachycardia, hypertension, peripheral edema, and rash [1].

Monitoring
Concurrent use with cortisone, hydrocortisone, spironolactone, or estrogen may alter the test results [1].
Method Options
Rapid Screening Test (Intramuscular Injection)
Collect blood sample of 6 to 7 mL in a heparinized tube before IM cosyntropin and exactly 30 minutes after IM cosyntropin. Refrigerate blood samples until sent to the laboratory.
Determine plasma cortisol response by some appropriate method. If it is not possible to send them to the laboratory or perform the fluorimetric procedure within 12 hours, then the plasma should be separated and refrigerated or frozen until ready to assay [1].
MECHANISM OF ACTION/PHARMACOKINETICS
Pharmacology
Mechanism of action: Cosyntropin, a synthetic subunit of natural adrenocorticotrophic hormone (ACTH), stimulates adrenal gland to secrete 17-OH corticosteroids, 17-ketosteroids, and/or 17-ketogenic steroids. Extra-adrenal effects include increased melanotropic activity, increased growth hormone secretion and an adipokinetic effect. [1].
ABOUT
Special Considerations/Preparation
Availability: 0.25 mg lyophilized cosyntropin [1].
Reconstitution: Add 1 mL of 0.9% sodium chloride. Discard any unused solution [1].
Dilution: Diluted cosyntropin in sodium chloride to 5 mcg/mL concentration and stored at

refrigeration (4C) in both glass and plastic tubes remained approximately 90% potent at 2 months and about 80% potent at 4 months [4].
A diluted (0.5 mcg/mL) cosyntropin solution stored in refrigerator for up to 60 days produced as expected peak 30-minute cortisol responses in healthy adult volunteers (n=49).
Cosyntropin 250 mcg/mL (Synacthen, Novartis, Manufactured by Alliance Pharmaceutical ltd Chippenham, Wiltshire U.K.) was diluted in 499 mL of 0.9% sodium chloride in a plastic IV fluid container and stored at 2 to 8C for up to 60 days [5].

Cyclopentolate (Ophthalmic)
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
1 or 2 drops instilled in the eye 10 to 30 minutes prior to funduscopy.
Use solutions containing concentrations of 0.5% or less in neonates.
May be used in conjunction with 1 drop of phenylephrine 2.5% ophthalmic solution.
Apply pressure to the lacrimal sac during and for 2 minutes after instillation to minimize systemic absorption.
Uses
Induction of mydriasis and cycloplegia for diagnostic and therapeutic ophthalmic procedures.
MEDICATION SAFETY
Adverse Effects
Feedings should be withheld for 4 hours following procedure. Systemic effects are those of anticholinergic drugs: Fever, tachycardia, vasodilatation, dry mouth, restlessness, delayed gastric emptying and decreased gastrointestinal motility, and urinary retention. The use of solutions with concentrations of 1% or greater have caused systemic toxicity in infants.
Monitoring
Monitor heart rate and assess for signs of ileus prior to feeding.
MECHANISM OF ACTION/PHARMACOKINETICS
Pharmacology
Anticholinergic drug that produces pupillary dilation by inhibiting the sphincter pupillae muscle, and paralysis of accommodation. Maximal mydriasis occurs 30 to 60 minutes following administration. Recovery of accommodation occurs in 6 to 24 hours. Without lacrimal sac occlusion, approximately 80% of each drop may pass through the nasolacrimal

system and be available for rapid systemic absorption by the nasal mucosa.
ABOUT
Special Considerations/Preparation
Supplied as ophthalmic solution 0.5% in 15-mL Drop-tainers, and 1% and 2% concentrations in 2-, 5- and 15-mL Drop-tainers. Store away from heat. Do not refrigerate. A preparation containing cyclopentolate 0.2% and phenylephrine 1% (Cyclomydril) is commercially available in 2- and 5-mL Drop-tainers.
A combination eye drop solution ("Caputo drops") may be prepared in a 15-mL bottle with 3.75 mL of cyclopentolate 2%, 7.5 mL of tropicamide 1%, and 3.75 mL of phenylephrine 10%. The final solution contains cyclopentolate 0.5%, tropicamide 0.5%, and phenylephrine 2.5%.

Dexamethasone
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
DART trial protocol: 0.075 mg/kg/dose every 12 hours for 3 days, 0.05 mg/kg/dose every 12 hours for 3 days, 0.025 mg/kg/dose every 12 hours for 2 days, and 0.01 mg/kg/dose every 12 hours for 2 days [1]. Doses may be administered IV slow push or orally.
Inflammatory ophthalmic conditions: Instill 1 to 2 drops topically in the conjunctival sac(s) every hour for severe disease or up to 4 to 6 times daily for mild disease. In severe disease, taper the dose and then discontinue as the inflammation resolves [2].
Uses
Low-dose dexamethasone has been used successfully to facilitate extubation and improve lung function acutely in preterm infants at high risk for developing chronic lung disease. Low doses have not been associated with substantial effects with regard to mortality or development of bronchopulmonary dysplasia (BPD) at 36 weeks [14][1][15]. High-dose dexamethasone (eg, 0.5 mg/kg/day) has been associated with a reduction in the incidence of BPD, but also an increased risk for short-term adverse effects (hyperglycemia, hypertension,

gastrointestinal perforation, infection risk) and adverse long-term neurodevelopmental outcomes (cerebral palsy (CP)) [14][16][17]. A review of meta-analyses looking at the timing and dosage of postnatal steroids found the development of CP was associated with early steroid use (first week of life) in patients at lower risk for BPD [14]. A prospective cohort study found that higher steroid exposure was associated with an increased risk for CP [18].
High-dose dexamethasone in the first week of life is generally not recommended for the prevention of BPD or for the treatment of BPD after the first week of life [19][16]; however, the judicious use of late dexamethasone may be considered for infants who cannot be weaned from the ventilator [19][20].
A shorter course, 7 days, compared with a longer course, 10 days, of dexamethasone for bronchopulmonary dysplasia was as effective in facilitating extubation (56% vs 67%, p=0.42) within 14 days of starting dexamethasone in mechanically-ventilated preterm infants (less than 29 weeks' gestational age) in a retrospective study (n=59). Mean postnatal age was 36 days and 33 days for the infants treated for 7 days and 10 days, respectively. The total dose for the 7-day regimen was 0.72 mg/kg (0.075 mg/kg/dose every 12 hours for 3 days, 0.05 mg/kg/dose every 12 hours for 2 days, 0.025 mg/kg/dose every 12 hours for 1 day, and 0.01 mg/kg/dose every 12 hours for 1 day). The total dose for the 10-day regimen was 0.89 mg/kg [21].
Anthrax, adjunct: Although data are lacking, consider adjunctive corticosteroids for the treatment of severe cerebral edema or meningoencephalitis [22].
Pediatric FDA Approved Indications
Ophthalmic
Indicated in pediatric patients of all ages for steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe such as

allergic conjunctivitis, acne rosacea, superficial punctate keratitis, herpes zoster keratitis, iritis, cyclitis, selected infective conjunctivitides when inherent hazard of steroid use is accepted to obtain an advisable diminution in edema and inflammation; corneal injury from chemical, radiation, or thermal burns, or penetration of foreign bodies [2].
Systemic

Use as an immunosuppressant and in a variety of antiinflammatory disorders to reduce edema (eg, due to tumors, infection) and to lessen the effects of neurologic disorders based on adult studies. For the treatment of nephrotic syndrome, dexamethasone is approved in patients older than 2 years of age, and for the palliative management of aggressive lymphomas and leukemias, it is approved in patients 29 days and older. Due to its lack of mineralocorticoid effects, dexamethasone is not indicated as replacement therapy for patients with adrenal insufficiency [7][8][6][23].

Administration

Intravenous: Can be administered undiluted or can be diluted to a concentration of 0.1 to 1 mg/mL in NS for intravenous infusion [3][4][5][6].

Ophthalmic: Shake well before use [2].

Oral: Take large doses with meals and take antacids between meals to prevent peptic ulcer.

Mix the concentrate solution with liquid or semi-solid food such as water, juices, soda, applesauce or puddings and consume immediately; do not store for future use [7][8].

The IV formulation of dexamethasone has been used orally in pediatric patients [9], including a one-time dose for asthma exacerbation in a retrospective study. Injectable dexamethasone was mixed with a small amount of juice [10]. Stability data are available [11][12]; however, there are no bioequivalence data in pediatric patients [13].

MEDICATION SAFETY

Contraindications/Precautions

CONTRAINDICATIONS

Systemic Use: Contraindicated in patients with systemic fungal infection [7][8].

Ophthalmic Use: Contraindicated in acute, untreated bacterial infections; mycobacterial ocular infections; epithelial herpes simplex (dendritic keratitis); vaccinia, varicella, and most other viral diseases of the cornea and conjunctiva; fungal disease of ocular structures; and in those persons who have shown hypersensitivity to any component of this preparation [2].

PRECAUTIONS

Systemic Use

Administration: Injecting corticosteroids into the epidural space of the spine may result in rare but serious neurologic problems (ie, spinal cord infarction, loss of vision, stroke, seizure, paralysis, or death) [24].

Immunologic: Contains bisulfate, a sulfite that can cause anaphylactic allergic-type reactions seen more frequently in asthmatic patients [7][8].

Ophthalmic: Use of corticosteroid-containing product for more than 6 weeks or

development of ocular symptoms; consider ophthalmologist referral [25]

Ophthalmic Use
Ophthalmic: Prolonged use may result in ocular hypertension and/or glaucoma, with damage to the optic nerve, defects in visual acuity and fields of vision, and posterior subcapsular formation; monitoring recommended during long-term (10 day or longer) therapy [2]
Ophthalmic: Prolonged use may increase the risk of secondary ocular infections due to reduced host response [2]
Ophthalmic:Prolonged use may result in persistent fungal infection of the cornea [2]
Ophthalmic:Perforations may occur in patients receiving topical corticosteroids in diseases known to cause thinning of the cornea or sclera [2]
Ophthalmic: Corticosteroids may mask infection or enhance existing infection in the presence of acute purulent conditions or parasitic infections of the eye [2].
Adverse Effects
The February 2002 AAP and CPS statement strongly discourages routine use of dexamethasone. If dexamethasone is used for CLD risk reduction, 1) Treat only those infants at highest risk; 2) Use lower than traditional pharmacologic doses; 3) Begin treatment after Day 7 but before Day 14 of life; 4) Do not give concurrently with indomethacin; 5) Use preservative-free drug wherever possible.
The DART trial found no association with long-term morbidity, but other studies have reported an increased risk of cerebral palsy. Most evidence suggests no increase in the incidence of ROP or the need for cryotherapy. Gastrointestinal perforation and GI hemorrhage occur more frequently in patients treated beginning on Day 1 and in those also being treated concurrently with indomethacin. Hyperglycemia and glycosuria occur frequently after the first few doses, and one case of diabetic ketoacidosis has been reported. Blood pressure increases are common, and hypertension occurs occasionally. Cardiac effects noted by Day 14 of therapy include increased left ventricular wall thickness with outflow tract obstruction and transient impairment of left ventricular filling, systolic anterior motion of the mitral valve, and ST-segment depression. Other potential short-term adverse effects include

sodium and water retention, hypokalemia, hypocalcemia, hypertriglyceridemia, increased risk of sepsis, renal stones (in patients receiving furosemide), osteopenia, and inhibition of growth. Adrenal insufficiency may occur secondary to pituitary suppression.

Solution Compatibility

D5W, D10W, and NS.

Terminal Injection Site Compatibility

Acyclovir, amikacin, aminophylline, aztreonam, caffeine citrate, cefepime, cimetidine, famotidine, fentanyl, fluconazole, furosemide, heparin, hydrocortisone succinate, lidocaine, linezolid, lorazepam, meropenem, methadone, metoclopramide, milrinone, morphine, nafcillin, netilmicin, piperacillin/tazobactam, potassium chloride, propofol, ranitidine,

remifentanil, sodium bicarbonate, and zidovudine.

Terminal Injection Site Incompatibility

Glycopyrrolate, midazolam, and vancomycin.

Monitoring

Systemic Use:

Assess for hyperglycemia and hyperlipidemia. Monitor blood pressure. Guaiac gastric aspirates. Echocardiogram if treating longer than 7 days.

Ophthalmic use: Monitor intraocular pressure during long-term (10 day or longer) therapy [2]

Periodic slit-lamp microscopy is required in the treatment of herpes simplex [2]

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Stabilizes lysosomal and cell membranes, inhibits complement-induced granulocyte aggregation, improves integrity of alveolar-capillary barrier, inhibits prostaglandin and leukotriene production, rightward shifts oxygen-hemoglobin dissociation curve, increases surfactant production, decreases pulmonary edema, relaxes bronchospasm. Hyperglycemia is caused by inhibition of glucose uptake into cells and decreased glucokinase activity.

Increased triglyceride synthesis is due to hyperinsulinemia and increased acetyl-CoA carboxylase activity. Blood pressure is increased due to increased responsiveness to endogenous catecholamines. Increases protein catabolism with potential loss of muscle tissue, increases urinary calcium excretion because of bone resorption, and suppresses pituitary ACTH secretion. Biologic half-life is 36 to 54 hours.

ABOUT
Special Considerations/Preparation
Injection
Availability: Dexamethasone sodium phosphate for injection is available in concentrations of 4 mg/mL (benzyl alcohol preservative 10 mg/mL) and 10 mg/mL (preservative free or benzyl alcohol preservative 10 mg/mL).
Stability: Stable for 30 days under refrigeration at dilutions of 0.2 mg/mL and 0.4 mg/mL in NS in PVC minibags [5]. Stable for 22 days at room temperature at dilutions of 0.1 mg/mL and 1 mg/mL in NS in polypropylene syringes [3]. Stable for 28 days under refrigeration and

at room temperature at a dilution of 1 mg/mL in bacteriostatic NS in glass vials [4]. Stable for up to 14 days at room temperature at dilutions of 0.08 mg/mL and 0.6 mg/mL in D5W in polyvinyl chloride bags [26].
Ophthalmic
Availability: Dexamethasone 0.1% ophthalmic suspension [2]
Oral
Availability:[7][8]
Oral solution 0.5-mg/5 mL (0.1-mg/mL) and 1-mg/mL (Intensol concentrate).
Intensol concentrate contains alcohol 30%. Discard opened bottle of Intensol after 90 days.
Tablets 0.5-, 0.75-, 1-, 1.5-, 2-, 4-, and 6-mg strengths.
Extemporaneous Oral Suspension
0.5 mg/mL oral suspension: Dilute 1 mL of the 4 mg/mL IV solution up to a total volume of 8 mL with a 1:1 mixture of Ora-Sweet and Ora-Plus. The oral suspension was physically and chemically stable for up to 91 days with or without refrigeration [11].
1 mg/mL oral suspension: Dilute dexamethasone 4 mg/mL solution for injection with either Oral Mix or Oral Mix SF to make 1 mg/mL oral suspension. The oral suspension was stable for up to 91 days when stored in amber glass, plastic bottles, or plastic syringes at 25 degrees C or in amber glass bottles or plastic bottles at 4 degrees C [12].

Dextrose

NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
Hypoglycemia
IV
Initial Dose: 0.2 g/kg IV (2 mL/kg) as D10W [1][2][3].
Maintenance Dose: Continuous infusion of a 5% to 10% dextrose IV solution with appropriate maintenance electrolytes at an initial glucose infusion rate of 5 to 8 mg/kg/minute. Titrate rate to attain normoglycemia [1][2]. Higher doses may be necessary (10 to 20 mg/kg/minute) to maintain acceptable blood glucose levels, particularly in patients with persistent hyperinsulinemic hypoglycemia. Abruptly discontinuing a dextrose infusion is not recommended due the risk for rebound hypoglycemia [4].
Buccal
48 hours or younger (35 weeks gestation or more): 200 mg/kg of dextrose gel (40%) massaged into the buccal mucosa, may be repeated up to 6 doses over 48 hours [5].
Hyperkalemia
Initial, continuous IV infusion of 0.5 g/kg/hour dextrose and 0.1 to 0.2 units/kg/hour regular insulin. Dextrose and insulin dosages are adjusted based on serum glucose and potassium concentrations.
Parenteral Nutrition Recommendations
An initial dextrose infusion rate of 6 to 8 mg/kg/minute, advanced as tolerated to a goal rate of 10 to 12 mg/kg/minute, is recommended in neonates. An initial rate of 4 to 8 mg/kg/minute should be considered in preterm neonates.
Uses
Hyperkalemia in combination with insulin
Hypoglycemia, Prophylaxis: The incidence of hypoglycemia was reduced with prophylactic dextrose buccal gel compared with placebo in babies at 1 hour of age at risk of developing neonatal hypoglycemia in a randomized, double-blind, placebo-controlled, dosefinding study (n=416); relative risk was 0.68 (95% CI, 0.47 to 0.99) for the 200 mg/kg single dose. There was no difference between any dextrose dose and placebo in the rate of intensive care admission, breast feeding rates, and supplementary dextrose. The majority of babies (73%) were born to mothers with diabetes [6].
Hypoglycemia, Treatment: Administration of buccal dextrose gel (40%) improved blood glucose better than feedings alone in at-risk late preterm and term babies who became hypoglycemic within the first 48 hours of birth in a randomized, double-blind, placebocontrolled study (n=237). Treatment failure rates were 14% and 24% (relative risk, 0.57

(95% CI, 0.33 to 0.98)) for the dextrose and placebo groups, respectively. Rebound and recurrent hypoglycemia were no different between dextrose gel and placebo groups. Almost

all babies were breastfed [5]. No additional risks or benefits were identified in 184 out the 237 eligible infants evaluated at 2 years' corrected age. There was no difference between dextrose gel and placebo in neurosensory impairment or processing difficulties [7].

Dextrose IV is recommended for hypoglycemia in the setting of cardiopulmonary resuscitation [8][9].

Nutritional supplement in parenteral nutrition solutions

Administration

IV: Generally, glucose concentrations greater than 15% should be administered via a central vein to minimize risk of phlebitis and thrombosis. However, in one study in term neonates (n=121), peripheral infusion of a 20% glucose solution did not cause a higher rate or severity of phlebitis compared with peripheral infusion of a 15% glucose solution. Bolus doses should be administered only by slow IV injection. Abruptly discontinuing a dextrose infusion is not recommended due the risk for rebound hypoglycemia.

For Hypoglycemia, use continuous infusion of a 5% to 10% dextrose IV solution with appropriate maintenance electrolytes [1][2].

Buccal: Prior to application, dry the mouth with a gauze [5]. Massage the gel into the buccal mucosa [6][5] followed by breastfeeding [6].

MEDICATION SAFETY

Contraindications/Precautions

Contraindicated when intracranial or intraspinal hemorrhage is present. Concentrated dextrose solutions (ie, 25% and 50%) are hypertonic and may cause phlebitis and thrombosis at injection site. Rapid administration may cause significant hyperglycemia and possible hyperosmolar syndrome.

Adverse Effects

Excessive glucose provided by parenteral nutrition is associated with promotion of fat deposition, liver impairment and steatosis, and impairment of protein metabolism [11].

Solution Compatibility

Most standard IV solutions.

Terminal Injection Site Compatibility

Most drugs.
Terminal Injection Site Incompatibility
Caspofungin, erythromycin, phenytoin, and procainamide.
Monitoring
Laboratory[10][3]
Frequent monitoring of blood glucose is recommended; reasonable goal is blood glucose between 40 and 50 mg/dL.
Monitor sodium and potassium levels closely.
Obtain urine glucose and electrolytes periodically during therapy.
Monitor acid-base balance and fluid status.
MECHANISM OF ACTION/PHARMACOKINETICS
Pharmacology
Dextrose restores blood glucose levels in hypoglycemia and provides a source of carbohydrate calories. Intravenous dextrose provides 3.4 kcal/g [10]. When combined with insulin for the treatment of hyperkalemia, dextrose stimulates the sodium-potassium (Na-K) adenosine triphosphatase pump (ATP) leading to an intracellular shift of potassium.
ABOUT
Special Considerations/Preparation
Injection
Available: 50% concentrated solution in 50-mL single-dose vials and syringes, and 25% concentrated solution in single-use 10-mL syringes. Also available in various other concentrations in large-volume IV solutions.
Oral
Available: Dextrose gel
Dex4 contains d-glucose 15 g/33 g pouch
Glutose 15 gel contains d-glucose (dextrose) 15 g/37.5 g (40%) [12].
SugarUp 40% glucose gel contains 40% glucose in a 15-mL cup (http://www.sandboxmedical.com/PDF/5-17021-004-SugarBabies-40-Glucose-Datasheet.pdf).

Diazoxide
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION

Dose
Hypoglycemia due to Hyperinsulinism
Initial: 10 mg/kg/day orally divided every 8 hours [1].
Usual Maintenance: 8 to 15 mg/kg/day orally in equally divided doses every 8 to 12 hours [1].
Adjust doses to achieve desired clinical and laboratory effects. If not effective within 2 to 3 weeks, then discontinue [1].
Dose Adjustments
Renal Impairment: No specific dose adjustment recommendations are available for neonates, but a reduced dosage should be considered in patients with renal impairment [1].
Uses
Hypoglycemia due to Hyperinsulinism:In small for gestational age infants with hyperinsulinemic hypoglycemia during the first 5 days of life, serum glucose concentration normalized sooner with oral diazoxide compared with placebo, in a randomized, double-blind study (N=30). The median time to achieve hypoglycemia control (defined as glucose IV infusion of 4 mg/kg/min or less for a minimum of 6 hours) was 40 hours for the diazoxide group and 72 hours (p = 0.01) for the placebo group. The total duration of intravenous fluids (114 vs 164 hours; p=0.004) and time to achieve euglycemia (30 vs 60 hours, p = 0.001 or less) was less with diazoxide compared with placebo. Diazoxide dosage was 3 mg/kg/dose orally every 8 hours and increased to 4 mg/kg/dose every 8 hours if hypoglycemia persisted after 48 hours; subsequently tapered by 1 mg/kg/dose every 72 hours once the infant was euglycemic for at least 72 hours [2]
Pediatric FDA Approved Indications
Treatment of hypoglycemia due to hyperinsulinism associated with the following conditions: leucine sensitivity, islet cell hyperplasia, nesidioblastosis, extrapancreatic malignancy, islet cell adenoma, or adenomatosis. May also be used preoperatively and postoperatively, as a temporary measure for persistent hypoglycemia [1].
Administration
Shake suspension well before administration [1].
MEDICATION SAFETY

Contraindications/Precautions
Contraindications
Functional hypoglycemia [1]
Hypersensitivity to diazoxide or to other thiazides [1]

Precautions

Cardiovascular: Fluid retention from diazoxide may result in congestive heart failure for those with compromised cardiac reserve; diuretics may be used [1].

Cardiovascular: Antihypertensive effects may be enhanced when diazoxide is coadministered with antihypertensive agents [1].

Concomitant Use: Thiazides may potentiate the hyperglycemic and hyperuricemic actions of diazoxide [1].

Endocrine and Metabolic: Ketoacidosis and nonketotic hyperosmolar coma have been reported, usually during intercurrent illness and at recommended doses; monitoring required [1].

Endocrine and Metabolic: Hyperuricemia or history of gout; monitoring required [1].

Hepatic: Newborns with bilirubinemia; bilirubin may be displaced from albumin by diazoxide [1].

Musculoskeletal: Abnormal facial features developed in 4 children treated for more than 4 years with diazoxide [1]..

Ophthalmic: Cataracts (transient) have occurred in association with hyperosmolar coma in an infant; resolved with correction of hyper-osmolarity [1].

Pharmacokinetics: Oral suspension may result in higher blood concentrations than oral capsules; dosage adjustment may be necessary when switching between formulations [1].

Renal: Renal function, impaired; risk of drug toxicity [1].

Respiratory: Pulmonary hypertension has been reported in infants and newborns administered diazoxide [1] for treatment of low blood sugar and may occur within days or a few months of administration. Risk factors for pulmonary hypertension are those with meconium aspiration syndrome, respiratory distress syndrome, transient tachypnea, pneumonia, sepsis, congenital diaphragmatic hernia, or congenital heart disease. Symptoms may include difficulty breathing, flared nostrils, grunting, chest wall retractions, rapid breathing, difficulty feeding, bluish color of the lips or skin [3]. Discontinue use if pulmonary hypertension develops . Symptoms may be reversible upon discontinuation [1].

Adverse Effects

Hirsutism and hypertrichosis have been reported commonly in children. Hypotension, chest pain, thrombocytopenia, and neutropenia have been reported rarely [4][5][6][7][8].

Concurrent treatment with a thiazide diuretic is recommended to prevent associated fluid retention from diazoxide [9][10][7][8].

Monitoring
Laboratory Parameters
Careful monitoring of blood glucose concentrations is recommended during therapy,
particularly during treatment initiation and until stabilization. Monitoring urine for sugar and ketones is recommended for patients under stress. A dose reduction may be required in

patients with hyperglycemia or glucosuria [1].
Evaluate serum electrolyte levels in patients with impaired renal function [1].
Monitor BUN and creatinine clearance [1]
Monitor hematocrit, platelet counts, and leukocytes (total and differential) [1].
Monitor AST and serum uric acid level [1].
Physical Exam
Monitor for respiratory distress, especially in patients with risk factors for pulmonary hypertension [1].
MECHANISM OF ACTION/PHARMACOKINETICS
Pharmacology
Mechanism of action: Diazoxide is a nondiuretic benzothiadiazine derivative, and when
given orally induces a quick elevation in blood glucose level through inhibition of insulin release from the pancreas, and also due to an extrapancreatic effect. It also decreases sodium and water excretion, leading to fluid retention, which may be severe. May also cause increased heart rate and elevated serum uric acid levels [5].
Onset: Hyperglycemia begins within an hour and lasts no more than 8 hours in normal
patients.
Protein binding: Highly protein bound (more than 90%).
Elimination: Primarily in the kidneys.
Half-life: In children (4 months to 6 years of age) on long-term therapy, plasma half-life
after oral administration was 9.5 to 24 hours. Half-life is increased in patients with renal impairment [5].
ABOUT
Special Considerations/Preparation
Availability: Proglycem 50 mg oral capsules and oral suspension 50 mg/mL. Alcohol
content is 7.25%. Protect from light. Store at room temperature [1].
Extemporaneous Suspension 10 mg/mL[11]
Bulk diazoxide powder
Weigh bulk diazoxide powder (2 g)
Mix with mortar in glycerine (3 mL) until forming a smooth paste

Add enough Oral Mix or Oral Mix SF incrementally to form a uniform suspension and to
bring the total volume to 200 mL
Stable for 90 days at 5C (refrigeration) and 25C (room temperature) and stored in
amber plastic oral syringes or amber PET bottles
Diazoxide capsules
Pulverize the contents of 25 diazoxide 100 mg capsules using a pestle in a mortar

Mix with small amounts of Oral Mix or Oral Mix SF (10 mL) to form a homogenous paste
Add Oral Mix or Oral Mix SF in small increments to bring the required total volume (250
mL)
Thoroughly mix to form a uniform suspension
Stable for 90 days at 5C (refrigeration) and 25C (room temperature) and stored in
amber plastic oral syringes or amber PET bottles

Didanosine
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
HIV Infection
14 days or older: 100 mg/m2 orally twice daily (manufacturer dose) [1]; 50 mg/m2 twice
daily may be more appropriate for neonates (guideline dose) [2].
Uses
HIV-1 infection
Younger than 15 days: Data are insufficient to make a general recommendation for
complete combination antiretroviral therapy (cART) in preterm or term infants younger than
15 days (until 42 weeks' postmenstrual age). Consult a pediatric HIV expert if considering a
3-drug antiretroviral (ARV) regimen in infants younger than 2 weeks or premature infants.
The preferred initial regimen is 2 NRTIs (zidovudine plus either (lamiVUDine or
emtricitabine)) plus nevirapine. There are no data demonstrating improved outcomes when
starting treatment within the first 14 days of age compared with after 14 days of age [2].
14 days or older and 42 weeks' post-gestational age: The preferred initial regimen is 2
NRTIs (zidovudine plus (lamiVUDine or emtricitabine)) plus lopinavir/ritonavir-boosted. If the

infant is on nevirapine considering changing to lopinavir/ritonavir-boosted [2].
Pediatric FDA Approved Indications
Treatment of HIV-1 infection, in combination with other antiretroviral agents, in children 2 weeks or older [1].
Administration
Preferably, administer on an empty stomach (30 minutes before or 2 hours after a feeding).
Shake well before measuring dose [1].
MEDICATION SAFETY
Contraindications/Precautions
CONTRAINDICATIONS
Contraindicated with the coadministration of allopurinol, ribavirin, or stavudine [3][5].
PRECAUTIONS
Concomitant use: Avoid use with hydroxyurea [4][3] (with or without stavudine) [6]

Endocrine and metabolic: Lipoatrophy has been reported predominately in the face, limbs, and buttocks; severity related to cumulative exposure and is often not reversible.
Monitoring recommended and consider alternative regimen if there is a suspicion of lipoatrophy [4][3]
Hepatic: Severe hepatomegaly with steatosis, including fatalities, have been reported with nucleoside analogs; increased risk in obesity, female gender, prolonged nucleoside exposure, or known risk factors for liver disease; suspend treatment if signs or symptoms occur [4][3] [7].
Hepatic: Patients with preexisting liver dysfunction, including chronic active hepatitis, have increased risk of severe and potentially fatal hepatic adverse events; monitoring recommended and interruption or discontinuation of therapy may be necessary [7][6].
Hepatic: Non-cirrhotic portal hypertension has been reported, including fatalities or cases requiring liver transplantation; onset occurred months to years after start of therapy; discontinue use if suspected[7][6].
Immunologic: Autoimmune disorders (eg, Graves' disease, polymyositis, Guillain-Barr 錬 syndrome) have been reported; onset variable, may occur many months after treatment initiation [7][6].
Immunologic: Immune reconstitution syndrome has been reported including inflammatory response to indolent or residual opportunistic infections; occurs during initial treatment phase[7][6].

Neurologic: Peripheral neuropathy has been reported; increased risk in patients with advanced HIV disease, history of neuropathy, or concurrent neurotoxic drug therapy; discontinuation may be necessary [7][6].
Ophthalmic: Retinal changes and optic neuritis have been reported; monitoring recommended [7][6].

Adverse Effects

Pancreatitis occurred in 3% (2 out of 60) of pediatric patients during a clinical trial at doses below 300 mg/m(2)/day [1]. Common adverse events include diarrhea, abdominal pain, vomiting, rash, and increased liver enzymes [1].
Peripheral neuropathy, non-cirrhotic portal hypertension, retinal changes, optic neuritis, and insulin resistance/diabetes mellitus have also been reported in pediatric patients [2].

Black Box Warning

Warning: Pancreatitis, Lactic Acidosis and Hepatomegaly with Steatosis [3][4]
Fatal and nonfatal pancreatitis has occurred during therapy with didanosine used alone or in combination regimens in both treatment-naive and treatment-experienced patients, regardless of degree of immunosuppression. Didanosine should be suspended in patients with suspected pancreatitis and discontinued in patients with confirmed pancreatitis.
Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including didanosine and other antiretrovirals. Fatal lactic acidosis has been reported in pregnant women who received the combination of didanosine and stavudine with other antiretroviral agents. Coadministration of didanosine and stavudine is contraindicated because of increased risk of serious and/or life-threatening events. Suspend treatment if

clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occurs.

Monitoring

[2]
Antiretroviral Monitoring in Children (adjust schedule based on the specific antiretroviral regimen)

Baseline	1 to 2 weeks

after
initiation
2 to 4
weeks
after
initiation
Every 3 to 4
months
Only required every 6 to 12
months
Therapy
Switch
If clinical, immunologic, or virologic deterioration
is suspected, perform more
frequent CD4 cell count and plasma viral load
monitoring. If toxicity noted,
perform testing more frequently until toxicity
resolved
Adverse
Effects
X X X X X
Adherence
Evaluation

X X X X X
CBC with
differential

X X X X
Chemistries

X X X X
Lipid Panel X X
Random
Plasma
Glucose
X X
Urinalysis X X ?
CD4 count
?? X X X
HIV RNA
X X X X
Resistance
Testing
X X
Hepatitis B
screening
?
X X
KEY: CBC = complete blood count
Baseline may not be necessary if pre-therapy
monitoring was performed within 30 to 90 days.
Monitor for adherence, effectiveness (CD4 cell count
and plasma viral load [HIV RNA]), and
toxicities every 3 to 4 months.
Chemistries include electrolytes, creatinine,
glucose, and hepatic transaminases.

If lipids have been abnormal in the past, more frequent monitoring might be needed.
? Consider more frequent urinalysis in patients taking tenofovir disoproxil fumarate.
?? In all children, absolute CD4 cell count is recommended; CD4 percentage is an alternative for children younger than 5 years.
CD4 cell count, CBC, and chemistries can be monitored less frequently (every 6 to 12 months) in children and youth who are adherent to therapy and have CD4 cell count values well above the threshold for opportunistic infection risk, have sustained viral suppression, and have stable clinical

status for more than 2 to 3 years.
Obtain virus resistance testing even if antiretroviral therapy is not immediately started.
? Only if individual previously demonstrated no immunity to hepatitis B and when initiating a regimen that contains agents with activity against hepatitis B (ie, lamivudine, emtricitabine, tenofovir alafenamide, or tenofovir disoproxil fumarate.
Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection, April, 2019; AIDSinfo
Monitor for early signs and symptoms of portal hypertension (eg, thrombocytopenia and splenomegaly). Perform retinal examinations periodically to screen for retinal changes and optic neuritis [1].
MECHANISM OF ACTION/PHARMACOKINETICS
Pharmacology
Mechanism of action: Didanosine is a nucleoside reverse transcriptase inhibitor active against HIV type 1 [1].
Absorption: The AUC is equivalent for buffered or enteric-coated formulations. Mean bioavailability is approximately 25% in children. Cmax occurs from 0.25 to 1.5 hours following oral administration of the pediatric powder for solution. Food decreases absorption [1].
Distribution: Protein binding is less than 5% [1].
Excretion: Primarily eliminated renally (50%) [1].
Clearance: A population pharmacokinetic analysis from 9 clinical trials in 106 pediatric (neonate to 18 years of age) showed that body weight is the primary factor associated with oral clearance. Clearance was not affected by dosing schedule (once vs twice daily) or formulation (powder for oral solution, tablet, and delayed-release capsule) [1].
Half-life: Mean elimination half-life in children (8 months or older) is 0.8 hours [1].

ABOUT
Special Considerations/Preparation
Availability: Pediatric powder for oral solution in 4- and 8-ounce glass bottles containing 2 g and 4 g of didanosine, respectively.
Reconstitute each 2-g or 4-g bottle with 100 mL or 200 mL of purified water, USP, respectively, for an initial concentration of 20 mg/mL. This solution should be immediately mixed with one part Maximum Strength Mylanta Liquid, resulting in a final concentration of didanosine 10 mg/mL. Shake well before use. Refrigerate admixture at 2 to 8 degrees C (36 to 46 degrees F) for up to 30 days, and discard any unused portion after this time [1].

Digoxin Immune Fab (Ovine)
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
Digoxin Toxicity
There are limited safety data in neonatal patients. Dosing estimates are based on calculations derived for adult dosing [1].
Each vial of digoxin immune Fab (40 mg purified digoxin-specific Fab fragments) will bind approximately 0.5 mg of digoxin or digitoxin [1].
Acute Ingestion of Known Amount
Dose (in vials) = (digoxin ingested (mg) X bioavailability)/0.5 mg of digitalis bound per vial [1](bioavailability of digoxin solution = 0.85 [2]; bioavailability of digoxin tablets = 0.8). If in any case, the dose estimated based on ingested amount differs considerably from that calculated based on the serum digoxin, it may be preferable to use the higher dose estimate [1].
Chronic Digoxin Toxicity
Unknown digoxin level: single vial (40 mg) IV initially [1].
Known digoxin level: dose in mg = 40 mg x (serum digoxin concentration in nanogram (ng)/mL x weight in kg)/100 [1].
If toxicity has not adequately reversed after several hours, or appears to recur, readministration of digoxin immune Fab may be required [1].
Uses
Pediatric FDA Approved Indications
Digoxin immune Fab is indicated for life-threatening or potentially life-threatening digoxin toxicity or overdose in children, including the following situations: ingestion of fatal doses of

4 mg (or 0.1 mg/kg) or more, or amounts leading to serum concentrations of 10 ng/mL or greater; chronic ingestions leading to levels greater than 4 ng/mL; and in the presence of severe ventricular arrhythmias, bradycardia, second/third degree heart block that is unresponsive to atropine, or potassium levels greater than 6 mEq/L with rapidly progressive signs of toxicity [1][3][4][5][6].
ECG abnormalities [1][4] and hyperkalemia typically resolve within 4 hours after digoxin immune Fab administration [4].
Administration
Reconstitute the vial (40 mg) with 4 mL of Sterile Water for Injection and mix gently; the final concentration will be approximately 10 mg/mL (see Special Considerations section for storage and stability of the reconstituted vial). May dilute the reconstituted solution to an

appropriate volume of NS for administration. Very small doses (less than 1 mL) may be given undiluted via a tuberculin syringe or the reconstituted solution may be further diluted with 36 mL of NS to achieve a 1 mg/mL concentration.
Administer by slow IV infusion over 30 minutes; if cardiac arrest is imminent, the solution can be given by bolus injection [1].
Stop temporarily the IV infusion for any infusion-rate related anaphylactoid reactions (eg, hypotension, wheezing, urticaria) and restart at a lower rate. Incidence of infusion-related reactions may be increased with bolus injection [1].
MEDICATION SAFETY
Contraindications/Precautions
Anaphylaxis and hypersensitivity reactions may occur; higher risk in patients with sheep protein allergies or who have previously received intact ovine antibodies or ovine Fab.
Patients with poor cardiac function may deteriorate upon loss of inotropic effect of digoxin.
Hypokalemia may occur; monitoring recommended [1].
Adverse Effects
The most common adverse reactions are worsening congestive heart failure (13%), hypokalemia (13%) and worsening atrial fibrillation (7%) [1].
Monitoring
Monitor serum digoxin serum concentration before digoxin immune Fab administration, if possible, to establish the digitalis intoxication diagnosis. Serum digoxin concentrations may be inaccurate for a period of time (several days or a week, or more in patients with renal

impairment) after administration due to interference with digitalis immunoassay measurements. Monitor temperature, blood pressure, and ECG during and after administration. Monitor potassium levels frequently, particularly during the first several hours after administration. Consider assessing free digoxin levels after administration in patients with renal failure to detect a possible recurrence of toxicity. Monitor for signs and symptoms of hypersensitivity reactions [1].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Digoxin immune Fab (ovine) is a sterile, lyophilized preparation of digoxin-immune ovine Fab (monovalent) immunoglobulin fragments obtained from the blood of healthy sheep. Digoxin immune Fab referentially binds molecules of digoxin or digitoxin, and the complex is then excreted by the kidneys. As free serum digoxin is removed, tissue-bound digoxin is also

released into the serum to maintain the equilibrium and is bound and removed by digoxin immune Fab. The net result is a reduction in serum and tissue digoxin. Distributes extensively in the extracellular fluid. Digoxin-specific Fab fragments are excreted in the urine. The elimination half-life in patients with normal renal function is approximately 15 hours. In patients with renal impairment, the half-life may be increased by up to 10-fold [1]. Poorly removed by hemodialysis [3].

ABOUT

Special Considerations/Preparation

Available as a vial containing 40 mg of digoxin immune Fab protein. Store in refrigerator; do not freeze. Reconstitute the vial with 4 mL of Sterile Water for Injection and mix gently; the final concentration will be approximately 10 mg/mL. May dilute the reconstituted solution with NS to a concentration of 1 mg/mL for small doses or to an appropriate volume of NS for administration. Use reconstituted product immediately; if not used immediately, refrigerate and use within 4 hours [1].

Digoxin

NeoFax Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION
Dose
Loading dose ("Digitalization"): Generally used only when treating arrhythmias and acute congestive heart failure. Give over 24 hours as 3 divided doses.
Oral doses should be 25% greater than IV doses. Do not administer IM.
Note: These beginning doses are based primarily on studies that measured echocardiographic changes and EKG signs of toxicity and take into account renal maturation.
Titrate dosage based on clinical response. Decrease dose proportional to the reduction in creatinine clearance.
Total Loading Dose
PMA weeks
IV mcg/kg/total dose
Oral mcg/kg/total dose
Divide total dose into 3 doses over 24 hours
Divide total dose into 3 doses over 24 hours
?29 15 20
30 to 36
20 25
37 to 48
30 40
?49 40 50
Maintenance Doses
Titrate based on clinical response.
PMA weeks
IV mcg/kg/dose
Oral mcg/kg/dose
Interval hours
?29 4 5 24
30 to 36 5 6 24
37 to 48 4 5 12
?49 5 6 12
Uses
Heart Failure or Arrhythmias
Treatment of heart failure caused by diminished myocardial contractility. Treatment of SVT, atrial flutter, and atrial fibrillation.
In neonates with pulmonary hypertension, supportive care with digitalis may be used cautiously for signs of right-sided heart failure; however, the data are limited and digoxin is

rarely used in the pediatric population. Digoxin is not effective for acute deterioration [3].

Administration
Intravenous: Infuse concentrations of 20 mcg/mL or 100 mcg/mL over 15 to 30 minutes [1].
Oral: Give consistently with regard to feedings [2].
MEDICATION SAFETY
Contraindications/Precautions
Contraindicated with ventricular fibrillation or a history of hypersensitivity to digoxin or other digitalis preparations [4].
Use caution in patients with low body weight, hypokalemia, hypomagnesemia, hypercalcemia, and renal impairment, as risk of digoxin toxicity is higher in these patients; monitoring and dose adjustment may be required. Wolff-Parkinson-White syndrome patients with atrial fibrillation have an increased risk of ventricular fibrillation. Severe sinus bradycardia or sinoatrial block may occur, especially in patients with preexisting sinus node disease or incomplete atrioventricular block; consider pacemaker placement before initiating treatment. Decreased cardiac output may develop with use in patients with heart failure associated with preserved left ventricular systolic function. May induce ventricular arrhythmias in patients undergoing electrical cardioversion; consider reducing dose or discontinuing use 1 to 2 days prior to procedure. Avoid use in patients with myocarditis; use not recommended in patients with acute myocardial infarction. Drugs that affect renal function (eg, ACE inhibitors, angiotensin receptor blockers, NSAIDs, COX-2 inhibitors) may increase digoxin exposure [4][2].
Adverse Effects
Toxic Cardiac Effects:
PR interval prolongation
Sinus bradycardia or SA block
Atrial or nodal ectopic beats
Ventricular arrhythmias
Nontoxic Cardiac Effects:
QTc interval shortening
ST segment sagging
T-wave amplitude dampening
Heart rate slowing
Other Effects: Feeding intolerance, vomiting, diarrhea, and lethargy.
Treatment of Life-Threatening Digoxin Toxicity:

Digibind Digoxin Immune Fab, IV over 30 minutes through 0.22-micron filter.
Dose (# of vials) = (weight [kg]) x (serum digoxin concentration)/100
Each vial of digibind contains 38 mg (enough to bind 0.5 mg Digoxin).
Solution Compatibility
(only when diluted 4-fold or greater): D5W, D10W, NS, and sterile water for injection.
Terminal Injection Site Compatibility
Cimetidine, famotidine, furosemide, heparin, hydrocortisone succinate, insulin, lidocaine, linezolid, meropenem, midazolam, milrinone, morphine, potassium chloride, ranitidine, and remifentanil.
Terminal Injection Site Incompatibility
Amiodarone, dobutamine, fluconazole, and propofol.
Monitoring
Follow heart rate and rhythm closely. Periodic EKGs to assess both desired effects and signs of toxicity. Follow closely (especially in patients receiving diuretics or amphotericin B) for decreased serum potassium and magnesium, or increased calcium and magnesium, all of which predispose to digoxin toxicity. Assess renal function. Be aware of drug interactions.
May follow serum drug concentrations if assay is available that excludes endogenous digoxinlike substances. Therapeutic serum concentration is 1 to 2 nanograms/mL.
MECHANISM OF ACTION/PHARMACOKINETICS
Pharmacology
Digitalis glycoside with positive inotropic and negative chronotropic actions. Increases myocardial catecholamine levels (low doses) and inhibits sarcolemmal sodium-potassium-ATPase (higher doses) to enhance contractility by increasing systolic intracellular calcium-ion concentrations. Indirectly increases vagal activity, thereby slowing S-A node firing and A-V node conduction. Other effects include peripheral, splanchnic, and perhaps, pulmonary vasoconstriction, and reduced CSF production. Serum concentration peaks 30 to 90 minutes

after an oral dose, with myocardial peak occurring in 4 to 6 hours. Large volume of distribution that increases with age during infancy. Rapid absorption of oral dose from small intestine; reduced by antacids and rapid transit times. 20% protein bound. Probably not

significantly metabolized. Glomerular filtration and tubular secretion account for most of the total body clearance of digoxin, although significant nonrenal elimination has been proposed.
ABOUT
Special Considerations/Preparation
Pediatric dosage forms: Injectable (100 mcg/mL) and elixir (50 mcg/mL).
Store at room temperature and protect from light.
Dilute injectable as follows:
1) Draw up digoxin into syringe.
2) Inject desired amount of drug into second syringe containing a 4-fold or greater volume of solution-compatible diluent. Use diluted product immediately.
Drug Interactions: Amiodarone, indomethacin, spironolactone, quinidine, and verapamil decrease digoxin clearance. Cisapride and metoclopramide decrease digoxin absorption. Spironolactone interferes with radioimmunoassay. Erythromycin may increase digoxin absorption.

DOBUTamine
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
Usual dose: 2 to 25 mcg/kg per minute continuous IV infusion. Begin at a low dose and titrate by monitoring effects. Use a large vein for IV.
Uses
Hypoperfusion and Hypotension: Treatment of hypoperfusion and hypotension, especially if related to myocardial dysfunction.
Severe Sepsis and Septic Shock[4][5]
Hemodynamic Support - First 60 Minutes
Time Management- Proceed to next step if shock persists
0
minutes
Maintain airway and establish access
5
minutes
Push 10 mL/kg isotonic crystalloid or colloid boluses up to 40 mL/kg until improved perfusion or unless hepatomegaly.
Begin prostaglandin infusion until rule out ductal-dependent lesion.
15
minutes
DOPamine less than 10 mcg/kg/min +/- DOBUTamine for fluid-refractory shock

EPINEPHrine 0.05 to 0.3 mcg/kg/min for fluid-refractory DOPamine-resistant shock
60 min
Cold shock-Poor LV function
Normal blood pressure
ScvO(2) less than 70%*/Hgb greater than 12 g/dL
SVC flow less than 40 mL/kg/min or CI less than 3.3 L/min/m(2)
Add nitrovasodilator milrinone or inamrinone with volume loading
Cold shock- Poor RV function
PPHN
ScvO(2) less than 70%*
SVC flow less than 40 mL/kg/min or CI less than 3.3 L/min/m(2)
Inhaled nitric oxide
Inhaled iloprost or IV adenosine
IV milrinone or inamrinone
Warm shock- Low blood pressure
Titrate volume
Add norepinephrine
Vasopressin or terlipressin or angiotensin
Refractory shock
Hydrocortisone if absolute adrenal insufficiency.
Triiodothyronine if hypothyroid.
Begin pentoxifylline if VLBW newborn.
Consider closing PDA if hemodynamically significant.
ECMO
Goals
First Hour: restore and maintain heart rate thresholds, capillary refill of 2 seconds or less, and

normal blood pressure.
NICU: normal MAP-CVP, preductal and postductal oxygen saturation difference less than 5%,
*ScvO(2) greater than 70% (except congenital heart patients with mixing lesions), SVC flow greater than 40 mL/kg/min, or cardiac index greater than 3.3 L/min/m(2)
KEY: CI = cardiac index, Hgb = hemoglobin, LV function = left ventricle function, MAP-CVP = mean arterial pressure-central venous pressure, PDA = patent ductus arteriosus, PPHN = persistent pulmonary hypertension of the newborn, ScvO(2) = continuous central venous oxygen saturation, SVC = superior vena cava, VLBW = very low birth weight
Davis et al: Crit Care Med 2017;45(6)
Administration
May administer by IV or IO route as a continuous infusion. Avoid bolus administration of the

drug. Infusion into a large vein is preferred to minimize risk of tissue extravasation. Vials must be diluted prior to use in compatible diluent up to a concentration of 4000 mcg/mL.
Solutions containing DOBUTamine may exhibit a pink color which will increase with time due to oxidation of the drug. There is no significant loss of potency over 24 hours [1][2]. The recommended concentration in neonates is 2000 mcg/mL [3].
Solution Preparation Calculations
To calculate the AMOUNT of drug needed per defined final fluid volume:
Desired final concentration (mg/mL) x defined final fluid volume (mL) = AMOUNT of drug to add to final infusion solution (mg).
To calculate the VOLUME of drug needed per defined final fluid volume:
*AMOUNT of drug to add (mg) ug (vial) concentration (mg/mL) = VOLUME of drug to add (mL)
Example (for DOBUTamine): 30 mL of 2000 mcg/mL solution using DOBUTamine concentration of 12.5 mg/mL.
2000 mcg/mL = 2 mg/mL
2 mg/mL x 30 mL = 60 mg DOBUTamine
*60 mg .5 mg/mL = 4.8 mL of DOBUTamine
Add 4.8 mL of DOBUTamine (12.5 mg/mL) to 25.2 mL of compatible solution (eg, D5 W) to yield 30 mL of infusion solution with a concentration of 2000 mcg/mL.
Dobutamine Titration Chart
Concentration (mcg/mL)
Dose (mcg/kg/min)
IV Rate (mL/kg/hour)
2000
2.5
5
7.5
10
0.075
0.15
0.23
0.3
MEDICATION SAFETY
Adverse Effects

May cause hypotension if patient is hypovolemic. Volume loading is recommended before starting DOBUTamine therapy. Tachycardia occurs at high dosage. Arrhythmias,

hypertension, and cutaneous vasodilation. Increases myocardial oxygen consumption. Tissue ischemia occurs with infiltration.

Solution Compatibility

D5W, D5NS, D10W, LR, and NS.

Terminal Injection Site Compatibility

Alprostadil, amiodarone, atropine, aztreonam, caffeine citrate, calcium chloride, calcium gluconate, caspofungin, ceftazidime, ciprofloxacin, dopamine, enalaprilat, epinephrine, famotidine, fentanyl, fluconazole, flumazenil, heparin, hydralazine, insulin, isoproterenol, lidocaine, linezolid, lorazepam, magnesium sulfate, meropenem, midazolam, milrinone, morphine, nicardipine, nitroglycerin, nitroprusside, pancuronium bromide, phentolamine, potassium chloride, procainamide, propofol, propranolol, ranitidine, remifentanil, vecuronium, and zidovudine.

Terminal Injection Site Incompatibility

Acyclovir, alteplase, aminophylline, cefepime, bumetanide, diazepam, digoxin, furosemide, ibuprofen lysine, indomethacin, micafungin, phenytoin, phytonadione, piperacillintazobactam, and sodium bicarbonate.

Monitoring

Continuous heart rate and intra-arterial blood pressure monitoring preferable. Observe IV site for signs of extravasation.

For a full-term newborn, the target heart rate and perfusion pressure (mean arterial pressure minus central venous pressure) are 110 to 160 beats/min and 55 mm Hg, respectively [4].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Synthetic catecholamine with primarily ?1-adrenergic activity. Inotropic vasopressor.

Increases myocardial contractility, cardiac index, oxygen delivery, and oxygen consumption.

Decreases systemic and pulmonary vascular resistance (adults). DOBUTamine has a more prominent effect on cardiac output than dopamine but less of an effect on blood pressure.

Onset of action is 1 to 2 minutes after IV administration, with peak effect in 10 minutes. Must be administered by continuous IV infusion because of rapid metabolism of drug. Serum halflife is several minutes. Metabolized in the liver by sulfoconjugation to an inactive compound.

There is wide interpatient variability in plasma clearance due to differences in metabolism and renal excretion.

ABOUT

Special Considerations/Preparation
Supplied as 250 mg per 20-mL vial (12.5 mg/mL) and premixed bags in concentrations of 1,
2, and 4 mg/mL. Diluted solutions for infusion should be used within 24 hours. Solutions
containing DOBUTamine and dextrose may exhibit a pink color which will increase with time
due to oxidation of the drug. There is no significant loss of potency.
There are no specific data regarding the compatibility of DOBUTamine and fat emulsions.
DOBUTamine is most stable in solutions with a pH at or below 5. In alkaline solutions, the
catechol moieties are oxidized, cyclized, and polymerized to colored materials. All fat
emulsions have pH ranges from 6 to 9. Caution is urged when co-infusing DOBUTamine and
fat emulsion together; DOBUTamine may degrade over time in this alkaline pH resulting in
lower than expected clinical effects.

DOPamine
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
Usual dose: 2 to 20 mcg/kg per minute continuous IV infusion. Begin at a low dose and
titrate by monitoring effects; for fluid refractory shock start at less than 10 mcg/kg/min [1].
Use a large vein for IV.
Uses
Hypotension.
Severe Sepsis and Septic Shock[1][5]
Hemodynamic Support - First 60 Minutes
Time Management- Proceed to next step if shock persists
0
minutes
Maintain airway and establish access
5
minutes
Push 10 mL/kg isotonic crystalloid or colloid boluses up to 40 mL/kg until improved
perfusion or unless hepatomegaly.
Begin prostaglandin infusion until rule out ductal-dependent lesion.
15
minutes
DOPamine less than 10 mcg/kg/min +/- DOBUTamine for fluid-refractory shock
EPINEPHrine 0.05 to 0.3 mcg/kg/min for fluid-refractory DOPamine-resistant shock
60 min

Cold shock-Poor LV function
Normal blood pressure
ScvO(2) less than 70%*/Hgb greater than 12 g/dL
SVC flow less than 40 mL/kg/min or CI less than 3.3 L/min/m(2)
Add nitrovasodilator milrinone or inamrinone with volume loading
Cold shock- Poor RV function
PPHN
ScvO(2) less than 70%*
SVC flow less than 40 mL/kg/min or CI less than 3.3 L/min/m(2)
Inhaled nitric oxide
Inhaled iloprost or IV adenosine
IV milrinone or inamrinone
Warm shock- Low blood pressure
Titrate volume
Add norepinephrine
Vasopressin or terlipressin or angiotensin
Refractory shock
Hydrocortisone if absolute adrenal insufficiency.
Triiodothyronine if hypothyroid.
Begin pentoxifylline if VLBW newborn.
Consider closing PDA if hemodynamically significant.
ECMO
Goals
First Hour: restore and maintain heart rate thresholds, capillary refill of 2 seconds or less, and

normal blood pressure.
NICU: normal MAP-CVP, preductal and postductal oxygen saturation difference less than 5%,
*ScvO(2) greater than 70% (except congenital heart patients with mixing lesions), SVC flow greater than 40 mL/kg/min, or cardiac index greater than 3.3 L/min/m(2)
KEY: CI = cardiac index, Hgb = hemoglobin, LV function = left ventricle function, MAP-CVP = mean arterial pressure-central venous pressure, PDA = patent ductus arteriosus, PPHN = persistent pulmonary hypertension of the newborn, ScvO(2) = continuous central venous oxygen saturation, SVC = superior vena cava, VLBW = very low birth weight
Davis et al: Crit Care Med 2017;45(6)
There was no difference between epinephrine and dopamine for fluid-refractory septic shock in a randomized, double-blind controlled trial (n=40) in India; however, the study was underpowered. After persistent shock despite 2 boluses of normal saline 10 mL/kg,

epinephrine 0.2 mcg/kg/min or dopamine 10 mcg/kg/min were started. Doses were increased, if needed, after 15 minutes to epinephrine 0.3 mcg/kg/min or dopamine 15 mcg/kg/min; then again, if needed, after another 15 minutes to epinephrine 0.4 mcg/kg/min or dopamine 20 mcg/kg/min. The mean gestational age was 30.3 weeks (1.1 kg birth weight) for epinephrine group and 30.7 weeks (1.181 kg birth weight) for dopamine group [6].

Administration

May administer by IV or IO route as a continuous infusion. Avoid bolus administration of the drug. Infusion into a large vein is preferred to minimize risk of tissue extravasation. Vials must be diluted prior to use in compatible diluent up to a concentration of 3200 mcg/mL [2] [3]. The recommended standard neonate concentration is 1600 mcg/mL [4].

Solution Preparation Calculations

To calculate the AMOUNT of drug needed per defined final fluid volume:

Desired final concentration (mg/mL) ɹdefined final fluid volume (mL) = AMOUNT of drug to add to final infusion solution (mg).

To calculate the VOLUME of drug needed per defined final fluid volume:

*AMOUNT of drug to add (mg) ug (vial) concentration (mg/mL) = VOLUME of drug to add (mL)

Example (for DOPamine): 30 mL of 1600 mcg/mL solution using DOPamine concentration of 40 mg/mL.

1600 mcg/mL = 1.6 mg/mL

1.6 mg/mL 30ɹmL = 48 mg DOPamine

*48 mg mg/mL = 1.2 mL of DOPamine

Add 1.2 mL of DOPamine (40 mg/mL) to 28.8 mL of compatible solution (eg, D5W) to yield 30 mL of infusion solution with a concentration of 1600 mcg/mL.

Dopamine Titration Chart

Concentration (mcg/mL)	Dose (mcg/kg/min)	IV Rate (mL/kg/hour)
1600	2.5	0.094
	5	0.19
	7.5	0.28
	10	0.38

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MEDICATION SAFETY
Adverse Effects
Tachycardia and arrhythmias. May increase pulmonary artery pressure. Reversible suppression of prolactin and thyrotropin secretion.
Black Box Warning
Tissue sloughing may occur with IV infiltration. According to the manufacturer's black box warning, to prevent sloughing and necrosis in areas of extravasation, the area should be infiltrated as soon as possible with a saline solution containing phentolamine mesylate.
Suggested treatment for extravasation: Inject a 0.5 mg/mL solution of phentolamine into the affected area. The usual amount needed is 1 to 5 mL, depending on the size of the infiltrate.
Solution Compatibility
D5W, D5NS, D10W, LR, and NS.
Terminal Injection Site Compatibility
Aminophylline, amiodarone, aztreonam, caffeine citrate, calcium chloride, caspofungin, cefotaxime, cefoxitin, ceftazidime, chloramphenicol, dobutamine, enalaprilat, epinephrine, esmolol, famotidine, fentanyl, fluconazole, flumazenil, gentamicin, heparin, hydrocortisone succinate, ibuprofen lysine, lidocaine, linezolid, lorazepam, meropenem, metronidazole, micafungin, midazolam, milrinone, morphine, nicardipine, nitroglycerin, nitroprusside, oxacillin, pancuronium bromide, piperacillin/tazobactam, potassium chloride, propofol, prostaglandin E1, ranitidine, tobramycin, vecuronium, and zidovudine.
Terminal Injection Site Incompatibility
Acyclovir, alteplase, amphotericin B, ampicillin, cefepime, furosemide, indomethacin, insulin, penicillin G, and sodium bicarbonate.
Monitoring

Continuous heart rate and intra-arterial blood pressure monitoring is preferable. Assess urine output and peripheral perfusion frequently. Observe IV site closely for blanching and infiltration.
MECHANISM OF ACTION/PHARMACOKINETICS
Pharmacology
Catecholamine that is metabolized rapidly. Serum half-life is 2 to 5 minutes, but clearance is

quite variable. DOPamine increases blood pressure primarily by increasing systemic vascular resistance via ?-adrenergic effects. Effects on cardiac output vary with gestational age and baseline stroke volume. Selective renal vasodilation associated with increases in urine output has been noted in preterm neonates at doses of 2 to 5 mcg/kg/minute. No changes in mesenteric or cerebral blood flow were observed. Mechanism of action in neonates is controversial. Relative effects of DOPamine at different doses are uncertain because of developmental differences in 1) endogenous norepinephrine stores, 2) ?-adrenergic, ?-adrenergic, and dopamine receptor functions, and 3) the ability of the neonatal heart to increase stroke volume. Responses tend to be individualized. Use higher doses with caution in patients with persistent pulmonary hypertension of the newborn.

ABOUT

Special Considerations/Preparation

Available in 40-mg/mL, 80-mg/mL, and 160-mg/mL vials for injection and premixed bags in concentrations of 800, 1600, and 3200 mcg/mL. Diluted solutions stable for 24 hours.

Admixtures exhibiting a color change should not be used.

There are no specific data regarding the compatibility of DOPamine and fat emulsions.

DOPamine is most stable in solutions with a pH at or below 5. In alkaline solutions, the catechol moieties are oxidized, cyclized, and polymerized to colored materials. All fat emulsions have pH ranges from 6 to 9. Caution is urged when co-infusing DOPamine and fat emulsion together; DOPamine may degrade over time in this alkaline pH resulting in lower than expected clinical effects.

Dornase alfa

NeoFax Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

1.25 mL to 2.5 mL via nebulizer, or 0.2 mL/kg instilled directly into the endotracheal tube. Administer once or twice per day.

Uses

Treatment of atelectasis secondary to mucus plugging, that is unresponsive to conventional therapies.

MEDICATION SAFETY

Adverse Effects

Desaturation and/or airway obstruction may occur due to rapid mobilization of secretions.
Monitoring
Monitor airway patency. Suction the airway as needed.
MECHANISM OF ACTION/PHARMACOKINETICS
Pharmacology
Pulmozyme is a highly purified solution of recombinant human deoxyribonuclease
(rhDNase, an enzyme that selectively cleaves DNA). The protein is produced by genetically
engineered Chinese hamster ovary cells. Purulent pulmonary secretions contain very high
concentrations of extracellular DNA released by degenerating leukocytes. rhDNase hydrolyzes
this DNA to decrease the viscoelasticity of the secretions. Clinical improvements in the
thickness of secretions and ventilation usually occur within 3 hours of administration.
ABOUT
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cexpert/ND_T/evidencexpert/PFActionId/evidencexpert.Pr
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Special Considerations/Preparation
Pulmozyme is supplied in single-use ampules. Each ampule contains 2.5 mL of a sterile,
clear, colorless, aqueous solution containing 1 mg/mL dornase alfa (2.5 mg per ampule),
0.15 mg/mL calcium chloride dihydrate, and 8.77 mg/mL sodium chloride (22 mg per
ampule) with no preservative. The nominal pH of the solution is 6.3. The ampules should be
stored in their protective foil pouch under refrigeration at 2 to 8 degrees C (36 to 46 degrees
F) and protected from strong light. Do not use beyond the expiration date on the ampule [1].

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https://www.micromedexsolutions.com/micromedex2/librar
ian/CS/3208DF/ND_PR/evidencexpert/ND_P/evidencexpert/D
UPLICATIONSHIELDSY 1/1
Electrolytes/Minerals
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
Daily Requirement: Recommendations from the American Society for Parenteral and
Enteral Nutrition [1].
Daily Electrolyte and Mineral Requirements*

Electrolyte	Preterm neonates	Infants/children
Sodium	2 to 5 mEq/kg/day	2 to 5 mEq/kg/day
Potassium	2 to 4 mEq/kg/day	2 to 4 mEq/kg/day
Calcium	2 to 4 mEq/kg/day	0.5 to 4 mEq/kg/day
Phosphorus	1 to 2 mmol/kg/day	0.5 to 2 mmol/kg/day
Magnesium	0.3 to 0.5 mEq/kg/day	0.3 to 0.5 mEq/kg/day

Acetate As needed to maintain acid-base balance As needed to maintain acid-base balance
Chloride As needed to maintain acid-base balance As needed to maintain acid-base balance
*Assumes normal age-related organ function and normal losses.
ABOUT
References
1. Mirtallo J, Canada T, Johnson D, et al: Safe practices for parenteral nutrition. JPEN J Parenter Enteral Nutr 2004; 28(6):S39-S70.PubMed Abstract: http://www.ncbi.nlm.nih.gov/...PubMed Article: http://www.ncbi.nlm.nih.gov/...

Emtricitabine
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
Prior to or during initiation, test patients for hepatitis B virus infection[1].
HIV Infection
3 mg/kg orally once daily [1].
Dose Adjustments
Renal Impairment
There are no published recommendations available for dose adjustment in neonatal patients with renal impairment. Since elimination of emtricitabine is primarily dependent on CrCl, dose adjustments in neonates should be similar to CrCl-based dose adjustments for adults. The following dose adjustments are consistent with recommendations in adult patients with renal impairment [2]:
CrCl 30 to 49 mL/min: 1.5 mg/kg (0.15 mL/kg) every 24 hours.
CrCl 15 to 29 mL/min: 1 mg/kg (0.1 mL/kg) every 24 hours.
CrCl less than 15 mL/min or receiving hemodialysis: 0.75 mg/kg (0.075 mL/kg) every 24 hours; give dose after hemodialysis on hemodialysis days.
Uses
Antiretroviral Management in the Newborn[3]

Risk of HIV in Newborn	Description	Antiretroviral (ARV) Management
Low risk of transmission	Mother had consistent viral suppression near delivery with standard combination ARV therapy during pregnancy and was adherent	

to the regimen
Zidovudine for 4 weeks
Higher risk
of
transmission
Mother has not received antepartum
or intrapartum ARV therapy.
Mother has received only
intrapartum ARV therapy
Mother has received antepartum
and intrapartum ARV drugs but does
not have viral suppression near
delivery, particularly with vaginal
delivery
Mother has acute or primary HIV
infection during pregnancy or
breastfeeding #
Dual ARV prophylaxis with 6 weeks zidovudine
and 3 doses of nevirapine (prophylaxis dosage,
with doses within 48 hours of birth, 48 hours
later, and 96 hours after the second dose) OR
Empiric therapy: zidovudine, lamiVUDine, and
treatment doses of nevirapine OR
 Empiric therapy: zidovudine, lamiVUDine, and
raltegravir
Presumed
exposure
Mother with unknown HIV status
who test positive at delivery or
ARV management is the same as those with
higher risk of transmission (see above).

postpartum or whose newborn has
positive HIV antibody test.
Discontinue immediately if supplemental
testing confirms mother does not have HIV.
Confirmed
Confirmed positive newborn HIV
virologic test/nucleic acid test.
3-drug regimen (zidovudine, lamiVUDine, and
nevirapine) at treatment dosage OR
3-drug regimen (zidovudine, lamiVUDine and
raltegravir)
KEY
 = Initiate ARV drugs as close to the time of birth as
possible, preferably within 6 to 12 hours of
delivery.
 = Optimal duration is unknown, zidovudine should
always be continued for 6 weeks. When the
nucleic acid test at birth is negative, some experts
may discontinue nevirapine, raltegravir, and/or
lamiVUDine while others may continue empiric therapy
for 6 weeks.

= Due to a higher risk for in utero transmission to infants whose mothers had acute HIV during pregnancy, most experts would administer empiric HIV therapy. Discontinue breastfeeding if acute or primary HIV infection occurs during breastfeeding.
AIDSinfo, April 2019
Pediatric FDA Approved Indications
Treatment of HIV-1 infection, in combination with other antiretroviral agents, in children starting at birth [2].
Administration
May be administered with or without feedings [2].
MEDICATION SAFETY
Contraindications/Precautions
Precautions
Hepatic: Lactic acidosis and severe hepatomegaly with steatosis, including fatalities, have been reported; suspend treatment if lactic acidosis or hepatotoxicity (including hepatomegaly and steatosis) are suspected, even without marked elevations in transaminases [1]
Immunologic: Autoimmune disorders, including Graves disease, polymyositis, and Guillain-Barr 頼yndrome, have been reported in the setting of immune reconstitution; may occur many months after initiation of therapy [1]
Immunologic: Immune reconstitution syndrome has been reported; inflammatory response to opportunistic infections (eg, Mycobacterium avium, cytomegalovirus, Pneumocystis jirovecii pneumonia, TB) may occur during initial phase of antiretroviral therapy [1]
Renal: Dose adjustment recommended in patients with CrCl of less than 50 mL/min or receiving hemodialysis treatment; monitoring recommended [1]
Adverse Effects

In a 96-week, phase 2, open-label, non-randomized, multicenter study of HIV-infected pediatric patients 3 months to 17 years of age (n=116), skin discoloration, presenting as small, asymptomatic maculae on the palms or soles, occurred in 13% (annual incidence rate) of patients. All cases were mild (grade 1) and self-limiting with one exception (moderate, grade 2). Other common adverse events (all reported as annual incidence rates) were the following: infection (26%), increased cough (17%), otitis media (13%), rhinitis (13%), vomiting (12%), rash (11%), diarrhea (10%), pneumonia (8%), and gastroenteritis (8%).
Grade 3 or 4 adverse events considered to be probably or possibly related to emtricitabine

included leukopenia, anemia, gastroenteritis, and pancreatitis, all occurring at a frequency of less than 1% (annual incidence rate) [4].

Black Box Warning

Severe acute exacerbations of hepatitis B (HBV) have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued emtricitabine. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who are coinfected with HIV-1 and HBV and discontinue emtricitabine. If appropriate, initiation of anti-hepatitis B therapy may be warranted [1].

Monitoring

[3]

Antiretroviral Monitoring in Children (adjust schedule based on the specific antiretroviral regimen)

Baseline	1 to 2 weeks after initiation	2 to 4 weeks after initiation	Every 3 to 4 months	Only required every 6 to 12 months
Therapy Switch				
If clinical, immunologic, or virologic deterioration is suspected, perform more frequent CD4 cell count and plasma viral load monitoring. If toxicity noted, perform testing more frequently until toxicity resolved				
Adverse Effects	X	X	X	X
Adherence Evaluation	X	X	X	X
CBC with differential	X	X	X	X
Chemistries	X	X	X	X
Lipid Panel	X	X		
Random Plasma Glucose	X	X		

Urinalysis X X ?
CD4 count
?? X X X
265

HIV RNA

X X X X
Resistance
Testing
X X
Hepatitis B
screening
?
X X
KEY: CBC = complete blood count
Baseline may not be necessary if pre-therapy monitoring was performed within 30 to 90 days.
Monitor for adherence, effectiveness (CD4 cell count and plasma viral load [HIV RNA]), and toxicities every 3 to 4 months.
Chemistries include electrolytes, creatinine, glucose, and hepatic transaminases.
If lipids have been abnormal in the past, more frequent monitoring might be needed.
? Consider more frequent urinalysis in patients taking tenofovir disoproxil fumarate.
?? In all children, absolute CD4 cell count is recommended; CD4 percentage is an alternative for children younger than 5 years.
CD4 cell count, CBC, and chemistries can be monitored less frequently (every 6 to 12 months) in children and youth who are adherent to therapy and have CD4 cell count values well above the threshold for opportunistic infection risk, have sustained viral suppression, and have stable clinical status for more than 2 to 3 years.
Obtain virus resistance testing even if antiretroviral therapy is not immediately started.
? Only if individual previously demonstrated no immunity to hepatitis B and when initiating a regimen that contains agents with activity against hepatitis B (ie, lamivudine, emtricitabine, tenofovir alafenamide, or tenofovir disoproxil fumarate.
Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection, April, 2019; AIDSinfo
In patients co-infected with HBV and HIV who have discontinued emtricitabine, monitor liver function closely for at least several months after discontinuing therapy [1].
Monitor renal function in patients with moderate to severe renal impairment [1].
MECHANISM OF ACTION/PHARMACOKINETICS
Pharmacology

Emtricitabine a synthetic nucleoside analog with activity against HIV-1 reverse transcriptase and HBV DNA polymerase, and is consistently 4 to 10 times more potent than lamivudine, the other NRTI with similar activity. Mean absolute bioavailability of emtricitabine is 93% and 75% for the capsules and the oral solution, respectively, and the relative bioavailability of the oral solution is approximately 80% of the capsules [2][5]. In a pharmacokinetic study in infants younger than 3 months (n=20), after receipt of two short course of emtricitabine oral solution (each 3 mg/kg once daily for 4 days) during the first 3 months of life, emtricitabine exposure was similar to the exposures achieved in patients 3 months to 17 years of age with a 6 mg/kg-dose and adults with a 200-mg dose. Emtricitabine AUC decreased with increasing age over the first 3 months of life, correlating with an increase in total body clearance of the drug [3]. Rapidly and extensively absorbed following oral administration with peak plasma concentrations occurring at 1 to 2 hours post-dose. Protein binding is less than 4%. Primarily eliminated renally. Following emtricitabine administration, approximately 86% and 14% of the dose was recovered in the urine and feces, respectively. Clearance is decreased in patients with renal impairment. Half-life is approximately 12 hours in neonates [2].

ABOUT

Special Considerations/Preparation

Availability: Oral solution 10 mg/mL.

Storage: Refrigerate oral solution at 2 to 8 degrees C (36 to 46 degrees F). If stored at room temperature, the oral solution is stable for up to 90 days, and any unused portion must be discarded after this time [2].

Enalapril maleate

NeoFax Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Begin with 40 mcg/kg per dose (0.04 mg/kg per dose) given orally every 24 hours. Usual maximum dose 150 mcg/kg per dose (0.15 mg/kg per dose), as frequently as every 6 hours.

Titrate subsequent doses and interval based on amount and duration of response. Dosage may need to be increased every few days.

Uses

Treatment of moderate to severe hypertension. Afterload reduction in patients with congestive heart failure.

MEDICATION SAFETY

Contraindications/Precautions

Use with extreme caution in patients with impaired renal function: oliguria and increased serum creatinine occur frequently.

Adverse Effects

The most common adverse event in infants (cohort study; n=662) younger than 120 days, including term and preterm infants without significant congenital anomalies, on enalapril were hyperkalemia (13%), elevated serum creatinine (5%), hypotension (4%), and death (0.5%). Risk factors for adverse events were postnatal age younger than 30 days at first exposure and longer duration of therapy [1].

The CrCl significantly decreased in preterm and term neonates with cardiovascular disease after initiation of ACEIs (captopril or enalapril) in a retrospective review (n=206). The body surface area was less than 0.33 m2 for all neonates [2].

Monitoring

Frequent assessment of blood pressure, particularly after the first dose. Periodic assessment of renal function and serum potassium.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Enalapril is a prodrug that is hydrolyzed in the liver to form the active ACE inhibitor enalaprilat, which blocks the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor. It thereby decreases plasma and tissue concentrations of angiotensin II and aldosterone, and increases plasma and tissue renin activity. Enalaprilat also prevents the breakdown of bradykinin, a potent vasodilator. Vascular resistance is reduced without reflex tachycardia. Beneficial effects are thought to be caused by a combination of afterload reduction and long-term inhibition of salt and water retention. Bioavailability of oral dosage form is uncertain in neonates, but is significantly less than the 60% reported in adults. Onset of action after oral dose is 1 to 2 hours. Duration of action is quite variable in neonates, ranging from 8 to 24 hours.

ABOUT
Special Considerations/Preparation
Oral Powder for Solution: Available as a kit containing 1 bottle of enalapril maleate 150 mg powder for solution and 1 bottle of Ora-Sweet SF diluent. Once reconstituted, solution contains 1 mg/mL of enalapril maleate. Store at room temperature; protect from moisture and from freezing [3].
Prepare oral solution by adding approximately 75 mL of supplied Ora-Sweet SF diluent to 150-mL bottle of enalapril powder. Shake well for 30 seconds. Reopen the bottle and add the remaining diluent. Shake for an additional 30 seconds. Solution is stable for 60 days after reconstitution [3].
Oral Solution: Available in a ready-to-use oral solution containing 1 mg/mL of enalapril maleate in a 150-mL bottle [4].
Store under refrigerated conditions between 2 and 8 degrees C (36 and 46 degrees F). May be stored at a room temperature of 20 to 25 degrees C (68 to 77 degrees F) for up to 60 days. Protect from freezing or excessive heat [4].
Oral Tablets: Available as enalapril maleate 2.5-mg, 5-mg, 10-mg, and 20-mg oral tablets; also contains lactose. The 10-mg and 20-mg tablets also contain iron oxides. Protect from moisture [5].
Extemporaneous Preparation
To prepare 200 mL of a 1 mg/mL suspension: Place ten 20-mg enalapril tablets in a standard polyethylene terephthalate bottle. Add 50 mL of Bicitra (sodium citrate 500 mg/5 mL and citric acid 334 mg/5 mL). Shake for at least 2 minutes; let concentrate stand for 60 minutes; then shake for at least 1 additional minute. Add 150 mL of Ora-Sweet SF to the concentrate, shake well. Shake well before each use. Product stability is 30 days when refrigerated at 2 to 8 degrees C (36 to 46 degrees F) [5].
Oral suspension of enalapril maleate 1 mg/mL was stable for 50 days at 5 degrees C or 30 days at room temperature. A buffer solution was prepared with citric acid 592 mg,

hydrochloric acid 0.1 molar (M) 40.9 mL, sodium hydroxide 1 M 5.7 mL, and purified water 28.4 mL. Pure enalapril maleate powder 100 mg was dissolved in the solution and a simple syrup was added in sufficient quantity to achieve a final volume of 100 mL. The pH of the formulation was 2.55 to 2.78 [6].

Oral suspensions of enalapril maleate 0.1 mg/mL and 1 mg/mL, prepared with either hydroxyethylcellulose 0.5% solution (sugar-free) or a 1:10 mixture of raspberry syrup and hydroxyethylcellulose 0.5% solution (sugar added), were stable with a minimum of 98% retention of initial concentration for at least 30 days at 4 and 25 degrees C. In both formulations, methyl hydroxybenzoate 0.2% was included as a preservative, and citric acid 1 M was used to adjust the pH to 3. Over the 30 days of storage, pH and viscosity were not significantly altered with either of the enalapril suspension formulations [7].

Oral solutions of enalapril 1 mg/mL, using a citric acid buffer (pH 5) or a 1:1 mixture of Ora-Sweet and Ora-Plus as vehicles, were found to be stable for 91 days at both 4 and 25 degrees C with greater than 92% retention of labeled strength [8]. In another 60-day observation study, the stability of oral solutions of enalapril prepared with crushed tablets and 3 different vehicles (1:1 mixture Ora-Plus and Ora-Sweet; 1:1 mixture Ora-Plus and Ora-Sweet SF; cherry syrup) was confirmed with greater than 94% retention of the original strength during dark storage at 5 and 25 degrees C. No visual or olfactory changes were evident [9].

When admixed with deionized water, enalapril 1 mg/mL was stable for 56 days at 25 degrees C with greater than 90% retention of labeled strength [8], which extended an earlier report of 30-day stability at 5 degrees C for both 0.1 and 1 mg/mL concentrations [10].

Tablet dosage forms were crushed, extracted in isotonic citrate buffer (pH 5), and filtered. Hydroxybenzoate preservative did not prevent enalapril degradation [10].

Enalaprilat

NeoFax Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Begin with 10 mcg/kg per dose (0.01 mg/kg per dose) IV over 5 minutes every 24 hours.

Titrate subsequent doses and interval based on amount and duration of response. Dosage may need to be increased every few days.

Uses

Treatment of moderate to severe hypertension.

Afterload reduction in patients with congestive heart failure.

Administration
Administer over 5 minutes undiluted, or diluted to a concentration as low as 0.025 mg/mL [1].

MEDICATION SAFETY

Contraindications/Precautions
Use with extreme caution in patients with impaired renal function: oliguria and increased serum creatinine occur frequently.

Adverse Effects
Hypotension occurs primarily in patients who are volume-depleted. Hyperkalemia occurs primarily in patients receiving potassium-sparing diuretics or potassium supplements. Cough has been reported frequently in adults.
The CrCl significantly decreased in preterm and term neonates with cardiovascular disease after initiation of ACEIs (captopril or enalapril) in a retrospective review (n=206). The body surface area was less than 0.33 m2 for all neonates [2].

Solution Compatibility

D5W, D5NS, NS, and D5LR.

Terminal Injection Site Compatibility
Amikacin, aminophylline, ampicillin, aztreonam, calcium gluconate, cefazolin, ceftazidime, chloramphenicol, cimetidine, clindamycin, dobutamine, dopamine, erythromycin lactobionate, esmolol, famotidine, fentanyl, gentamicin, heparin, hydrocortisone succinate, lidocaine, linezolid, magnesium sulfate, meropenem, metronidazole, morphine, nafcillin, nicardipine, nitroprusside, penicillin G, phenobarbital, piperacillin, piperacillin/tazobactam, potassium chloride, propofol, ranitidine, remifentanil, sulfamethoxazole/trimethoprim, tobramycin, and vancomycin.

Terminal Injection Site Incompatibility
Amphotericin B, cefepime, and phenytoin.

Monitoring
Frequent assessment of blood pressure, particularly after the first dose. Periodic assessment of renal function and serum potassium.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology
Enalaprilat is an ACE inhibitor which blocks the production of the potent vasoconstrictor angiotensin II. It thereby decreases plasma and tissue concentrations of angiotensin II and aldosterone, and increases plasma and tissue renin activity. Enalaprilat also prevents the breakdown of bradykinin, a potent vasodilator. Vascular resistance is reduced without reflex

tachycardia. Beneficial effects are thought to be caused by a combination of afterload reduction and long-term inhibition of salt and water retention. Duration of action is quite variable in neonates, ranging from 8 to 24 hours.
ABOUT
Special Considerations/Preparation
Enalaprilat is supplied as a 1.25-mg/mL solution for injection in 1-mL and 2-mL vials. Benzyl alcohol content is 9 mg/mL. To make a dilution for IV use, take 1 mL (1.25 mg) of solution

and add 49 mL NS to make a final concentration of 25 mcg/mL (0.025 mg/mL). Dilution stable for 24 hours.

Enoxaparin
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
Evaluate all patients for a bleeding disorder before starting treatment, unless treatment is urgently needed[1].
Treatment of Thrombosis:
Term infants: initial, 1.7 mg/kg per dose subQ every 12 hours [2][3].
Preterm infants: initial, 2 mg/kg per dose subQ every 12 hours [2][3].
Adjust dosage to maintain anti-factor Xa level between 0.5 and 1.0 unit/mL. It will usually take several days to attain levels in the target range.
Dosage requirements to maintain target anti-factor Xa levels in preterm infants are quite variable, ranging from 0.8 to 3 mg/kg every 12 hours.
Low-risk prophylaxis: 0.75 mg/kg per dose subQ every 12 hours.
Adjust dosage to maintain anti-factor Xa level between 0.1 and 0.4 units/mL [4][5][6].
Dose Adjustments
Renal Impairment: No dosage adjustment recommendations are available for pediatric patients with renal impairment. However, in adult patients dosages are reduced in the presence of renal impairment [1].
A dose reduction of approximately 30% in pediatric patients (older than 1 year) with a creatinine clearance of 30 mL/min/1.73 2 or less was recommended based on a retrospective pharmacokinetic study (n=853) [7].
Uses
Anticoagulation. Advantages over standard unfractionated heparin:

(1) May be given subcutaneously,
(2) More predictable pharmacokinetics,
(3) Minimal monitoring,
(4) Dosing every 12 hours,
(5) Less frequent bleeding complications. .
One disadvantage is the inability to quickly and completely reverse its anticoagulant effects [9].

Treatment of Thrombosis

Several retrospective studies have suggested that higher initial doses are required to more quickly achieve therapeutic anti-Xa levels and reduce the number of dosage adjustments. In a retrospective study (n=33), initial doses of 1.8 +/- 0.4 mg/kg in full-term infants (younger than 2 months) and 2.2 +/- 0.5 mg/kg in preterm infants (37 weeks gestation or less) would have been necessary to achieve therapeutic anti-factor Xa levels [10]. In another retrospective study in children (n=192), higher initial doses (1.7 mg/kg every 12 hours for children 3 months of age and younger; 1.2 mg/kg every 12 hours for children greater than 3 months of age) achieved more rapid therapeutic anti-factor Xa levels resulting in fewer venipunctures,

without an increase in adverse events, compared with standard doses. Treatment outcomes (resolution or reduction of thrombus) were not different between groups. The authors concluded a higher starting dose of 1.8 mg/kg every 12 hours for infants less than 3 months of age and 1.5 mg/kg every 12 hours for children 3 to 12 months of age may be considered [11]. A third retrospective study (n=150) found that only 41% of patients attained therapeutic anti-Xa levels with initial dosing consistent with current standard treatment guidelines. The following doses were required to achieve a therapeutic anti-Xa level (dose given every 12 hours): less than one month of age, 1.8 mg/kg; one month to 1 year, 1.64 mg/kg [12]. A fourth retrospective study (n=140) also revealed that less than half of the population achieved therapeutic anti-Xa levels following the initial dose with the current standard treatment guidelines. The following higher doses were required to achieve a therapeutic anti-Xa level (dose given every 12 hours): less than 2 months of age, 1.6 mg/kg; 2 months to 1 year, 1.5 mg/kg [13].

In a retrospective study, whole-milligram enoxaparin dosing using insulin syringes (undiluted 100 mg/mL; 1 mg enoxaparin = 0.01 mL = 1 unit) was associated with therapeutic anti-Xa levels and no reported dose measurement errors. The study included neonates, infants and

children (n=514); 27% were infants less than 3 months of age (900 to 4700 g in weight). Five children (less than 1%) had a supra-therapeutic initial anti-Xa level without hemorrhagic consequences. No patients needed decimal dosing to attain therapeutic levels [8].
Call 1-800-NOCLOTS for case reporting and treatment guidance.
Administration
Administer by deep subQ injection. Not for IM administration.
Insulin syringes have been used to administered enoxaparin (undiluted 100 mg/mL; 1 mg enoxaparin = 0.01 mL = 1 unit) [8].
Administration may be aided by using a small plastic indwelling subcutaneous catheter (Insuflon, Hypoguard USA). Adverse events related to these catheters are much more frequent in ELBW infants.
MEDICATION SAFETY
Contraindications/Precautions
CONTRAINDICATIONS
Presence of active major bleeding[18]
History of immune-mediated heparin-induced thrombocytopenia within the past 100 days or in the presence of circulating antibodies [18].
Known hypersensitivity to enoxaparin, heparin or pork products, or benzyl alcohol (multidose form contains alcohol)[18]
PRECAUTIONS
Major bleeding may occur even with anti-factor Xa levels in the therapeutic range. The overall incidence is approximately 4% in children [6].
Reported complications include major bleeding or hematoma at the administration site, compartment syndrome, intracranial hemorrhage, and gastrointestinal hemorrhage [15][6].

Bleeding can occur at any site [1].
Use with caution in patients with a bleeding diathesis, uncontrolled arterial hypertension or a history of recent gastrointestinal ulceration, diabetic retinopathy, renal dysfunction and hemorrhage [18]
Epidural hematoma has been reported in pediatric patients who underwent lumbar puncture while receiving enoxaparin. It is recommended that 2 doses of enoxaparin be held prior to spinal invasive procedures and if possible, anti-Xa levels should be obtained prior to high-risk procedures [19]. Risk of epidural or spinal hemorrhage and subsequent hematomas is increased with the use of postoperative indwelling epidural catheters, with concomitant use of additional drugs affecting hemostasis (e.g. NSAIDs), with traumatic or repeated epidural or spinal puncture, or in patients with a history of spinal surgery or spinal deformity [18]

Heparin-induced thrombocytopenia or heparin-induced thrombocytopenia with thrombosis (HITTS) may occur [1] and was reported (with normal platelet count) in one case study in a child. Although HIT is rare with enoxaparin therapy (less than 1%), children are still at risk for developing it [20]; consider risk/benefit and alternative non-heparin treatment options in patients with history of HIT; monitoring required [1].
Thrombocytopenia of any severity may occur; closely monitor, discontinuation may be required
Serious and fatal adverse events including "gasping syndrome" may occur in neonates and low birth weight infants with use of the multiple-dose vials, which contain benzyl alcohol[18].
Adverse Effects
Major and minor bleeds occurred in 4% and 17% of pediatric patients (1 day to 18 years of age (median 3.5 years)) receiving enoxaparin for 146 courses of therapeutic uses and 0% and 6% of 31 pediatric patients (1 week to 17 years of age (median 5.5 years)) receiving prophylactic enoxaparin. Major bleeds were 2 gastrointestinal, 3 (2 of whom were neonates) intracranial bleeds, and 2 thigh hematomas in extremely premature neonates [6].
Black Box Warning
Epidural or spinal hematomas, which may result in long-term or permanent paralysis, may occur in patients who are anticoagulated with low molecular weight heparins or heparinoids and are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing these hematomas include:
Use of indwelling epidural catheters
Concomitant use of other drugs that affect hemostasis, such as non-steroidal antiinflammatory drugs (NSAIDs), platelet inhibitors, and other anticoagulants
A history of traumatic or repeated epidural or spinal punctures
A history of spinal deformity or spinal surgery
Optimal timing between the administration of Lovenox and neuraxial procedures is not known
Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary [1].
Consider the benefits and risks before neuroaxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis [1].

Solution Compatibility
NS, D5W, and sterile water.
Monitoring
Prothrombin time and aPTT are not adequate for monitoring anticoagulant effects [1].
Measure anti-factor Xa concentrations:
4 to 6 hours after a subQ dose - target 0.5 to 1 units/mL
2 to 6 hours after a subQ dose - target 0.5 to 0.8 units/mL
. Preterm infants are likely to require several dosage adjustments to achieve the target levels.
Obtain anti-factor Xa levels initially, weekly during hospitalization, and then every 3 to 4 weeks in stable patients. After attaining target levels, dosage adjustments will be necessary once or twice a month, perhaps more often in preterm infants and infants with hepatic or renal dysfunction [14][15][9][16]. Anti-factor Xa concentrations vary with the assay method; there is a lack of standardization for methods [17].
Obtain CBC (including platelet count), stool occult blood, and liver function tests during therapy. Monitor blood pressure. Monitor patients with renal impairment closely during therapy (dose reduction necessary). Assess for signs of bleeding and thrombosis. Patients undergoing concomitant neuraxial anesthesia or spinal puncture should be monitored frequently for neurological impairment indicating possible spinal or epidural hematoma [1][14][9][16].
MECHANISM OF ACTION/PHARMACOKINETICS
Pharmacology
Enoxaparin is a low-molecular weight heparin that has considerably less activity against thrombin than does standard heparin. Efficacy in neonates is decreased due to low antithrombin plasma concentrations. It is also much less likely to interfere with platelet function or cause osteoporosis. It activates antithrombin III, which progressively inactivates both thrombin and factor Xa, key proteolytic enzymes in the formation of fibrinogen and activation of prothrombin. Bioavailability is almost 100% after subcutaneous administration, with peak activity 2.5 to 4 hours later. The apparent half-life of anti-Xa activity is 4 to 5 hours. Clearance in neonates is more rapid than in older infants, children or adults.
ABOUT
Special Considerations/Preparation
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Availability: 100-mg/mL concentration as 30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, 100 mg/mL in preservative-free prefilled syringes [18]. Multidose vial available in

100-mg/mL concentration with 15 mg benzyl alcohol per 1 mL as a preservative (not approved for use in neonates or infants) [18].
Undiluted enoxaparin (100 mg/mL) transferred to tuberculin syringes and stored under refrigeration retained anti-Xa activity for 10 days. Syringes stored at room temperature did not retain anti-Xa activity [21].
Enoxaparin Dilution
A 20-mg/mL enoxaparin dilution (in preservative-free sterile water) was stable for 4 weeks in glass vials stored at room temperature. The same dilution was stable in 1-mL tuberculin syringes (6 mg/0.3 mL) for 2 weeks stored at room temperature or under refrigeration. The stability end-point was significant loss of anti-Xa activity; sterility and pyrogenicity tests were not performed [22].
In another stability study, enoxaparin (20 mg/mL in 1-mL tuberculin syringes) diluted in 4% glucose retained greater than 99% of the baseline anti-Xa activity when stored under refrigeration (4 degrees C) for 31 days. A decrease of 10% (statistically significant) of the initial anti-Xa activity was noted when enoxaparin (20 mg/mL in 1 mL tuberculin syringes) was diluted with sterile water and stored under the same conditions. Stability of enoxaparin in commercially available 5% glucose solution was not tested in this study; however, the authors suggest that an increase in glucose concentration would not affect the stability of the dilution [23].
A 20-mg/mL enoxaparin dilution in 0.9% normal saline (in 1-mL polypropylene syringes; 10 mg/0.5 mL) was stable for up to 43 days when stored at room temperature or under refrigeration (2 to 8 degrees C). At least 90% of the baseline anti-Xa activity was retained under these conditions [24].
Enoxaparin 120 mg (1.2 mL) diluted to 100 mL in 0.9% normal saline (1.2 mg/mL final concentration) in polyvinyl chloride containers was stable for up to 48 hours at room temperature; greater than 94% of the baseline anti-Xa activity was retained during the time period [25].

EPINEPHrine (Adrenaline)
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose

Hypotension or Persistent Bradycardia; Prevention of Cardiac Arrest
Intravenous/Intraosseous (Low-dose): 1 mcg/kg (0.001 mg/kg) IV/IO via central administration for hypotension or persistent bradycardia with a pulse in a patient with an atrisk myocardium [1]; doses were repeated within 5 to 10 minutes and/or alternative therapies started in retrospective pediatric studies [2][3]; may be followed by 0.01 to 0.2 mcg/kg/min [1].
Resuscitation and severe bradycardia:
Intravenous 0.01 to 0.03 mg/kg (10 to 30 mcg/kg) IV with 0.1 mg/mL EPINEPHrine solution . Follow IV administration with 0.5 to 1 mL flush of normal saline [4][5].
IV continuous infusion: Start at 0.1 mcg/kg per minute and adjust to desired response, to a maximum of 1 mcg/kg per minute.
If possible, correct acidosis before administration of EPINEPHrine to enhance the effectiveness of the drug.
Resuscitation and severe bradycardia:
Endotracheal 0.05 to 0.1 mg/kg (50 to 100 mcg/kg) via endotracheal tube with 0.1 mg/mL EPINEPHrine solution. Follow ET administration with several positive pressure ventilations [4] [5]. Do not administer these higher doses of EPINEPHrine intravenously.
Septic Shock; Fluid-Refractory DOPamine-Resistant:
Intravenous 0.05 to 0.3 mcg/kg/min IV [6]
Uses
Acute cardiovascular collapse. Short-term use for treatment of systemic hypotension.
Despite the widespread use of EPINEPHrine/adrenaline during resuscitation, no placebocontrolled studies have evaluated either the tracheal or intravenous administration of EPINEPHrine at any stage during cardiac arrest in human neonates. Nonetheless, it is reasonable to continue to use EPINEPHrine when adequate ventilation and chest compressions have failed to increase the heart rate to greater than 60 beats per minute [5].
The American Heart Association (AHA) did not review the use of EPINEPHrine in the 2015 Neonatal Resuscitation guidelines; therefore, the 2011 AHA and AAP guidelines still apply [11].
Delayed administration of epinephrine during an in-hospital cardiac arrest with an initial nonshockable rhythm was associated with decreased chance of survival to hospital discharge, decreased chance of return of spontaneous circulation, decreased survival at 24 hours, and decreased survival to hospital discharge with a favorable neurological outcome in a

retrospective analysis of registry data (n=1558; median age, 9 months; interquartile range, 13 days to 5 years) [12].
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Bronchiolitis: Adrenergic agents are not recommended for the routine treatment of bronchiolitis in infants and children. Although no evidence supports this use, epinephrine as rescue therapy in rapidly deteriorating patients may have potential [13].
Hypotension or Persistent Bradycardia; Prevention of Cardiac Arrest: A pre-arrest small dose may avert cardiac arrest and allow time to treat an acute critical problem or to initiate extracorporeal life support without requiring extracorporeal cardiopulmonary resuscitation for hypotension or persistent bradycardia with a pulse in a patient with an atrisk myocardium [1]. Two retrospective studies demonstrated significant increases in mean arterial blood pressure, systolic blood pressure, and heart rate during acute episodes of hypotension in critically ill children administered low-dose EPINEPHrine boluses [2][3] at median doses of 0.7 mcg/kg IV (interquartile range (IQR) 0.3 to 2 mcg/kg) [3] and 1.3 mcg/kg IV (range, 0.2 to 5 mcg/kg). The median age was 9 years (IQR, 1 to 15 years) in one study (n=19 patients; 24 episodes) [2]. In the other study (n=144), the age groups were younger than 1 year (gestational age 37 weeks or longer) (47%), 1 to 5 years (17%), 5 to younger than 12 years (15%), and 12 to younger than 18 years (22%) [3]. Other terms used for this treatment was low-dose, dwindle dose, push-dose pressor, bolus-dose, spritzer vasopressor, or pre-arrest bolus dilute EPINEPHrine [2][3].
Severe Sepsis and Septic Shock[6]
Hemodynamic Support - First 60 Minutes
Time Management- Proceed to next step if shock persists
0
minutes
Maintain airway and establish access
5
minutes
Push 10 mL/kg isotonic crystalloid or colloid boluses up to 40 mL/kg until improved perfusion or unless hepatomegaly.
Begin prostaglandin infusion until rule out ductal-dependent lesion.
15
minutes

DOPamine less than 10 mcg/kg/min +/- DOBUTamine for fluid-refractory shock
EPINEPHrine 0.05 to 0.3 mcg/kg/min for fluid-refractory DOPamine-resistant shock
60 min
Cold shock-Poor LV function
Normal blood pressure
ScvO(2) less than 70%*/Hgb greater than 12 g/dL
SVC flow less than 40 mL/kg/min or CI less than 3.3 L/min/m(2)
Add nitrovasodilator milrinone or inamrinone with volume loading
Cold shock- Poor RV function
PPHN
ScvO(2) less than 70%*
SVC flow less than 40 mL/kg/min or CI less than 3.3 L/min/m(2)
Inhaled nitric oxide
Inhaled iloprost or IV adenosine
IV milrinone or inamrinone
Warm shock- Low blood pressure
Titrate volume
Add norepinephrine
Vasopressin or terlipressin or angiotensin
Refractory shock
Hydrocortisone if absolute adrenal insufficiency.
Triiodothyronine if hypothyroid.
Begin pentoxifylline if VLBW newborn.
Consider closing PDA if hemodynamically significant.
ECMO
Goals
First Hour: restore and maintain heart rate thresholds, capillary refill of 2 seconds or less, and normal blood pressure.

NICU: normal MAP-CVP, preductal and postductal oxygen saturation difference less than 5%,
*ScvO(2) greater than 70% (except congenital heart patients with mixing lesions), SVC flow greater than 40 mL/kg/min, or cardiac index greater than 3.3 L/min/m(2)
KEY: CI = cardiac index, Hgb = hemoglobin, LV function = left ventricle function, MAP-CVP = mean arterial pressure-central venous pressure, PDA = patent ductus arteriosus, PPHN = persistent pulmonary hypertension of the newborn, ScvO(2) = continuous central venous oxygen saturation, SVC = superior vena cava, VLBW = very low birth weight
Davis et al: Crit Care Med 2017;45(6)
There was no difference between epinephrine and dopamine for fluid-refractory septic shock

in a randomized, double-blind controlled trial (n=40) in India; however, the study was underpowered. After persistent shock despite 2 boluses of normal saline 10 mL/kg, epinephrine 0.2 mcg/kg/min or dopamine 10 mcg/kg/min were started. Doses were increased, if needed, after 15 minutes to epinephrine 0.3 mcg/kg/min or dopamine 15 mcg/kg/min; then again, if needed, after another 15 minutes to epinephrine 0.4 mcg/kg/min or dopamine 20 mcg/kg/min. The mean gestational age was 30.3 weeks (1.1 kg birth weight) for epinephrine group and 30.7 weeks (1.181 kg birth weight) for dopamine group [14].

Administration

Intravenous: When giving IV push, follow administration with 0.5 to 1 mL flush of normal saline. Always use the 0.1 mg/mL concentration for individual doses and the 1 mg/mL concentration to prepare continuous infusion solution. For continuous infusion, 10 mcg/mL is the recommended concentration for neonates [7].

Some institutions use standard concentrations of 10, 16, 20, 32, 40, 50, 60, 64, 100, 200, or 700 mcg/mL for continuous infusions in pediatric patients [8].

Endotracheal: Instill directly into ET tube and follow with several positive-pressure ventilations [5].

Intravenous infusion:

Solution Preparation Calculations

To calculate the AMOUNT of drug needed per defined final fluid volume:

Desired final concentration (mg/mL) x defined final fluid volume (mL) = AMOUNT of drug to add to final infusion solution (mg).

To calculate the VOLUME of drug needed per defined final fluid volume:

*AMOUNT of drug to add (mg) ug (vial) concentration (mg/mL) = VOLUME of drug to add (mL)

Example (for EPINEPHrine): Mix 50 mL of 20 mcg/mL solution using EPINEPHrine concentration of 1 mg/mL.

20 mcg/mL = 0.02 mg/mL

0.02 mg/mL 50mL = 1 mg EPINEPHrine

*1 mg mg/mL = 1 mL of EPINEPHrine

Add 1 mL of EPINEPHrine (1 mg/mL) to 49 mL of compatible solution (eg, D5 W) to yield 50 mL of infusion solution with a concentration of 20 mcg/mL.

Maximum concentration 60 mcg/mL.

Epinephrine Titration Chart

Concentration (mcg/mL)

Dose (mcg/kg/min)

IV Rate
(mL/kg/hour)
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10 0.05
0.1
0.5
1
0.3
0.6
36
20
0.05
0.1
0.5
1
0.15
0.3
1.5
3
30
0.05
0.1
0.5
1
0.1
0.2
12
40
0.05
0.1
0.5
1
0.075
0.15
0.75
1.5
50
0.05
0.1
0.5
1
0.06
0.12
0.6
1.2
60
0.05
0.1
0.5
1
0.05
0.1
0.5
1

IV Low-dose EPINEPHrine: Concentrations of 0.01 mg/mL (10 mcg/mL) may be used [2]
[3][9]; via central administration [1]. Preparation (10 mcg/mL): Draw up 9 mL of normal saline into a 10 mL syringe, then draw up 1 mL of EPINEPHrine 0.1 mg/mL [10].

MEDICATION SAFETY

Adverse Effects

Compared to dopamine, continuous infusions at doses yielding similar changes in blood pressure are more likely to cause hyperglycemia, tachycardia, and elevations in serum lactate. Cardiac arrhythmias (PVCs and ventricular tachycardia) are also more likely. Renal vascular ischemia may occur at higher doses. Bolus doses are associated with severe hypertension and intracranial hemorrhage. Increased myocardial oxygen requirements.

IV infiltration may cause tissue ischemia and necrosis. Suggested treatment: Inject a 1 mg/mL solution of phentolamine into the affected area. The usual amount needed is 1 to 5 mL, depending on the size of the infiltrate.

Solution Compatibility

D5W, D10W, and NS. Although NS is compatible, administration in saline solution alone is not recommended. Dextrose protects against oxidation of epinephrine [15].

Terminal Injection Site Compatibility

Amikacin, amiodarone, caffeine citrate, calcium chloride, calcium gluconate, ceftazidime, cimetidine, dobutamine, dopamine, famotidine, fentanyl, furosemide, heparin, hydrocortisone succinate, ibuprofen lysine, lorazepam, midazolam, milrinone, morphine, nicardipine, nitroglycerin, nitroprusside, pancuronium bromide, potassium chloride, propofol, ranitidine, remifentanil, vecuronium, and vitamin K1.

Terminal Injection Site Incompatibility

Aminophylline, ampicillin, hyaluronidase, micafungin, and sodium bicarbonate.

Monitoring

Monitor heart rate and blood pressure continuously. Observe IV site for signs of infiltration.

For a full-term newborn, the target heart rate and perfusion pressure (mean arterial pressure minus central venous pressure) are 110 to 160 beats/min and 55 mm Hg, respectively [6].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

EPINEPHrine (adrenaline) is the major hormone secreted by the adrenal medulla. It is a

potent stimulator of both alpha and beta adrenergic receptors, with complex effects on body organ systems. Low doses are associated with systemic and pulmonary vasodilation. Higher doses increase blood pressure by direct myocardial stimulation, increases in heart rate, and vasoconstriction. Myocardial oxygen consumption is increased. Blood flow to skeletal muscle, brain, liver, and myocardium is increased. However, blood flow to the kidney is decreased due to increased vascular resistance.
ABOUT
Special Considerations/Preparation
Available: 0.1 mg/mL and 1 mg/mL concentrations. Always use the 0.1 mg/mL concentration for individual doses and the 1 mg/mL concentration to prepare continuous infusion solution. Protect from light. Store at room temperature. Do not use if solution is discolored or precipitation occurs [15].
Stability of Prepared IV Solutions
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/evidencexpert/ND_B/evidencexpert/ND_AppProduct/evidencexpert/ND_T/evidencexpert/PFActionId/evidencexpert.PrintLandingPageDocument 6/6
EPINEPHrine solutions of 25, 50, 100 mcg/mL in D5W protected from light in sterile infusion bags (IntraVia container, Baxter) and stored at either 4 or 25 Celsius maintained at least 90% potency for up to 30 days [16].
EPINEPHrine solutions of 20, 300, 900 mcg/mL in D5W, D10W, or sodium chloride 0.9% in polypropylene syringes (Becton-Deckinson) and stored at 23 Celsius maintained at least 95% potency for at least 84 hours [17].
An EPINEPHrine solution of 100 mcg/mL in D5W protected from light in polyvinyl chloride minibags and stored at 23 Celsius maintained at least 99% potency for at least 24 hours [18].
An EPINEPHrine solution of 16 mcg/mL in D5W protected from light in Viaflex bags (Baxter) and stored at 5 Celsius was unstable after 20 days [19].
Some EPINEPHrine formulations contain sodium metabisulfite.

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5/7/2020 NeoFax Drug Monograph Summary - MICROMEDEX
https://www.micromedexsolutions.com/micromedex2/librarian/CS/093F05/ND_PR/evidencexpert/ND_P/evidencexpert/DUPLICATIONSHIELDSY 1/5
Epoetin alfa
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose

200 to 400 units/kg/dose, 3 to 5 times per week, for 2 to 6 weeks.
Total dose per week is 600 to 1400 units per kg.
Short course: 300 units/kg/dose daily for 10 days.
Supplemental iron therapy should be initiated concurrently.
Anemia of prematurity: Neither early [1]nor late [2]erythropoietin administration provided clinically significant benefit with regard to donor blood exposure in 2 meta-analyses (n=34 studies (3643 preterm and/or low birth weight infants) [1]and n=31 studies (1651 preterm infants)).[3]Therefore, erythropoietin is not recommended [1].
Uses
Hypoxic-ischemic Encephalopathy (HIE): Multiple high-doses of erythropoietin resulted in significantly improved short-term (12 months) motor outcomes in one, but not both, neurodevelopment assessment tests in newborns (mean gestational age, 38.7 weeks) undergoing hypothermia for moderate to severe HIE in a phase II double-blind, placebocontrolled trial (n=50). Less MRI brain injury was observed at a mean age of 5.2 days in the erythropoietin group compared with placebo group. Dosage of erythropoietin was 1000 units/kg IV on days 1, 2, 3, 5, and 7 (total, 5 doses) starting within the first 24 hours of life [4]. In term neonates with moderate or severe HIE who received 5 doses of erythropoietin 500 units/kg initiated by 6 hours of age without hypothermia therapy (n=100), composite death or moderate or severe disability at 19 months of age was significantly reduced by 43% (95% CI, 15% to 62%) and survival without neurological abnormality was significantly improved by 35% (95% CI, 6% to 55%; p=0.016) compared with placebo. However, there was no significant difference from placebo for death or disability in those with severe encephalopathy [5].
Neurocognitive Development - Prematurity:
Summary: Erythropoietin may provide a benefit in mental development but not other areas such as cerebral palsy, vision, or hearing in preterm newborns [6][7][8]. The benefit in preterm newborns may be limited to newborns 28 weeks or older gestation [9][6].
There was no significant difference between high-dose erythropoietin and placebo administered to extremely preterm newborns (24 weeks to 27 weeks 6 days gestation) in the primary outcome of death or severe neurodevelopment impairment at 22 to 26 months postmenstrual age in a double-blind, randomized trial (N=941). The relative risk for severe

neurodevelopment impairment was 0.79 (95% CI, 0.51 to 1.22); 11% in the erythropoietin group and 14% in the placebo group. Severe neurodevelopment was defined as the presence of severe cerebral palsy or a Bayley III Scales of Infant Development motor or cognitive score of less than 70. For moderate neurodevelopment impairment, there was no clinical difference between groups. Adverse events (severe bronchopulmonary dysplasia, medically

or surgically treated patent ductus arteriosus, intracranial hemorrhage, necrotizing enterocolitis, and retinopathy of prematurity) were not different between the groups. The dosages of erythropoietin were 1000 units/kg IV every 48 hours for 6 doses, then 400 units/kg subQ 3 times a week through 32 weeks 6 days of postmenstrual age [9].

In a meta-analysis including 4 randomized studies with 1133 preterm infants, prophylactic erythropoietin significantly reduced the incidence of a mental development index (MDI; Bayley Scales of Infant Development) of less than 70 at 18 to 24 months' corrected age compared with placebo or no treatment (odds ratio, 0.51; 95% CI, 0.31 to 0.81). However, there was no significant difference in psychomotor development index of less than 70, or in development of cerebral palsy, visual impairment, or hearing impairment. With limited data in infants less than 28 weeks' gestation, no significant difference in MDI less than 70 was observed [6]. In one of the included studies that showed no difference in neurodevelopmental outcomes at 2 years' corrected age in infants with a mean gestational age of 29 weeks (n=450), the dosage was erythropoietin 3000 international units/kg/dose (max 4500 international units/dose for weight 1.5 kg or greater) IV within 3 hours, at 12 to 18 hours, and at 36 to 42 hours after birth [10].

Another of the studies included in the metaanalysis showed neurocognitive outcomes that were minimally better in preterm infants treated with erythropoiesis stimulating agents (ESA) (erythropoietin or darbepoetin) compared with placebo, at 18 to 22 months of age (n=80) at high-altitude institutions. The study only used the Bayley Scales of Infant Development III to evaluate the infants. ESAs were continued until 35 weeks' gestation was completed; 400 units/kg/dose subQ 3 times

weekly for erythropoietin and 10 mcg/kg/dose subQ once weekly for darbepoetin [7]. At 2.5 to 4 years of age the same children (n=53) had significantly higher cognitive scores and improved executive function in the ESA group compared with placebo. When compared with term infants without complications, the cognitive performance in the ESA group were lower. Dosages were erythropoietin 400 units/kg/dose subQ 3 times a week and darbepoetin 10 mcg/kg/dose subQ once weekly until 35 completed weeks's gestation, discharge, transfer to another hospital, or death [8].

Anemia of prematurity

Early administration (before 8 days of age): Although there was a reduction in the use of RBC transfusions (RR 0.79 (95% CI 0.74 to 0.85)), volume of RBCs transfused, and number of donor exposures, with erythropoiesis-stimulating agents (ESAs; mostly epoetin alfa) compared with placebo, the differences were not clinically significant. This was demonstrated in a meta-analysis (n=34 studies; 3643 preterm and/or very low birthweight infants). ESAs did not have a significant effect on mortality. Retinopathy of prematurity (stage 3 or more) was not different between the 2 groups. There were conflicting results for neuroprotection, neurodevelopmental outcomes, intraventricular hemorrhage (grades III and IV), periventricular leukomalacia, and necrotizing enterocolitis [1].

Late administration: Although, the use of late administration (between 8 to 28 days of age) reduced the number of RBC transfusion per infant (by less than 1 transfusion/infant) the total volume of RBC transfused/infant was not reduced. Furthermore, most infants received blood transfusions prior to erythropoietin administration. Clinically significant adverse outcomes did not increase or decrease with late administration [3].

Administration

Note: Do not use epoetin alfa from multidose vials in neonates or infants; contains benzyl alcohol. Do not use single-dose vials admixed with bacteriostatic saline containing benzyl alcohol in neonates and infants.

Administer subQ, or IV over at least 4 hours (even continuously in total parenteral nutrition).

MEDICATION SAFETY

Contraindications/Precautions

Contraindicated in patients with a known hypersensitivity to mammalian cell-derived products or albumin (human), patients with uncontrolled hypertension, or in patients with pure red cell aplasia that develops with epoetin or other erythropoietin protein drugs.
Multidose vials contains benzyl alcohol; use single-dose vials in neonates.
Benzyl alcohol: Multidose vial contains benzyl alcohol which has been associated with fatal gasping syndrome in neonates and infants [12]
Dermatologic: Blistering and skin exfoliation reactions, including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported; discontinue use immediately if suspected [12]
Adverse Effects
An adverse effect in premature neonates is neutropenia, which occurs rarely and resolves with discontinuation of the drug.
Although data are conflicting, erythropoietin may be associated with retinopathy of prematurity (ROP). The risk may be reduced for stage greater than 3 ROP if erythropoietin is initiated before 8 days of age [13]
Treatment of preterm infants (median gestational age, 29 weeks) with epoetin was associated with an increased risk of infantile hemangiomas in a retrospective study; hazard ratio of 2.82 (n=2563) [14].
Black Box Warning
Adult patients with chronic kidney disease treated with erythropoiesis-stimulating agents (ESAs) to target a hemoglobin levels greater than 11 g/dL had a greater risk of serious cardiovascular reactions, stroke, and death. In addition, ESAs reduced survival and increased the risk of tumor progression or recurrence in studies of adult patients with cancers of the breast, non-small cell lung, head and neck, lymphoid, and cervix. No clinical trial has identified a risk-free hemoglobin target level, ESA dose, or dosing strategy.
The manufacturer recommends the lowest epoetin alpha dose needed to reduce RBC transfusion requirements for both chronic kidney disease and cancer indications. Prescribers and hospitals must enroll in the ESA APPRISE Oncology Program to prescribe and dispense epoetin alpha to patients with cancer. In patients with cancer, use ESAs only to treat anemia associated with myelosuppressive therapy, and discontinue treatment when a chemotherapy course is completed. ESAs are not indicated with myelosuppressive therapy for patients with cancer with a high probability of cure. Due to an increased risk of DVT, presurgical

prophylaxis is recommended. These findings have unknown relevance in the neonatal population [11].

Monitoring
Weekly CBC to check for neutropenia and monitor RBC response.
MECHANISM OF ACTION/PHARMACOKINETICS
Pharmacology
Mechanism of action: Epoetin alfa is a 165-amino acid glycoprotein manufactured by recombinant DNA technology that has the same biological effects as endogenous erythropoietin. It acts on mature erythroid progenitors, CFU-E, by binding to cell surface receptors and stimulating differentiation and cell division. Noticeable effects on hematocrit and reticulocyte counts occur within 2 weeks. Adequate iron and protein intake is necessary for epoetin to be effective (additional Vitamin E intake may be necessary as well).
Subcutaneously administered drug appears to be pharmacodynamically as effective as IV, despite only 40% bioavailability. Half-life of r-HuEPO in preterm infants is approximately 12 hours. Doses reported in the literature are all stated as units/kg per week. Efficacy may be dose dependent in the range of 500 to 1500 units/kg per week (see meta-analysis by Garcia et al), but no differences were observed in the randomized trial by Maier et al.
Hypoxic-ischemic Encephalopathy (HIE) treated with hypothermia: Target neuroprotective AUC48 hours of 140,000 milliUnits x hr/mL was achieved in all neonates (36 weeks' gestational age or older) receiving erythropoietin 1000 units/kg every 24 hours for 3 doses followed by every 48 hours for 2 doses (n=23), but in none of those who received a dose of 1000 units/kg every 48 hours to a maximum of 6 doses (n=7). For a typical 3.4 kg neonate receiving hypothermia, clearance was estimated at 0.0289 (standard error, 4.5%) L/hr and Vd of the central and peripheral compartments at 0.25 (4.1%) and 0.326 L (10.9%) [15].
ABOUT
Special Considerations/Preparation
Available in preservative-free, single-use, 1-mL vials containing 2000, 3000, 4000, or 10,000 units formulated in an isotonic, sodium chloride/sodium citrate buffered solution with 2.5 mg human albumin. Store refrigerated at 2 to 8 degrees C (36 to 46 degrees F). Do not freeze

or shake. Undiluted epoetin is stable in plastic syringes for 2 weeks. For IV infusion, dilute epoetin in 2 mL of solutions containing at least 0.05% protein and infuse over 4 hours. These dilutions are stable for 24 hours. Product support for use in neonates is handled by Ortho Biotech, Inc. (Procrit). Multidose 1-mL (20,000 units/mL) and 2-mL (10,000 units/mL) vials are also available from both Ortho Biotech (Procrit) and Amgen (Epogen) containing 1% (10 mg/mL) benzyl alcohol solution with 2.5-mg albumin per mL. Discard multidose vials 21 days after initial entry.
Enrollment in the ESA APPRISE Oncology program is required to prescribe and dispense

epoetin alpha to patients with cancer and anemia due to myelosuppressive chemotherapy (www.esa-apprise.com or 1-866-284-8089). Both prescribers and patients must acknowledge the risks of epoetin alpha treatment in writing before initiation of each new course of therapy [16].

Erythromycin
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
Oral
Treatment of pneumonitis and conjunctivitis due to Chlamydia trachomatis: 12.5 mg/kg per dose orally every 6 hours for 14 days [1].
Treatment and prophylaxis of pertussis: 12.5 mg/kg per dose orally every 6 hours for 14 days. The drug of choice in infants younger than 1 month of age is azithromycin.
Administer with infant formula to enhance absorption of the ethylsuccinate and reduce possible GI side effects.
Treatment of feeding intolerance due to dysmotility: 10 mg/kg per dose orally every 6 hours for 2 days, followed by 4 mg/kg per dose orally every 6 hours for 5 days.
Other infections and prophylaxis: 10 mg/kg per dose orally every 6 hours.
Intravenous
Severe infections when oral route unavailable: 5 to 10 mg/kg per dose IV infusion by syringe pump over at least 60 minutes every 6 hours.

Do not administer IM.
Ophthalmic
Prophylaxis of gonococcal ophthalmia neonatorum: Ribbon of 0.5% ointment instilled in each conjunctival sac [2][1].
Uses
General: Treatment of infections caused by Chlamydia, Mycoplasma, and Ureaplasma.
Treatment for and prophylaxis against Bordetella pertussis. As a substitute for penicillin in situations of significant allergic intolerance. As a prokinetic agent in cases of feeding intolerance.
Chlamydial Infection: Oral erythromycin base or erythromycin ethylsuccinate is recommended as the first-line agent for the treatment of ophthalmia neonatorum or pneumonia caused by Chlamydia trachomatis [1].
Gonococcal Ophthalmia Neonatorum; Prophylaxis: Universal prophylaxis with ophthalmic erythromycin to all newborns, regardless of gestational age, is recommended to prevent gonococcal ophthalmia neonatorum [2].
Administration

Intravenous: Give as intermittent infusion over at least 60 minutes at a concentration of 1 to 5 mg/mL. IV push administration is not recommended [3].
MEDICATION SAFETY
Contraindications/Precautions
Contraindications
Concomitant use with astemizole, terfenadine, cisapride, pimozide, ergotamine, or dihydroergotamine [4]
Concomitant use with HMG CoA reductase inhibitors (statins) that are extensively metabolized by CYP3A4 (lovastatin or simvastatin) [5]
Precautions
Cardiovascular: Life-threatening episodes of ventricular tachycardia associated with prolonged QT intervals (torsades de pointes) have been reported; increased risk in patients with electrolyte imbalance, hepatic dysfunction, myocardial ischemia, left ventricular dysfunction, idiopathic QT prolongation, and concurrent antiarrhythmic treatment [4].
Cardiovascular: QT interval prolongation, including rare cases of arrhythmia, torsade de pointes, and fatalities, has been reported; avoid use with known QT prolongation, uncorrected hypokalemia or hypomagnesemia, clinically significant bradycardia, and with

Class IA (quinidine, procainamide), or Class III (dofetilide, amiodarone, sotalol) antiarrhythmic agents [6]
Gastrointestinal: Clostridium difficile associated diarrhea (CDAD) has been reported; may range in severity from mild diarrhea to fatal colitis. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against C. difficile may need to be discontinued; initiate appropriate fluid/electrolyte management, protein supplementation, antibacterial drug treatment for C difficile, and surgical evaluation if clinically indicated [4].
Gastrointestinal: Infantile hypertrophic pyloric stenosis (IHPS) has been reported in infants following erythromycin treatment; weigh benefits against potential risk of developing IHPS [4]
Hepatic: Hepatic dysfunction, with or without jaundice, has been reported with oral erythromycin products; monitoring recommended for patients with impaired liver function [4]
Immunologic: Superinfection may occur with prolonged or repeated use; discontinue treatment and institute appropriate therapy [4]
Musculoskeletal: Exacerbation of weakness in patients with myasthenia gravis has been reported [4]
Adverse Effects
The use of macrolide antibiotics was associated with infantile hypertrophic pyloric stenosis with a 30-fold increased risk in infants exposed at 0 to 13 days of age and 3-fold increased risk in infants exposed at 14 to 120 days of age in an observational study (n=6591) [7].
Similar outcomes (highest risk of pyloric stenosis when exposed within the first couple weeks of life; although risk still present at 6 weeks of life) were demonstrated in another observational study (n=1902 exposed to erythromycin) [8].
Two reported cases of severe bradycardia and hypotension occurring during IV administration of erythromycin lactobionate.
Intrahepatic cholestasis. Loose stools occur

infrequently. Bilateral sensorineural hearing loss has been reported rarely in adults, usually associated with IV administration and renal or hepatic dysfunction. The hearing loss occurred after the first few doses and was reversible after discontinuing the drug. Venous irritation is common when using the IV dosage form.
Solution Compatibility

NS and sterile water for injection.
Solution Incompatibility
D5W and D10W (unless buffered with 4% sodium bicarbonate to maintain stability).
Terminal Injection Site Compatibility
Acyclovir, aminophylline, amiodarone, cimetidine, enalaprilat, esmolol, famotidine, heparin, hydrocortisone succinate, lidocaine, lorazepam, magnesium sulfate, midazolam, morphine, nicardipine, penicillin G, pentobarbital, potassium chloride, ranitidine, sodium bicarbonate, and zidovudine.
Terminal Injection Site Incompatibility
Ampicillin, cefepime, cefotaxime, ceftazidime, chloramphenicol, fluconazole, furosemide, linezolid, and metoclopramide.
Monitoring
Watch for diarrhea and signs of abdominal discomfort. CBC for eosinophilia. Monitor heart rate and blood pressure closely during IV administration. Observe IV site for signs of infiltration.
MECHANISM OF ACTION/PHARMACOKINETICS
Pharmacology
Mechanism of action: Erythromycin may be bacteriostatic or bactericidal depending on the tissue concentration of drug and the microorganism involved. The drug penetrates poorly

into the CNS, is concentrated in the liver, and is excreted in the bile [3][9].
Pharmacokinetics
IV administration of E. lactobionate to preterm infants, using doses of 6.25 to 10 mg/kg, yielded peak serum concentrations of 1.9 to 3.7 mcg/mL and a half-life of 2 hours. The drug penetrates poorly into the CNS, is concentrated in the liver and bile, and is excreted via the bowel. It is a motilin receptor agonist and induces stomach and small intestine motor activity.
Plasma clearance of midazolam is reduced by 50%. Digoxin, midazolam, theophylline and carbamazepine serum concentrations may be significantly increased because of prolongation of their half-life.
ABOUT
Special Considerations/Preparation
Oral: Erythromycin ethylsuccinate oral suspension is available in concentrations of 200 mg/5 mL (40 mg/mL) and 400 mg/5 mL (80 mg/mL). Refrigeration not required except to preserve taste. Shake suspension well before administering. To prepare a 20 mg/mL dilution of the

oral suspension, dilute 5 mL of the 200 mg/5 mL (40 mg/mL) erythromycin ethylsuccinate suspension (suspension made from powder for suspension only) up to a final volume of 10 mL with sterile water. Erythromycin ethylsuccinate suspension made from powder for suspension, at usual concentrations of 40 mg/mL and 80 mg/mL, is stable for 35 days at room temperature.
Injection: Available as powder for injection in 500-mg and 1-g vials. Reconstitute 500-mg vial with 10 mL of sterile water for injection to concentration of 50 mg/mL. Reconstituted solution stable for 24 hours at room temperature or 2 weeks in refrigerator. After reconstitution, dilute to a concentration of 1 to 5 mg/mL for infusion. To make a 5-mg/mL dilution, add 1 mL of reconstituted solution to 9 mL sterile water for injection. Use diluted drug within 8 hours [3].
Ophthalmic: Erythromycin ophthalmic is available as a 0.5% ointment.

Esmolol
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
Starting IV doses:
Supraventricular tachycardia (SVT): 100 mcg/kg per minute continuous infusion.
Increase in increments of 50 to 100 mcg/kg per minute every 5 minutes until control of the ventricular rate is achieved.
Acute management of postoperative hypertension: 50 mcg/kg per minute continuous infusion. Increase in increments of 25 to 50 mcg/kg per minute every 5 minutes until desired blood pressure is achieved.
Usual maximum dosage: 200 mcg/kg per minute.
Doses greater than 300 mcg/kg per minute are likely to cause hypotension.
Uses
Short term treatment of postoperative hypertension, supraventricular tachycardia (SVT), and ventricular tachycardia (VT).
Administration
Iso-somotic solutions of esmolol are available as 10 mg/mL and 20 mg/mL [1].
MEDICATION SAFETY
Contraindications/Precautions
Contraindicated in patients with sinus bradycardia, heart block greater than first degree, cardiogenic shock or overt heart failure [2].

Adverse Effects
May cause hypotension in high doses. Adverse effects reversible with discontinuation of drug.
Monitor IV site closely for vein irritation and phlebitis, especially at high concentrations

(greater than 10 mg/mL).
Solution Compatibility
D5W, LR, D5LR, NS, NS, D5 NS, and D5NS.
Terminal Injection Site Compatibility
Amikacin, aminophylline, atracurium, calcium chloride, cefazolin, ceftazidime,
chloramphenicol, cimetidine, clindamycin, dopamine, enalaprilat, erythromycin lactobionate,
famotidine, fentanyl, gentamicin, heparin,
hydrocortisone, insulin, linezolid, magnesium sulfate, metronidazole, micafungin, midazolam,
morphine, nafcillin, nicardipine, nitroglycerin,
norepinephrine, pancuronium, penicillin G, phenytoin,
piperacillin, potassium chloride,
propofol, ranitidine, remifentanil, sodium nitroprusside, tobramycin,
trimethoprim/sulfamethoxazole, vancomycin, and vecuronium.
Terminal Injection Site Incompatibility
Amphotericin B, diazepam, furosemide, procainamide, and sodium bicarbonate 5% injection.
Monitoring
Continuous EKG monitoring during acute treatment of arrhythmias. Measure systemic blood
pressure and heart rate frequently.
MECHANISM OF ACTION/PHARMACOKINETICS
Pharmacology
Esmolol is a potent cardio-selective beta-blocking agent with a uniquely short half-life (2.8 to
4.5 minutes) and a brief (10 to 15 minute) duration of action. There appears to be no
correlation between age and pharmacodynamic response or pharmacokinetic profile. Esmolol
is cleared primarily by red blood cell esterases. Renal or hepatic failure does not effect elimination.
ABOUT

Special Considerations/Preparation
Esmolol is supplied in preservative-free 10-mL (10 mg/mL) vials, and 2500 mg/250 mL and
2000 mg/100 mL ready-to-use premixed bags. The pH is approximately 4.5 to 5.5.

Osmolarity is 312 mOsm/L. Store at room temperature. Stable for at least 24 hours at room temperature or refrigeration when diluted in compatible solutions to a concentration of 10 mg/mL [2].

Factor IX (Recombinant), Fc Fusion Protein
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
Hemophilia B
Dose and duration of treatment depend on severity of deficiency, location and extent of bleeding, patient's pharmacokinetic profile, and clinical condition of the patient [1].
On average, one international unit per kg increases the circulating level of Factor IX by approximately 0.6% (international units/dL) in children younger than 6 years [1].
Estimate the required dose or the expected in vivo peak increase in Factor IX level using the following 2 formulas [2]:
International units/dL (or % of normal) = [Total Dose (international unit/body weight (kg)] X Recovery (international units/dL per international unit/kg)
OR
Dose (international units) = Body Weight (kg) X Desired Factor IX Rise (international units/dL or, % of normal) X Reciprocal of Recovery (international units/kg per international units/dL)
Dosing for On-demand Treatment and Control of Bleeding Episodes, Perioperative Management, and Routine Bleeding Prophylaxis
Bleeding Episodes, On-demand Treatment and Control
Type of Bleeding
Circulating Factor IX Level Required (international units/dL or % of normal)
Dosing Interval (hours)
Minor and Moderate (eg, uncomplicated hemarthroses, superficial muscle (except iliopsoas) without neurovascular compromise, superficial soft tissue, mucous membranes)
30 to 60 Repeat every 48 hours if there is further evidence of bleeding.

Major
(eg, iliopsoas and deep muscle with
neurovascular injury, or substantial
blood loss; pharyngeal, retropharyngeal,
retroperitoneal, CNS)
80 to 100
Consider a repeat dose after 6 to 10 hours,
and then every 24 hours for the first 3 days.
Due to the long half-life, the dose may be
reduced and frequency of dosing may be
extended after 3 days to every 48 hours or
longer until bleeding stops and healing is
achieved.
Perioperative Management
Type of Bleeding Circulating
Factor IX
Level
Required
(international
Dosing Interval (hours)
297

units/dL or
% of normal)
Minor
(including uncomplicated dental
extractions)
50 to 80
A single infusion may be sufficient.
Repeat as needed after 24 to 48 hours
until bleeding stops and healing is achieved.
Major 60 to 100
(initial level)
Consider a repeat dose after 6 to 10 hours,
and then every 24 hours for the first 3 days.
Due to the long half-life, the dose may be
reduced and frequency of dosing may be
extended after 3 days to every 48 hours or
longer until bleeding stops and healing is
achieved.
Routine Bleeding Prophylaxis
Starting Dose (12 years or older)
50 international units/kg once weekly
or
100 international units/kg once every 10 days
Starting Dose (younger than 12 years)
60 international units/kg once weekly
Reference: Alprolix PI, 2017
Each vial label states the factor IX potency in
international units, which is assigned using an
in vitro aPTT-based, 1-stage clotting assay calibrated
against the WHO international standard
for factor IX concentrates. Factor IX activity
measurements may be affected by the type of
reagent or reference standard used[2].

Uses
Hemophilia B (congenital factor IX deficiency)
Bleeding episodes, control and prevention: Control of bleeding was achieved with 1 dose of coagulation factor IX Fc fusion protein recombinant in the majority of patients with factor IX deficiency for prophylaxis and management of bleeding episodes. Patients with severe factor IX deficiency (age range, 12 to 71 years old; n=123) were evaluated in trials for 2 prophylactic treatment regimens (fixed weekly and individualized interval prophylaxis) and an episodic (ie, on-demand) treatment, and to determine hemostatic efficacy of coagulation factor IX Fc fusion protein recombinant for bleeding episodes and perioperatively in major surgery. In the fixed interval prophylaxis arm, patients received an initial dose of 50 international units/kg, which was then dose adjusted to maintain a factor IX trough of at least 1% to 3% above baseline (median study dose, 45.2 international units/kg). Patients in the individualized interval arm received factor IX Fc fusion protein recombinant 100 international units/kg every 10 days, with the dosing interval adjusted to maintain a factor IX trough of at least 1% to 3% greater than baseline as clinically indicated (median dosing interval, 12.5 days). Patients in the episodic treatment arm received therapy only as needed. Across all groups, 636 bleeding episodes were assessed in 114 patients, who received a median total dose per bleeding episode of 46.99 international units/kg. Most patients were treated with 1 dose (90.4%); 6.9% of patients required 2 doses, and 2.7% required 3 doses.
At 8 to 12 hours after treatment, 83.7% of patients treated with 1 dose had excellent or good response, 14.7% had moderate response, and 1.6% had no response. [2].

Bleeding, prophylaxis: In patients with factor IX deficiency, overall annualized bleeding rates were lower in fixed weekly and individualized weekly prophylaxis groups compared with an episodic (ie, on-demand) treatment group in a small study (n=123; 12 to 71 years of age). In the fixed-interval prophylaxis arm, patients received an initial dose of 50 international units/kg, which was then adjusted to maintain a factor IX trough level of at least 1% to 3% above baseline (median dose, 45.2 international units/kg). Patients in the

individualized interval arm received factor IX Fc fusion protein recombinant 100 international units/kg every 10 days, with the dosing interval adjusted to maintain a factor IX trough of at least 1% to 3% greater than baseline as clinically indicated (median dosing interval, 12.5 days). Patients in the episodic treatment arm received therapy only as needed. Across all treatment groups, 636 bleeding episodes were assessed in 114 patients, who received a median total dose of 46.99 international units per bleeding episode. During a median followup of 51.4 weeks, the annualized bleeding rates were decreased by 83% in the fixedweekly interval group and 87% in the individualized group compared with the episodic treatment group. The median annualized overall bleeding rates were 2.95% in the fixed prophylaxis group, 1.38% in the individualized prophylaxis group, and 17.69% in the episodic treatment group [2].

Perioperative Management: In 14 major surgeries (eg, knee replacement, abdominal surgery, complex dental procedure) in patients with factor IX deficiency, hemostatic response of coagulation factor IX Fc fusion protein recombinant was rated as excellent (n=13) or good (n=1) in all patients, 24 hours after surgery There were 15 minor surgical procedures in 13 subjects, all without thrombotic events [2].

FDA approved indication

Coagulation Factor IX Fc fusion protein is indicated for perioperative management, ondemand treatment and control of bleeding episodes, and routine prophylaxis to decrease the frequency of bleeding episodes in adults and children with hemophilia B (congenital factor IX deficiency). The product is not indicated for induction of immune tolerance in patients with hemophilia B [1].

Administration

Allow vial and prefilled diluent syringe to reach room temperature. Using the vial adapter, slowly inject all the diluent provided into the drug vial and gently swirl until completely dissolved; do not shake vial. Then turn vial upside down and draw entire vial content into syringe. Following reconstitution, do not refrigerate, protect from direct sunlight, and use within 3 hours. The actual factor IX potency is stated on each vial, but the range is approximately 250, 500, 1000, 2000, 3000, or 4000 international units/vial. When reconstituted with the 5-mL syringe [1], the concentration will approximately range from 50 to 800 international units/mL.

For IV use only. Administer as an IV bolus no faster than 10 mL per minute, according to

patient comfort level. Do not administer in the same tubing or container with other drugs [2].
MEDICATION SAFETY
Contraindications/Precautions
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cexpert/ND_T/evidencexpert/PFActionId/evidencexpert.Pr
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Contraindications
Known hypersensitivity to product or its excipients including sucrose, mannitol, sodium chloride, L-histidine, and polysorbate 20 [1].
Precautions
Hematologic: Thromboembolic complications may occur; increased risk with continuous infusion through central venous catheter; administer as a bolus infusion over several minutes [1]
Immunologic: Hypersensitivity reactions, including anaphylaxis, have been reported; increased risk with the presence of neutralizing antibodies to Factor IX; monitoring recommended; discontinue use if hypersensitivity occurs [1]
Immunologic: Neutralizing antibody formation has been reported; monitoring recommended [1]
Renal: Nephrotic syndrome has been reported following attempted immune tolerance induction in hemophilia B patients with Factor IX inhibitors and a history of allergic reactions to Factor IX [3].
Adverse Effects
The most common adverse effects during clinical trials (n=153) were headache, oral paresthesia, and obstructive uropathy, reported in 1.3% each. Dizziness, dysgeusia, breath odor, fatigue, infusion site pain, palpitations, hematuria, renal colic, hypotension, and decreased appetite were reported in 0.7% each [1].
Monitoring
Monitor plasma factor IX activity, using a one-stage clotting assay, to confirm adequate factor IX levels have been achieved and maintained. The type of aPTT reagent used will affect the factor IX results. An underestimation of activity level will occur if a kaolin-based aPTT reagent is used in the one-stage clotting assay [2].
Regularly monitor for the development of neutralizing antibodies (inhibitors) to factors IX using the Bethesda assay. Furthermore, monitor for antibodies if the expected factor IX activity levels in plasma are not attained or if bleeding is not controlled with the recommended dose. Closely observe for signs and symptoms of acute hypersensitivity

reactions, particularly during the early phases of exposure to factor IX [2].
MECHANISM OF ACTION/PHARMACOKINETICS
Pharmacology
Fully recombinant, fusion protein which temporarily replaces the missing coagulation Factor IX required for effective hemostasis. Provides the Fc region of human IgG1, which binds to the neonatal FC receptor (FcRn), thereby delaying lysosomal degradation of immunoglobulins by cycling them back into circulation. Incremental recovery is lower and body weightadjusted clearance is higher in children younger than 12 years compared with adults,
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particularly in those younger than 6 years. The following table provides pediatric pharmacokinetic parameters [1].
Comparison of Pharmacokinetic Parameters by Age
Pharmacokinetic Parameter
2 to 5 years (n=11) *
6 to 10 years (n=13) *
12 to 17 years (n=8) *
12 to 17 years (n=3) **
Cmax (international units/dL) 30 37 43 96
Incremental recovery (international units/dL per international units/kg)
0.6 0.74 0.87 0.96
AUC(infinity) (international units X hr/dL)
1169 1471 1439 3420
Half-life (hours) 68 72 80 94
Mean residence time (hours) 86 84 95 95
Clearance (mL/hr/kg) 4.4 3.6 3.7 3
Vd at steady state (mL/kg) 373 302 345 275
* Dose of 50 international units/kg
** Dose of 100 international units/kg
Reference: Alprolix PI, 2017
ABOUT
Special Considerations/Preparation
Available: Lyophilized powder in single-use vials containing nominally 250, 500, 1000, 2000, 3000, or 4000 international units and a prefilled diluent 5-mL syringe. The actual factor IX potency is stated on each vial.

Storage: Refrigerate at 2 to 8 degrees C (36 to 46 degrees F); do not freeze. May also store unreconstituted product at room temperature (do not exceed 30 degrees C or 86 degrees F) for a single period of 6 months; discard after this 6-month period. Do not place carton back into refrigeration after warming to room temperature. Reconstituted product may be stored at room temperature, not to exceed 30 degrees C (86 degrees F) for up to 3 hours, protect from direct sunlight, and discard any unused product [1].

Factor VIIa, recombinant

NeoFax Drug Monograph Summary - MICROMEDEX

DOSING/ADMINISTRATION

Dose

Congenital Hemophilia A or B with inhibitors:

Acute bleeding episode

Hemostatic: 90 mcg/kg IV every 2 hours until hemostasis is achieved or treatment failure; dosage may be adjusted based on severity of bleed [1]; however, higher initial doses (120 mcg/kg) may be necessary in children [2].

Post-Hemostatic (severe bleeds): 90 mcg/kg every 3 to 6 hours to maintain hemostasis.

Duration of treatment is unknown [1].

Perioperative management: 90 mcg/kg IV immediately before surgery and every 2 hours during surgery; followed by 90 mcg/kg IV every 2 hours for 48 hours then every 2 to 6 hours until healing occurs for minor surgery. Following major surgery, dose every 2 hours for 5 days then every 4 hours until healing occurs. Administer additional boluses if needed [1].

Congenital Factor VII Deficiency

Acute bleeding episode: 15 to 30 mcg/kg IV every 4 to 6 hours until hemostasis is achieved. Adjust dose to the individual needs of the patient. Doses as low as 10 mcg/kg have been effective [1].

Perioperative management: 15 to 30 mcg/kg IV immediately before surgery and every 4 to 6 hours during surgery until hemostasis is achieved. Adjust dose to the individual needs of the patient. Doses as low as 10 mcg/kg have been effective [1].

Glanzmann's Thrombasthenia

Acute bleeding episode: 90 mcg/kg IV every 2 to 6 hours until hemostasis is achieved [1].

Perioperative management: 90 mcg/kg IV immediately before surgery and every 2 hours

during the procedure, then every 2 to 6 hours following surgery. A median dose of 100 mcg/kg (interquartile range 90 to 140 mcg/kg) has been used in surgical patients who had clinical refractoriness with or without platelet-specific antibodies compared with those with neither [1].

Uses

Cardiac surgery in non-hemophiliacs: There is a lack of evidence to support the use of recombinant coagulation factor VIIa as prophylactic or routine use in non-hemophiliac pediatric patients undergoing cardiac surgery. Although the data are mostly observational [3][4][5], the benefits may outweigh the risk as rescue therapy for refractory blood loss in pediatric patients undergoing cardiac surgery [6][4]. Doses have varied but if recombinant factor VIIa is used the Congenital Cardiac Anesthesia Society Task Force recommends 90 mcg/kg every 2 hours for a maximum of 2 doses based on adult and pediatric clinical studies and pharmacokinetic studies. However, larger doses may be necessary in neonates and infants due to increased volume of distribution [4].

Other uses in non-hemophiliacs: Factor VIIa has been used in non-hemophiliac pediatric patients for coagulopathies or hemorrhage primarily during cardiac surgery or liver

transplantation. Recombinant factor VIIIa has also been used for hemorrhage in pediatric patients with chronic liver disease or failure, disseminated intravascular coagulation, trauma, intracranial hemorrhage, and bleeding associated with malignancy and prophylaxis prior to invasive procedures. Data are limited to small controlled or observational studies; therefore, the evidence for safety and efficacy are inconclusive [3][5].

FDA approved indication

Recombinant Factor VIIa is indicated for perioperative management treatment of bleeding episodes in children with hemophilia A or B with inhibitors, and congenital factor VII deficiency. For Glanzmann's thrombasthenia with refractoriness to platelet transfusions (with or without antibodies to platelets); platelet transfusions are the primary treatment but recombinant factor VIIa is used in severe bleeding episodes requiring systemic hemostatic therapy until hemostasis is achieved and for perioperative management [1].

Administration

Administer 1000 mcg/mL solution as an IV bolus over 2 to 5 minutes, depending on the dose administered. Flush line with 0.9% sodium chloride before or after injection (if needed). Do not mix with other infusion solutions [1].

MEDICATION SAFETY

Contraindications/Precautions

Precautions

Serious arterial and venous thrombotic events, including a fatal event, have been reported and caution is advised in patients at increased risk of thromboembolic events or complications (DIC or history of DIC, crush injury, concomitant treatment with activated or nonactivated prothrombin complex concentrates (aPCCs/PCCs), liver disease, postoperative immobilization, and septicemia) [1]. Furthermore, caution is advised when using higher doses and when used concomitantly with other coagulants [5]. Neonates in general are at risk for thromboembolic complications. Dose reduction or discontinuation may be necessary [1].

Hypersensitivity reactions, including anaphylaxis, have been reported. Administer only if clearly needed to patients with history of known hypersensitivity to recombinant coagulation factor VIIa, any of the product components, or to mouse, hamster, or bovine proteins.

Discontinue if symptoms occur, administer appropriate treatment, and weigh benefit and risks before restarting therapy [1].

Factor VII antibodies may develop leading to ineffectiveness or reduced effectiveness [1].

Adverse Effects

Thrombotic events are the most common and serious adverse reactions [1]; However, no thromboembolic events were observed in 29 neonates with intractable bleeding who were administered recombinant factor VIIa at a dose of 100 mcg/kg every 4 hours (maximum 23

doses) [7]. Furthermore, a retrospective study (n=134) of non-hemophilic, non-congenital factor VII deficient neonates demonstrated no increased risk of thrombosis or ischemic events when administered recombinant factor VIIa and other blood products (7.5%) compared with fresh frozen plasma alone (7%) [8].

Black Box Warning

Serious arterial and venous thrombotic events following administration of recombinant factor VIIa have been reported [1]

Monitoring

Monitor prothrombin time and factor VII coagulant activity prior to and following administration in factor VII deficient patients.
Evaluate for antibodies if expected levels are not reached, prothrombin time is not corrected, or bleeding is uncontrolled [1].
Evaluate hemostasis as indicator of efficacy and to determine treatment schedule;
coagulation parameters do not necessarily correlate with or predict effectiveness [1].
Monitor for signs or symptoms of thrombosis or activation of the coagulation system [1].
MECHANISM OF ACTION/PHARMACOKINETICS
Pharmacology
When complexed with tissue factor, coagulation factor VIIa activates coagulation factor X to factor Xa and coagulation factor IX to factor IXa. This process converts prothrombin to thrombin, leading to the formation of a hemostatic plug by converting fibrinogen to fibrin and thereby inducing local hemostasis [1].
ABOUT
Special Considerations/Preparation
Available as lyophilized powder in single use vials containing 1, 2, 5, or 8 mg of recombinant coagulation factor VIIa per vial and a L-histidine (10 mmol) in water diluent as a vial or prefilled syringe [1].
Prior to reconstitution, store between 2 and 25 degrees C (36 and 77 degrees F); protect from freezing and light. Do not use past expiration date [1].
Preparation: Allow recombinant factor VIIa and histidine diluent to reach room temperature. Add appropriate volume of diluent to the vial of lyophilized powder (see below).
Do not inject the diluent directly onto the powder. Aim the needle towards the side of the vial so the liquid streams down vial wall. Gently swirl the vial until the powder is dissolved. Do

not freeze. Do not store in syringes. May be stored at either room temperature or refrigerated. Use product within 3 hours of reconstitution [1]:
Vials
1.1 mL histidine diluent + 1000 mcg vial
2.1 mL histidine diluent + 2000 mcg vial
5.2 mL histidine diluent + 5000 mcg vial
8.1 mL histidine diluent + 8000 mcg vial
Pre-filled histidine diluent syringe + Vial of powder
1 mL histidine diluent + 1000 mcg vial
2 mL histidine diluent + 2000 mcg vial
5 mL histidine diluent + 5000 mcg vial

8 mL histidine diluent + 8000 mcg vial

Factor X Human
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
Control and Treatment of Bleeding; Hereditary Factor X Deficiency Disease
Initial, 30 international units/kg IV infusion at the first sign of bleeding. Repeat every 24 hours until bleeding stops. MAX 60 international units/kg/day.[1].
Perioperative Management of Bleeding; Hereditary Factor X Deficiency Disease, Mild to Moderate
Pre-surgery: To get initial dose, calculate dose to raise factor X levels to between 70 and 90 international units/dL. MAX 60 international units/kg/day[1].
Post-surgery: Repeat dose as needed to maintain factor X levels at a minimum of 50 international units/dL until risk of bleeding subsides. MAX 60 international units/kg/day[1].
Prophylaxis of Bleeding Episodes; Hereditary Factor X Deficiency Disease
Initial, 40 international units/kg IV infusion twice weekly. Adjust dosage regimen to clinical response and trough levels of Factor X of at least 5 international units/dL. Do not exceed a peak level of 120 international units/dL. MAX 60 international units/kg/day[1].
Dose Calculations
Individualize dose according to clinical situation.
Dose (international units) = body weight (kg) times desired factor X increase (international units/dL) times 0.6; MAX 60 international units/kg/day IV infusion [1]
Estimate the expected in vivo peak increase in factor X level expressed as international unit/dL (or % normal), using following formula:
Estimated increment of factor X (international unit/dL or % of normal) = [total dose (international units)/body weight (kg)] times 1.7[1]
Uses
Pediatric FDA Approved Indications
Routine prophylaxis to reduce the frequency of bleeding episodes in pediatric patients with hereditary factor X deficiency [1].
On-demand control and treatment of bleeding episodes in pediatric patients with hereditary factor X deficiency [1].

Perioperative management of bleeding in pediatric patients with mild to moderate hereditary factor X deficiency. Use of factor X human for perioperative management of bleeding with major surgery in patients with severe hereditary factor X deficiency has not been studied [1].
Administration
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Administer by IV infusion at a rate of 10 mL/min; MAX rate 20 mL/min. After dilution, the final concentration is approximately 100 international units/mL [1].
MEDICATION SAFETY
Contraindications/Precautions
Precautions
Allergic hypersensitivity reactions may occur, including anaphylaxis [1].
Factor X human neutralizing antibodies or inhibitors may develop [1].
Infectious agent transmission may occur, including a risk of exposure to viruses, Creutzfeldt-Jakob disease or variant Creutzfeldt-Jakob disease, and other pathogens [1].
Adverse Effects
During clinical trials, adverse reactions were reported in 2 out of 18 patients. The reported adverse effects were infusion site erythema (5.6%), fatigue (5.6%), back pain (5.6%), and infusion site pain (5.6%) [1].
Monitoring
Monitor plasma factor X activity and confirm adequate levels have been achieved and maintained by performing a validated test (eg, one-stage clotting assay) [1].
For perioperative use, measure post-infusion factor X activity before and after surgery [2].
For prophylaxis of bleeding episodes, trough blood levels of Factor X should be monitored at intervals, especially in the first weeks of therapy or after dosages changes. [1].
Monitor for development of neutralizing antibodies (inhibitors). If expected activity levels are not attained or if bleeding is not controlled with an appropriate dose, perform an assay measuring inhibitor concentration (Nijmegen-Bethesda inhibitor assay) [1].
MECHANISM OF ACTION/PHARMACOKINETICS
Pharmacology
Mechanism of Action
Factor X is converted from its inactive form to the active form (factor Xa) and with factor Va on the phospholipid surface forms a prothrombinase complex, which activates prothrombin to

thrombin in the presence of calcium ions. Thrombin acts upon soluble fibrinogen and factor XIII to generate a cross-linked fibrin clot [2].
Concentrations
The mean AUC0 to infinity of factor X was 18 international units x hr/mL and mean factor X

Cmax was 0.504 international units/mL in patients with severe or moderate Factor X
deficiency following a single IV dose of 25 international units/kg. The pharmacokinetics of factor X is similar following single and repeat dosing [2].
Distribution
The factor X Vd at steady state is 56.3 mL/kg [2].
Total Body Clearance
The clearance of factor X is 1.35 mL/kg/hr [2].
Half-life
The half-life of factor X is 30.3 hours [2].
ABOUT
Special Considerations/Preparation
Supplied as single use vials with 250 or 500 international units packaged with 2.5 or 5 mL of sterile water for injection, respectively. Each vial is labeled with the actual factor X potency/content in international units [1].
Refrigerate in original package or store at room temperature between 36 and 86 degrees F.
Protect from light and do not freeze [1].
Preparation
Reconstitute with provided diluent (sterile water for injection) and transfer device (Mix2Vial);
a suitable needle and syringe will also be necessary (not provided) [1]
Vials and diluent should be brought to room temperature before reconstitution. Final concentration is approximately 100 international units/mL after reconstitution [1]
When reconstituting, the diluent will automatically transfer into the drug vial by the vacuum contained within it. Do not use if the diluent is not pulled into the vial of the drug. Swirl, do not shake the vial [1]
If more than 1 vial is needed, use a new Mix2Vial for each [1]
Final product should be clear to slightly pearl in color. Do not use if discolored or particulate matter is present [1]
Use the product immediately after reconstitution [1]
After reconstitution, administer within 1 hour [1].

Factor XIII Concentrate, Human
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
Congenital factor XIII (FXIII) deficiency
Optimal dosage in neonates is unknown; individualize dose based on FXIII activity level and clinical response or if applicable, type of surgery. The following are the recommendations for adults and children.
Initial dose, 40 international units/kg IV every 28 days for prophylaxis[1][2]. For perioperative management, administer full prophylactic dose if it has been 21 to 28 days since last dose. Administer a partial or full dose (based on FXIII activity level) if it has been 8 to 21 days since last dose. An additional dose may not be needed if it has been 7 days or less since last dose [1].
Dosage adjustment: Children younger than 16 years may require dose adjustments based on a shorter half-life and faster clearance compared with adults [1]. Neonates may have shorter half-lives [3].
Using the Berichrom Activity Assay, increase dose by 5 international units/kg for a FXIII activity trough level of less than 5% or decrease dose by 5 international units/kg for 2 trough levels greater than 20% or one trough level greater than 25%. Maintain dose for trough level of 5% to 20% [1].
Uses
FDA approved indication
Coagulation factor XIII is indicated for prophylaxis and perioperative management of surgical bleeding in pediatric patients with congenital factor XIII deficiency [1].
Administration
Do not exceed 4 mL/min during administration. The final concentration of factor XIII solution is 50 to 80 international units/mL [1].
MEDICATION SAFETY
Contraindications/Precautions
Contraindicated in patients with anaphylactic or severe systemic reaction to human plasma-derived products or to any other component of the product [1].
Precautions

This product is a human plasma derivative and there is an increased risk of transmission of

infectious agents, including viruses and theoretical risk of Creutzfeldt-Jakob disease agent [1].
Hypersensitivity reactions have been reported. If anaphylaxis or hypersensitivity reaction occur, immediately discontinue and institute appropriate treatment [1].
Development of inhibitory antibodies have been detected [1].
Thromboembolic complications have been reported [1].
Adverse Effects
The most common adverse reactions are joint inflammation, hypersensitivity, arthralgia, rash, pruritus, erythema, hematoma, headache, elevated thrombin-antithrombin levels, and increased blood lactate dehydrogenase [1].
Monitoring
Monitor trough Factor XIII activity levels during treatment, and during and after surgery, to maintain an activity level of 5% to 20% [1].
Monitor for development of inhibitory antibodies. If an adequate response is not seen with appropriate doses or bleeding is not controlled, perform an assay that measures factor XIII inhibitory antibody concentrations [1].
Monitor for thromboembolic complications in patients with known risk factors [1].
MECHANISM OF ACTION/PHARMACOKINETICS
Pharmacology
Coagulation Factor XIII Concentrate (Human) is a heat-treated lyophilized concentrate made from pooled human plasma. Coagulation Factor XIII Concentrate is an endogenous plasma glycoprotein made up of both A and B subunits. Factor XIIIa promotes cross-linking of fibrin during coagulation and is essential to protecting against fibrinolysis. Cross-linked fibrin provides tensile strength to a primary hemostatic platelet plug [1].
Compared with adults, patients younger than 16 years had a shorter half-life (5.7 days vs 7.1 days) and faster clearance (0.29 mL/hr/kg vs 0.22 mL/hr/kg) [1].
ABOUT
Special Considerations/Preparation
Available as lyophilized powder in single use vials containing 1000 to 1600 international units. Each vial label and carton states the actual units of potency of factor XIII [1].

Prior to reconstitution, store between 2 and 8 degrees C (36 and 46 degrees F); protect from light. Do not freeze [1].

Factor XIII may be stored at 25 degrees C (77 degrees F) for up to 6 months. Do not return to refrigerator after it is stored at room temperature [1].
Preparation:
Allow Factor XIII and diluent to reach room temperature. Reconstitute factor XIII concentrate (human) with 20 mL sterile water for injection for a final concentration of 50 to 80 international units/mL. Do not shake vial [4].
The solution must be used within 4 hours after reconstitution. Do not refrigerate or freeze the reconstituted solution [4].
Once reconstituted, the solution should be at room temperature upon administration [4].

Famotidine
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
IV: 0.25 to 0.5 mg/kg/dose IV every 24 hours. Continuous infusion of the daily dose in adults provides better gastric acid suppression than intermittent dosing.
Oral: 0.5 to 1 mg/kg/dose orally every 24 hours.
Uses
Prevention and treatment of stress ulcers and GI hemorrhage aggravated by gastric acid secretion.
Apnea of prematurity: Reducing gastric acidity or increasing gastric motility for the sole purpose to reduce apnea episodes is not supported by the literature [3].
Crying and irritability: In otherwise healthy term infants, histamine2 receptor antagonists or proton pump inhibitors should not be used for the treatment of crying and distress [4].
Gastroesophageal Reflux (GER): The risks associated with acid reducing agents outweighs the benefits in preterm infants for GER. Acid blocking agents should not be used and if used in preterm infants, use sparingly [5]. In otherwise healthy term infants, histamine2 receptor antagonists or proton pump inhibitors should not be used for the treatment of visible regurgitation [4].
Gastroesophageal Reflux Disease (GERD): Proton pump inhibitors (PPIs) are the firstline agents for erosive esophagitis in infants and children with GERD. Histamine2 receptor antagonists are the second-line agent if PPIs are not available or are contraindicated. A

duration of treatment for 4 to 8 weeks for GERD symptoms is recommended. Regularly reassess the need for long-term acid suppression. If no response after 4 to 8 weeks, then reevaluate for other causes of symptoms. H2RAs and PPIs are not recommended for extraesophageal symptoms (e.g. cough, wheezing, asthma), unless GERD symptoms are present and/or GERD has been diagnosed [4].
A trial use of PPIs as a diagnostic test for GERD is not recommended in infants or in patients presenting with extraesophageal symptoms. However, in children with typical GERD symptoms, a trial of 4 to 8 weeks with a PPI may be used as a diagnostic test [4].
Pediatric FDA Approved Indications
Intravenous:
Treatment of pathological hypersecretory conditions or intractable duodenal and gastric ulcers, or as an alternative to the oral dosage form for short-term use in patients who are unable to take oral medication [6].
Oral
Suspension is indicated for [2]:
Short-term treatment of patients with symptoms of gastroesophageal reflux disease (GERD)

Short-term treatment of esophagitis due to GERD including erosive or ulcerative disease diagnosed by endoscopy
Peptic ulcer in pediatric patients 1 year or older
Administration
IV Intermittent: Dilute to concentration of 2 to 4 mg/mL with 0.9% NS; give over a period of at least 2 minutes. Alternatively, dilute to concentration of 0.2 mg/mL with D5W or other compatible solution and infuse over 15 to 30 minutes [1].
Oral: Shake oral suspension vigorously for 5 to 10 seconds prior to each use; unused constituted oral suspension should be discarded after 30 days [2].
MEDICATION SAFETY
Contraindications/Precautions
PRECAUTIONS
Gastrointestinal: Symptomatic response does not rule out gastric malignancy [2]
Infection: Increased risk of infections (necrotizing enterocolitis, pneumonia, upper respiratory tract infections, sepsis, urinary tract infections, and Clostridium difficile infections) in infants and children on H2 blockers or PPIs demonstrated in case-control studies [4][7].

Renal: CNS adverse effects have been reported in patients with moderate and severe renal insufficiency; dosage adjustment recommended [2]

Adverse Effects

The use of H2 blockers in preterm infants has been associated with an increased risk for lateonset bacterial and fungal sepsis. Routine gastric acid suppression in neonates should be avoided. No short term adverse effects have been reported in infants and children, although data are limited to a few small studies. The most common (less than 5% of patients) adverse effects noted in adults were headache, dizziness, constipation, and diarrhea.

The use of H2-blockers in preterm infants has been associated with facilitating Candida species colonization [8], and an increased risk for late-onset bacterial and fungal sepsis [9] [8].

In a prospective, multicenter, observational study comparing VLBW neonates receiving raNITIdine (n=91) to those not receiving raNITIdine (n=183), neonates receiving raNITIdine had an increased rate of infection (37.4% versus 9.8%; OR 5.5; 95% CI, 2.9 to 10.4), increased risk for NEC (9.8% versus 1.6%; OR 6.6; 95% CI, 1.7 to 25), and increased mortality (9.9% versus 1.6%) [10].

In a retrospective, case-control study, H2-blocker use in VLBW infants was associated with an increased incidence of NEC (OR 1.7; 95% CI, 1.34 to 2.19) [11].

Solution Compatibility

D5W, D10W, and NS

Terminal Injection Site Compatibility

Acyclovir, aminophylline, amiodarone, ampicillin, atropine, aztreonam, calcium gluconate, caspofungin, cefazolin, cefotaxime, cefoxitin, ceftazidime, ceftriaxone, dexamethasone, digoxin, dobutamine, dopamine, enalaprilat, epinephrine, erythromycin lactobionate, esmolol, fluconazole, flumazenil, furosemide, gentamicin, heparin, hydrocortisone succinate, imipenem/cilastatin, insulin, isoproterenol, lidocaine, linezolid, lorazepam, magnesium sulfate, metoclopramide, mezlocillin, midazolam, morphine, nafcillin, nicardipine, nitroglycerin, oxacillin, phenytoin, piperacillin, potassium chloride, procainamide, propofol, remifentanil, sodium bicarbonate, sodium nitroprusside, ticarcillin/clavulanate, vancomycin, and vitamin K1.

Terminal Injection Site Incompatibility

Azithromycin, cefepime and piperacillin/tazobactam.
Monitoring
Gastric pH may be measured to assess efficacy (greater than 4).
MECHANISM OF ACTION/PHARMACOKINETICS
Pharmacology
Mechanism of action: Inhibits gastric acid secretion by histamine H2-receptor antagonism.
Elimination half-life is dependent on renal function, and decreases with age from 11 hours (range 5 to 22) in neonates to 8 hours (range 4 to 12) by 3 months of age. Oral bioavailability is 42 to 50%.
ABOUT
Special Considerations/Preparation

Availability
Injection: 0.4 mg/mL and 10 mg/mL.
10-mg/mL solution for intravenous use in 2-mL preservative-free single-dose vials, and 4-mL multidose vials containing 0.9% (9 mg/mL) benzyl alcohol as a preservative. A 1-mg/mL dilution may be made by adding 1 mL of the 10 mg/mL concentrated solution to 9 mL of sterile water for injection. Dilution stable for 7 days at room temperature. Although diluted Pepcid Injection has been shown to be physically and chemically stable for 7 days at room temperature, there are no data on the maintenance of sterility after dilution. Therefore, it is recommended that if not used immediately after preparation, diluted solutions of Pepcid Injection should be refrigerated and used within 48 hours [6][12].
Oral: 10-mg, 20-mg, and 40-mg tablets; 40 mg/5 mL (8 mg/mL) oral powder for suspension.
Pepcid for oral suspension is supplied as a powder containing 400 mg famotidine.
Constitute by slowly adding 46 mL Purified Water and shaking vigorously for 5-10 seconds.
Final concentration 40 mg/5 mL (8 mg/mL). Stable at room temperature for 30 days. Shake bottle before each use.
Extemporaneous Oral Suspension
Famotidine 8 mg/mL oral suspension was stable in amber polyethylene tetraphthalate bottles for 95 days at 23 to 25C[13]:
Triturate seventy 40-mg tablets of famotidine into a paste with sterile water for irrigation
Dilute with equal volumes of Ora-Plus and Ora-Sweet to a final volume of 350 mL
Blend until uniform

Shake well before use

Fat Emulsion
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
Prior to initiation, determine serum triglyceride levels and correct severe fluid and electrolyte disorders [1][2].
Intralipid 20%
Total Parenteral Nutrition and Essential Fatty Acid Deficiency (treatment and prophylaxis)
Premature Infants: Initial, 0.5 g/kg/day IV increasing based on infant's ability to eliminate fat up to a maximum of 3 g/kg/day[3][4].
Infusion rate should be as slow as possible and not exceed 1 g fat/kg in 4 hours.
[4].
Nutrilipid 20%
Total Parenteral Nutrition and Essential Fatty Acid Deficiency (treatment and prophylaxis)
Nutrilipid(R) 20% Lipid Injectable Emulsion
Age
Nutritional Requirements Direct Infusion Rate
Recommended Initial Dosage and Maximum Dosage
Initial Maximum
Preterm and term infants* (less than 1 year of age)
Initial 1 to 2 g/kg/day not to exceed 3 g/kg/day** 0.05 mL/min for the first 10 to 15 minutes; gradually increase to the required rate after 15 minutes
0.75 mL/kg/hr
Pediatric patients 1 to 10 years of age
Initial 1 to 2 g/kg/day not to exceed 3 g/kg/day**
0.75 mL/kg/hr
Pediatric patients 11 to less than 17 years of age
Initial 1 g/kg/day not to exceed
2.5 g/kg/day**
0.5 mL/kg/hr
17 years or older 1 to 1.5 g/kg/day not to

exceed 2.5 g/kg/day**
0.5 mL/min for the first 15 minutes to 30 minutes; gradually increase to the required rate after 30 minutes
0.5 mL/kg/hr
*Do not exceed 0.75 mL/kg/hr; seriously consider administration of less than the maximum recommended doses in preterm and small for gestational age infants.
**Daily dose should not exceed a maximum of 60% of total energy requirements
Product information, 8/2014
Dosage Adjustment: Initiate at a lower dosage and increase in smaller increments in patients with elevated triglyceride levels [5].
Omegaven 10%
Total parenteral nutrition-associated cholestasis (treatment only)
1 g/kg/day; MAX 1 g/kg/day should be initiated as soon as direct or conjugated levels are

2 mg/dL or greater in pediatric patients who are expected to be parenteral nutritiondependent for at least 2 weeks [1]
If triglycerides are greater than 250 mg/dL in neonates, consider stopping infusion for 4 hours. Repeat serum triglyceride level and resume infusion based on triglyceride value. If triglycerides remain at elevated levels, consider a reduced dose to 0.5 to 0.75 g/kg/day with an incremental increase to 1 g/kg/day [1].
Administer Omegaven until bilirubin levels are less than 2 mg/dL or until the patient no longer requires parenteral nutrition.
Infusion rate: Initial rate, 0.05 mL/minute for the first 15 to 30 minutes of infusion. If tolerated, gradually increase until reaching the required rate after 30 minutes. MAX rate 1.5 mL/kg/hour (0.15 g/kg/hr) [1].
Smoflipid 20%
Total Parenteral Nutrition
Preterm and Term neonates: Initial 0.5 to 1 g/kg/day IV increasing daily by 0.5 to 1 g/kg/day [2] to a target dose of 3 g/kg/day [2][6][7][8][9][10]. Some studies used up to 3.5 g/kg/day for short-term use (around 7 days) in preterm neonates [11][12].
Infusion rate should not exceed 0.125 g/kg/hr. Infuse over about 24 hours in premature and low birthweight neonates [2].
Comparison of Fat Emulsions

[1][13][2][3][4][5]
Fat Emulsion
Intralipid
10%
Intralipid
20%
Nutrilipid
20%
Omegaven
10% *
Smoflipid
20%
Oils (%)
Soybean 10 20 20 0 6
Olive 0 0 0 0 5
Fish 0 0 0 10 3
Coconut
palm or oil palm (Mediumchain
triglycerides)
0 0 0 0 6
Fatty Acid Content (%)
Linoleic 44 to 62 44 to 62 48 to 58 1.5 14 to 25
Oleic 19 to 30 19 to 30 17 to 30 4 to 11 23 to 35
Caprylic 0 0 0 0 13 to 24
Palmitic 7 to 14 7 to 14 9 to 13 4 to 12 7 to 12
Capric 0 0 0 0 5 to 15
Linolenic 4 to 11 4 to 11 4 to 11 1.1 1.5 to 3.5
Stearic 1.4 to 5.5 1.4 to 5.5 2.5 to 5 0 1.5 to 4
Eicosapentaenoic 0 0 0 13 to 26 1 to 3.5
Docosahexaenoic 0 0 0 14 to 27 1 to 3.5
Palmitoleic 0 0 0 4 to 10 0
Myristic 0 0 0 2 to 7 0
Arachidonic acid 0 0 0 0.2 to 2 0
Egg yolk phospholipid (%) 1.2 1.2 1.2 1.2 1.2
Glycerin (%) 2.25 2.25 2.5 2.5 2.5
all-rac-?-tocopherol
(mg/mL) 0 0 0 0.15 to 0.3 0.163 to
0.225
Calories (Kcal/mL) 1.1 2 2 1.12 2
Osmolarity (mOsm/L) 260 260 not provided 373 270
Product Information: Omegaven 7/2018; Smoflipid,
Fresenius Kabi 5/2016; Patten,

2016; IntraLipid, Baxter 4/2015; Nutrilipid, Braun
8/2014;
KEY: * = Total omega-3 fatty acid content is 40% to
54%
Uses
Place in Therapy: Multicomponent fish oil-containing
lipid emulsions are recommended
when long-term use of parental nutrition in children
is anticipated. The optimal strategy (lipid
reduction or source of lipid) for IV lipids in
neonates and older children to prevent or treat

liver complications is unknown. Long-term effects on fatty acid profile, growth, and neurodevelopment in children are unknown [15].

Omegaven

In 2 prospective open-label trials in 80 pediatric patients (3 to 42 weeks of age, including preterm neonates with estimated gestational age of more than 24 weeks at birth) with parenteral nutrition-associated cholestasis (PNAC), administration of fish oil triglyceride emulsion as part of a parenteral nutrition regimen was associated with a median decrease in direct bilirubin level from 3.8 mg/dL at baseline to 0.6 mg/dL (interquartile range, 0.1 to 2.8 mg/dL). Historical control patients (n=41) who received a soybean oil-based lipid emulsion had similar age-appropriate growth; 63% of those receiving fish oil triglycerides and 59% of control patients achieved full enteral feeding by the end of the study [1].

Combination lipid emulsions vs Standard lipid emulsions

Combination lipid emulsions compared with standard lipid emulsions (soybean oil) were safe and well tolerated in 2 meta-analysis of infants younger than 12 months and neonates including preterm neonates [16][17]. Different lipid emulsion formulations during short-term use did not change the rate of cholestasis (6 studies) or elevated bilirubin concentrations (5 studies) in preterm infants, neonates, and children in a meta-analysis [15]. Another metaanalysis had similar findings [17]. Prolonged parenteral fish oil-containing lipid emulsions in children with intestinal failure may decrease bilirubin concentrations [15][18]. The mean changes in total bilirubin concentration from baseline to day 29 were significantly different between Smoflipid (-1.5 mcmol/L) and Intralipid (+2.3 mcmol/L) in a randomized, doubleblind study of 28 children (mean age 30.3 and 38.8 months, respectively) with short bowl syndrome, chronic intestinal pseudo-obstruction, or congenital disease of intestinal mucosa. Plasma ?-tocopherol and ?-3 fatty acid (eicosapentaenoic acid and docosahexaenoic acid) increased significantly more with Smoflipid. Lipid peroxidation indices were not different between the 2 groups [18]. No statistically significant differences in parenteral nutritionassociated liver disease and other clinical outcomes (death, growth, lung disease, infection, necrotizing enterocolitis (stage 2 or more), intraventricular hemorrhage (grade III to IV), difference in patent ductus arteriosus, or severe eye disease (retinopathy of prematurity

stage 3 or more) in preterm neonates were demonstrated between Smoflipid and standard lipid emulsion in a meta-analysis of 7 studies (n=469) [16].

Pediatric FDA Approved Indications

Nutrilipid: Indicated as a source of calories and essential fatty acids for parenteral nutrition and as a source of essential fatty acids when a deficiency occurs when oral or enteral nutrition is not possible, insufficiency, or contraindicated [5].

Omegaven: Indicated as a source of calories and fatty acids in pediatric patients with parenteral nutrition-associated cholestasis (PNAC) [1].

Omegaven not indicated for the prevention of PNAC. It has not been demonstrated that Omegaven prevents PNAC in parenteral nutrition-dependent patients [1].

It has not been demonstrated that the clinical outcomes observed in patients treated with Omegaven are a result of the omega-6:omega-3 fatty acid ratio of the product [1].

Smoflipid: Safety and effectiveness of Smoflipid have not been established in pediatric patients [14].

Administration

Administer via peripheral vein or by central venous infusion [1][14][5] over a 12 to 24 hour period for Nutrilipid [5] and 8 to 24 hours for Omegaven [1]. Solutions with osmolarity of 900 mOsm/L or greater must be infused through a central vein [1]

Admixture must be completely used within 24 hour after removal from refrigeration. Use a non-vented infusion set or close the air vent on a vented set. Use a dedicated line without any connections. Use filters with pore size of 1.2 microns [1][14][5][4]. Use a vented infusion set when Omegaven is infused from the bottle [1].

Do not use di(2-ethylhexyl)phthalate (DEHP) containing administration sets or lines [1][14] [5][3][4].

Discard emulsion if frozen [14][5].

Do not use and discard admixture if a yellowish streak or accumulation of yellowish droplets appear, which is evidence of separation of the emulsion. Discard if any particulates appear [1][14][5]

May be infused into the same vein as carbohydrate/amino acid solutions by a Y-connector [1][14][5][3][4].

MEDICATION SAFETY
Contraindications/Precautions
Contraindications
Severe hyperlipidemia (serum triglycerides greater than 1000 mg/dL) or severe disorders of lipid metabolism characterized by hypertriglyceridemia [1][14][5]
Pathologic hyperlipemia, lipoid nephrosis, or acute pancreatitis if accompanied by hyperlipidemia [3][4].
Nutrilipid
Hypersensitivity to egg or soybean proteins or to any of the ingredients, including excipients [5].
Omegaven
Hypersensitivity to fish or egg protein or to any of the active ingredients or excipients [1].
Smoflipid
Hypersensitivity to fish, egg, soybean, or peanut protein or to any of the active ingredients or excipients [14].
Precautions
General Information: Use with caution in neonates and premature neonates with hyperbilirubinemia and cases with pulmonary hypertension [2]
Aluminum toxicity: Fat emulsions contains less than 25 mcg/mL of aluminum but may reach toxic levels with prolonged administration. Aluminum toxicity may occur, particularly in patients with impaired kidney function and in preterm infants [14][5]
Endocrine and metabolic: Fat overload syndrome has been reported with IV lipid

formulations. Increased risk when lipid doses are exceeded, but also reported when administered as recommended; may be reversible upon discontinuation [14][5]
Endocrine and metabolic: Refeeding syndrome, particularly in severely undernourished, may occur; thiamine deficiency and fluid retention may also develop. Slowly increase nutrient intake while avoiding overfeeding [14][5]
Endocrine and metabolic: Parenteral nutrition associated liver disease (PNALD), (particularly in premature infants, or with prolonged administration, or with plant-derived lipid formulations) has been reported and may present as cholestasis or steatohepatitis. Dose reduction or discontinuation may be required [14][5]
Endocrine and metabolic: Hypertriglyceridemia may occur. Dose reductions

recommended. Increased risk of pancreatitis with serum triglyceride levels above 1000 mg/dL [5]

Immunologic: Hypersensitivity reaction may occur. If suspected, stop infusion immediately [14][5]

Immunologic: Cross reactions have been observed between soybean and peanut oil. Smoflipid contains soybean, fish oil, and egg phospholipids [14]

Immunologic: Infection and sepsis may occur. Increased risk associated with malnutrition and underlying disease state, poor catheter maintenance, use of immunosuppressive drugs or underlying immunosuppressive condition, or parenteral formulations [14][5]

Adverse Effects

Nutrilipid

The most commonly reported adverse effects were hyperlipidemia, hypercoagulability, thrombophlebitis, and thrombocytopenia. Additional adverse effects reported in long-term use include hepatomegaly, jaundice, splenomegaly, thrombocytopenia, leukopenia, liver function test abnormalities, brown pigmentation of the liver, and overloading syndrome [5].

Omegaven

The most common adverse reaction with Omegaven-treated pediatric patients were vomiting (46%), agitation (35%), bradycardia (35%), apnea (20%), viral infection (16%), and erythema (12%) [1].

Smoflipid

There was no difference in the incidence of infection between combination lipid emulsions (Smoflipid or Lipoplus) and standard lipid emulsions (soybean oil only) in a meta-analysis (6 trials) of neonates and infants younger than 12 months [17].

There were no differences observed between Smoflipid and Intralipid in acid-base status, platelet counts, and biochemical parameters (including triglycerides, bilirubin (total and direct), and alanine aminotransferase on postnatal days 2, 4, and 7 in a randomized trial of 96 very low birth infants. The potassium and aspartate aminotransferase concentrations were significantly higher, but within normal limits for preterm infants, in the Smoflipid group [8].

There was no difference in the elevation of triglycerides in preterm neonates (n=60) between Smoflipid for a mean duration of 11 days and Intralipid for a mean duration of 10 days [19].

The association between cholestasis and different lipid concentrations has not been established [15].

Black Box Warning

Deaths due to intravascular fat accumulation in the lungs of preterm infants after infusion of IV fat emulsion have been reported. Preterm infants and low birth weight infants have poor clearance of IV lipid emulsion and increased free fatty acid plasma levels following lipid emulsion infusion [14][5]. Strict adherence to the recommended total daily dose is required; hourly infusion rate should be as slow as possible in each case and should not in any case exceed 1 g fat/kg in 4 hours. Consider administering less than the maximum recommended doses in premature and small for gestational age infants due reduce the likelihood of IV fat overload. The lipemia must clear between daily infusions [3][4].

Monitoring

Laboratory Parameters

Obtain serum triglyceride concentrations at baseline, with each dose adjustment, and regularly throughout treatment [1][14][5].

Monitor fluid and electrolyte status, serum osmolarity, blood glucose, liver and kidney function, blood count, and coagulation parameters throughout treatment [1][14][5].

Monitor laboratory results that might indicate infection (including leukocytosis and hyperglycemia) [1]

Monitor platelet counts frequently in neonates [5]

Laboratory interference: Omegaven may interfere with some laboratory blood tests (e.g., hemoglobin, lactate dehydrogenase, bilirubin, and oxygen saturation) if blood is sampled before lipids have cleared from the bloodstream. Lipids are normally cleared after a period of 5 to 6 hours once the lipid infusion is stopped [1]

Physical Findings

Closely monitor fluid status in patients with pulmonary edema or heart failure [5].

Monitor for signs or symptoms of hypersensitivity [5].

Carefully monitor for signs or symptoms of early infection [14][5]

Carefully monitor for refeeding syndrome in severely undernourished patients [5].

Frequently check for edema, redness, and/or discharge at the site of injection [14]

Monitor for laboratory evidence of essential fatty acid deficiency [1][14]

Monitor for signs and symptoms of pleural or pericardial effusion [1]

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Mechanism of action: Intravenous fat emulsions provide a source of calories and essential

fatty acids. Beta oxidation of fatty acids provide energy. Fatty acids are necessary for membrane structure and function, precursors for bioactive molecules (e.g. prostaglandins), and as regulators of gene expression [14][5].
Pharmacokinetics: Infused fat particles cause a transient increase in plasma triglyceride concentrations. The triglycerides are then hydrolyzed to free fatty acids and glycerol by lipoprotein lipase. The free fatty acids either enter the tissues (to be oxidized or resynthesized to triglycerides for storage) or circulate, bound to albumin in the plasma, and subsequently may undergo hepatic oxidation or conversion to very lowdensity lipoproteins

(VLDL) that re-enter the bloodstream. Fat emulsions also contain phosphatides and glycerol. Phosphatides are involved in the formation of membrane structures; choline (a component of phosphatides) prevents deposition of fat in the liver; and glycerol is metabolized to carbon dioxide and glycogen or is used in the synthesis of fats [5].

ABOUT

Special Considerations/Preparation

Availability

Intralipid 10% and 20% is available in 100-, 250-, and 500-mL fill sizes. Intralipid 20% is also available in a 1000 mL bulk package. Lipid emulsion 10% is not recommended due to high phospholipid content [15].
Nutrilipid 20% is supplied as a sterile emulsion in 250, 350, 500 or 1000 mL volumes.
Nutrilipid 20% pharmacy bulk package (1000 mL) is not intended for direct IV administration [5].
Omegaven 10% is available as 5 g/50 mL and 10 g/100 mL [1].
Smoflipid 20% is available as a sterile lipid injectable emulsion in 100, 250, and 500 mL sizes [14]

Storage

Intralipid: Store at room temperature below 25 degrees C (77 degrees F). Do not freeze.
Nutrilipid: Store at a temperature below 25 degrees C (77 degrees F). Do not freeze [5].
Omegaven : Store at room temperature below 25 degrees C (77 degrees F). Do not freeze.
Start infusion of admixtures containing Omegaven immediately. If not used immediately, admixtures may be stored for up to 6 hours at room temperature or up to 24 hours under

refrigeration. Complete the infusion within 24 hours after removal from storage [1].
Smoflipid: Store between 20 and 25 degrees C (68 and 77 degrees F). Avoid excessive heat. Do not freeze. Use immediately upon removal of overpouch. If not used immediately, do not store for more than 24 hours at 2 to 8 degrees C (36 to 46 degrees F). Inspect the integrity indicator prior to removing overpouch; discard if indicator is black [14].

FentaNYL
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
Naloxone should be readily available to reverse adverse effects.
Analgesia
Single or intermittent dose: 0.5 to 3 mcg/kg per dose slow IV push [1][2]. Repeat as required (usually every 2 to 4 hours).
Continuous infusion: 0.5 to 2 mcg/kg/hr [1][2]. Tolerance may develop rapidly following constant infusion.
Anesthesia: 5 to 50 mcg/kg per dose.
Sedation
Single or intermittent dose: 0.5 to 4 mcg/kg per dose. Repeat as required (usually every 2 to 4 hours).
Continuous infusion: 1 to 5 mcg/kg/hr. Tolerance may develop rapidly following constant infusion.
Uses
Analgesia: A consensus of the International Evidence-Based Group for Neonatal Pain recommends the use of IV fentaNYL in newborns, using intermittent doses of 0.5 to 3 mcg/kg or a continuous infusion of 0.5 to 2 mcg/kg/hour [2]. Investigators of one clinical trial in preterm neonates (32 weeks or younger) suggested bolus doses only when ventilation will be of short duration and before major painful procedures and to reserve continuous infusions when ventilation is expected to be of longer duration [1].
A continuous infusion of fentaNYL 1 mcg/kg/hr, plus bolus doses of 1 mcg/kg prior to painful procedures, or as needed for severe pain, reduced the incidence of severe, acute procedural pain and severe prolonged pain compared with intermittent 1 mcg/kg bolus doses alone in a randomized, double-blind, placebo-controlled study of use initiated within 72 hours of birth in

preterm newborns on mechanical ventilation (n=131; gestational age 22 to 32 weeks).
However, no clinically significant difference was demonstrated for prolonged pain. Side effects, including longer duration of mechanical ventilation, longer time to first meconium passage, and higher mean airway pressure levels, were more common in the infusion versus bolus dose only group [1]. Follow-up in 78 newborns (39 in both the fentaNYL and placebo groups) at 2 years of corrected age demonstrated a significant decrease in eye and hand coordination skills in the newborns administered fentaNYL continuous infusion versus bolus only. No difference was demonstrated for locomotor, personal and social skills, hearing and language, and performance [4].
Anesthesia.
Sedation.

Administration
Intravenous: For continuous infusion, further dilute in compatible solution to a concentration of 10 mcg/mL. For intermittent infusions, administer over 15 to 30 minutes at concentrations of 10 mcg/mL [3].
MEDICATION SAFETY
Contraindications/Precautions
Precautions
Addiction: Abuse, misuse, or opioid addiction may occur; increased risk in patients with a personal or family history of substance abuse or mental illness; monitoring recommended [5]
Cardiovascular: Bradyarrhythmias may occur; monitoring recommended, particularly when initiating therapy [5]
Cardiovascular: Severe hypotension, including orthostatic hypotension and syncope, may occur in ambulatory patients, especially those with decreased blood volume or concurrent use of CNS depressants (eg, phenothiazides, general anesthetics). Avoid use in patients with circulatory shock [5].
Cardiovascular: Increased blood pressure may occur when coadministered with a neuroleptic agent; monitoring recommended [5].
Concomitant use: Avoid use with mixed agonists/antagonists and partial agonist analgesics [5]
Concomitant use: Use not recommended within 14 days of MAOI administration [5]
Concomitant Use: Potentially life-threatening serotonin syndrome may occur with

concomitant use of serotonergic drugs. In general, symptom onset occurs within several hours to a few days of concomitant use, but may occur later [5].
Endocrine: Adrenal insufficiency, typically with more than 1 month of use, has been reported. If adrenal insufficiency is suspected, perform diagnostic testing, treat with corticosteroids if confirmed, wean patient off of opioid if appropriate, and continue to assess adrenal function [5].
Gastrointestinal: Spasm of sphincter of Oddi may occur. Serum amylase may increase; monitoring recommended [5].
Hepatic: Biliary tract disease, including acute pancreatitis; use may cause spasm of the sphincter of Oddi and exacerbate symptoms; monitoring recommended [5]
Hepatic: Clearance may be decreased in patients with hepatic impairment; dose adjustments recommended in patients with mild to moderate hepatic impairment ; monitoring recommended [5]
Hepatic: Avoid use in patients with severe hepatic impairment [5].
Neurologic: Increased frequency of seizures may occur; monitoring recommended [5].
Neurologic: Decreased respiratory drive and subsequent carbon dioxide retention may occur, which may further increase intracranial pressure in susceptible patients (eg, brain tumors, elevated intracranial pressure); monitoring recommended especially at initiation [5]
Neurologic: Avoid use in patients with coma or impaired consciousness; opioids may obscure clinical course of head injury [5]
Musculoskeletal: Dose-related and rate-of-administration-related muscular rigidity, particularly involving muscles of respiration, has been reported with fentanyl injection; management protocol advised [6]
Renal: Clearance may be decreased in patients with renal impairment ; dose adjustments as needed ; monitoring recommended [5]

Respiratory: Decreased respiratory drive or apnea may occur in patients with chronic pulmonary disease (eg, chronic obstructive pulmonary disease, cor pulmonale, those with decreased respiratory reserve, hypoxia, hypercapnia, or respiratory depression); monitoring recommended, especially when given with other agents which depress respiration; consider nonopioid alternatives [5]

Respiratory: Sleep-related breathing disorders including central sleep apnea and sleeprelated hypoxemia may occur and risk increases in a dose-dependent fashion; dose reduction may be necessary [5]
Respiratory: Cachectic, or debilitated patients have an increased risk for respiratory depression; monitoring recommended, especially when given with other agents which depress respiration; consider nonopioid alternatives [5]
Withdrawal: Serious withdrawal symptoms, including uncontrolled pain, psychological distress, and suicide, may occur upon sudden dose decrease or discontinuation in patients who are physically dependent on opioid medications; do not discontinue abruptly and create a patient-specific plan to taper the opioid gradually [7].

Adverse Effects

Respiratory depression occurs when anesthetic doses (greater than 5 mcg/kg) are used and may also occur unexpectedly because of redistribution. Chest wall rigidity has occurred in 4% of neonates who received 2.2 to 6.5 mcg/kg per dose, occasionally associated with laryngospasm. This was reversible with administration of naloxone. Urinary retention may occur when using continuous infusions. Tolerance may develop to analgesic doses with prolonged use. Significant withdrawal symptoms have been reported in patients treated with continuous infusion for 5 days or longer.

Black Box Warning

Warnings: Addiction, abuse, and misuse; live-threatening respiratory depression; CYP450 3A4 interaction; and risks from concomitant use of benzodiazepines or other CNS depressants [5]

Addiction, Abuse, and Misuse

Fentanyl exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess patients risk before prescribing, and monitor regularly for these behaviors or conditions.

Life-threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur. Monitor for respiratory depression, especially during initiation of fentanyl or following a dose increase. Because of the risk of respiratory depression, fentanyl is contraindicated for use as an as-needed analgesic, in non-opioid tolerant patients, in acute pain, and in postoperative pain.

Cytochrome P450 3A4 Interaction

The concomitant use of fentanyl with all cytochrome P450 3A4 inhibitors may result in

an increase in fentanyl plasma concentrations, which could increase or prolong adverse
drug effects and may cause potentially fatal respiratory depression. In addition,
discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an

increase in fentanyl plasma concentration. Monitor patients receiving fentanyl and any
CYP3A4 inhibitor or inducer.

Risks From Concomitant Use With Benzodiazepines Or Other CNS
Depressants

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS)
depressants, including alcohol, may result in profound sedation, respiratory depression,
coma, and death.
Reserve concomitant prescribing for use in patients for whom alternative treatment
options are inadequate; limit dosages and durations to the minimum required; and
follow patients for signs and symptoms of respiratory depression and sedation.

Solution Compatibility

D5W, and NS.

Terminal Injection Site Compatibility

fentaNYL undiluted at 50 mcg/mL:
Acetaminophen (10 mg/mL), acyclovir (5 mg/mL and 7 mg/mL), aminocaproic acid (20
mg/mL), amphotericin B lipid complex (1 mg/mL), amphotericin B liposome (1 mg/mL),
anidulafungin (0.5 mg/mL), argatroban (1 mg/mL), bivalirudin (5 mg/mL), calcium gluconate
(100 mg/mL), caspofungin (0.5 mg/mL and 0.7 mg/mL), cefazolin (20 mg/mL), cefotaxime
(20 mg/mL), cefuroxime (15 mg/mL and 30 mg/mL), cimetidine (15 mg/mL), clindamycin (9
mg/mL), clonidine (18 mcg/mL), dactinomycin (10 mcg/mL), dexamethasone (4 mg/mL),
dexmedetomidine (4 mcg/mL), digoxin (0.1 mg/mL), diltiazem (1 mg/mL), dobutamine (2
mg/mL and 4 mg/mL), dolasetron (2 mg/mL), dopamine (1.6 mg/mL and 3.2 mg/mL),
epinephrine (20 mcg/mL), esmolol (10 mg/mL), etomidate (2 mg/mL), foscarnet (24
mg/mL), furosemide (10 mg/mL), gentamicin (10 mg/mL), granisetron (50 mcg/mL), heparin
(1 unit/mL and 100 units/mL), hydrocortisone succinate (10 mcg/mL), hydromorphone (1
mg/mL), labetalol (2 mg/mL), lansoprazole (0.55 mg/mL), levofloxacin (5 mg/mL), linezolid
(2 mg/mL), lorazepam (0.33 mg/mL and 0.5 mg/mL), methotrexate (15 mg/mL),

metronidazole (5 mg/mL), midazolam (2 mg/mL and 5 mg/mL), milrinone (0.2 mg/mL and 0.4 mg/mL), morphine (2 mg/mL), mycophenolate mofetil (6 mg/mL), nafcillin (33 mg/mL), nitroglycerin (0.2 mg/mL and 0.4 mg/mL), nicardipine (0.1 mg/mL), norepinephrine (0.128 mg/mL), octreotide (5 mcg/mL), ondansetron (1 mg/mL), palonosetron (50 mcg/mL), piperacillin/tazobactam (40/5 mg/mL), potassium chloride (0.04 mEq/mL), propofol (10 mg/mL and 20 mg/mL), quinupristin/dalfopristin (5 mg/mL), ranitidine (1 mg/mL), rocuronium (1 mg/mL), sargramostim (6 mcg/mL and 15 mcg/mL), sodium bicarbonate (1 mEq/mL), tacrolimus (20 mcg/mL), theophylline (1.6 mg/mL), tobramycin (10 mg/mL), vancomycin (5 mg/mL), vecuronium (1 mg/mL), and voriconazole (4 mg/mL).

fentaNYL diluted to 40 mcg/mL:

Midazolam (0.1 mg/mL)

fentaNYL diluted to 30 mcg/mL:

Esomeprazole (0.32 mg/mL).

fentaNYL diluted to 25 mcg/mL:

Amikacin (20 mg/mL), aminophylline (12.5 mg/mL), atracurium (5 mg/mL), atropine (0.4 mg/mL and 0.5 mg/mL), azathioprine (13.3 mg/mL), aztreonam (80 mg/mL), bretylium (40

mg/mL), bumetanide (0.125 mg/mL), calcium chloride (50 mg/mL), calcium gluconate (50 mg/mL), cefazolin (220 mg/mL), cefotaxime (285 mg/mL), cefotetan (400 mg/mL), cefoxitin (450 mg/mL), ceftazidime (400 mg/mL), ceftriaxone (165 mg/mL), cefuroxime (125 mg/mL), chloramphenicol (333 mg/mL), cimetidine (24 mg/mL), clindamycin (48 mg/mL), cyclosporine (2 mg/mL), dexamethasone (1 mg/mL and 12 mg/mL), digoxin (0.125 mg/mL), diphenhydramine (2 mg/mL and 25 mg/mL), dobutamine (6.25 mg/mL), dopamine (12.8 mg/mL), doxycycline (4 mg/mL), enalaprilat (0.625 mg/mL), epinephrine (0.5 mg/mL), epoetin alfa (5000 units/mL), erythromycin (20 mg/mL), esmolol (40 mg/mL), famotidine (5 mg/mL), fluconazole (2 mg/mL), furosemide (5 mg/mL), ganciclovir (40 mg/mL), gentamicin (6.4 mg/mL), heparin (160 units/mL), hydrocortisone succinate (62.5 mg/mL), imipenem/cilastatin (5 mg/mL), indomethacin (1 mg/mL), insulin (50 units/mL), isoproterenol (80 mcg/mL), ketorolac (1 mg/mL and 15 mg/mL), labetalol (2.5 mg/mL), lidocaine (10 mg/mL), lorazepam (0.1 mg/mL), magnesium sulfate (250 mg/mL), mannitol (150 mg/mL),

methyldopate (25 mg/mL), methylprednisolone (125 mg/mL), metoclopramide (2.5 mg/mL and 5 mg/mL), metoprolol (0.5 mg/mL), midazolam (0.2 mg/mL and 2.5 mg/mL), morphine (4 mg/mL), nafcillin (250 mg/mL), nalbuphine (10 mg/mL), naloxone (16 mcg/mL), netilmicin (50 mg/mL), nitroglycerin (1.6 mg/mL), nitroprusside (0.8 mg/mL), norepinephrine (0.5 mg/mL), ondansetron (1 mg/mL), oxacillin (160 mg/mL), papaverine (15 mg/mL), penicillin G potassium (500,000 units/mL), penicillin G sodium (500,000 units/mL), pentobarbital (25 mg/mL), phenobarbital (2 mg/mL and 65 mg/mL), phentolamine (5 mg/mL), phenylephrine (4 mg/mL), phytonadione (5 mg/mL), potassium chloride (1 mEq/mL), procainamide (250 mg/mL), propranolol (0.5 mg/mL), protamine (5 mg/mL), pyridoxine (50 mg/mL), quinidine gluconate (40 mg/mL), ranitidine (2 mg/mL), sodium bicarbonate (0.5 mEq/mL), succinylcholine (8 mg/mL), theophylline (4 mg/mL), ticarcillin/clavulanate (195 mg/mL), tobramycin (6.4 mg/mL), vancomycin (20 mg/mL), vasopressin (4 units/mL), and verapamil (1.25 mg/mL).

fentaNYL diluted to 20 mcg/mL:

Midazolam (0.1 mg/mL and 0.5 mg/mL).

fentaNYL diluted to 12.5 mcg/mL:

Cisatracurium (0.1 mg/mL, 2 mg/mL, and 5 mg/mL), and remifentanil (25 mcg/mL and 0.25 mg/mL).

fentaNYL diluted to 10 mcg/mL:

Alprostadil (7.5 mcg/mL), atracurium (0.5 mg/mL), pancuronium (50 mcg/mL), propofol (10 and 20 mg/mL), and vecuronium (0.1 mg/mL.

fentaNYL diluted to 2 mcg/mL:

Enalaprilat (50 mcg/mL).

Terminal Injection Site Incompatibility

Didiazoxide, pantoprazole, phenytoin, and sulfamethoxazole/trimethoprim.

Monitoring

Monitor respiratory and cardiovascular status closely. Observe for abdominal distention, loss of bowel sounds, and muscle rigidity.

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Synthetic opioid narcotic analgesic that is 50 to 100 times more potent than morphine on a weight basis. Extremely lipid soluble. Penetrates the CNS rapidly. Transient rebound in fentaNYL serum concentration may reflect sequestration and subsequent release of fentaNYL

from body fat. Metabolized extensively in the liver by CYP 3A4 enzyme system and then excreted by the kidney. Highly protein bound (80% to 85%). Apparent volume of distribution is approximately 4.5 L/kg in infants, decreasing to 3 L/kg in children. Distribution half-life of 3 to 5 minutes. Higher clearance and longer half-life in infants (less than 12 months of age) compared with children and adults [8][9][10][11][12].

Concentrations

FentaNYL AUC0 to 24 was 19.6 mcg x hr/L (interquartile range (IQR) 10.4, 33.5) for boluses of 1 mcg/kg/dose IV every 4 hours and 13.2 mcg x hr/L (IQR 10.8, 22.6) (p=0.12) for continuous infusion of 1 mcg/kg/hr IV administered fentaNYL for analgesia and sedation during mechanical ventilation (n=100). The median trough concentration was 0.41 to 0.97 ng/mL for the bolus dosing and the median serum fentaNYL concentration was 0.42 to 0.61 ng/mL for the continuous infusion. At all time points for both groups the pain scores demonstrated adequate relief of both acute and ongoing pain. The need for additional sedatives or analgesics were comparable between groups. The mean gestational age was 35.4 weeks for the bolus group and 36.5 weeks for the infusion group. The majority of infants were younger than 1 week (85.1% in the bolus group and 90.6% in the infusion group) [13].

Clearance: 4.1 L/hr (IQR 2, 6.4 L/hr) in 53 infants (median age 1 week; gestational age (GA) 36.5 weeks) administered fentanyl 1 mcg/kg/hr [13]

Half-life: 8.4 hours (IQR 7.9, 9.7 hr) in 53 infants (median age 1 week; gestational age (GA) 36.5 weeks) administered fentanyl 1 mcg/kg/hr and 26.7 hours (IQR 8.1, 65.2 hours; p=0.002) in 47 infants (median age 2 weeks; GA 35.4 weeks) administered 1 mcg/kg/dose IV every 4 hours [13]

ABOUT

Special Considerations/Preparation

Available: 2-, 5-, 10-, and 20-mL ampules in a concentration of 50 mcg/mL [14]. A 10-mcg/mL dilution may be made by adding 1 mL of the 50-mcg/mL concentration to 4 mL preservative-free normal saline.

Stability

At least 95% of the original concentration of fentaNYL remained on day 100 when fentaNYL 10 mcg/mL (0.01 mg/mL) in NS or D5W and fentaNYL 50 mcg/mL (0.05 mg/mL) were stored at room temperature in polypropylene syringes [15].

Ferrous sulfate
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
2 mg/kg/day of elemental iron for growing premature infants. (Maximum of 15 mg/day).
Begin therapy after 2 weeks of age.
Infants with birthweights less than 1000 grams may need 4 mg/kg/day.
6 mg/kg/day of elemental iron for patients receiving erythropoietin.
Administer orally in 1 or 2 divided doses, preferably diluted in formula.
Uses
Iron supplementation for prevention and treatment of anemia.
MEDICATION SAFETY
Adverse Effects
Nausea, constipation, black stools, lethargy, hypotension, and erosion of gastric mucosa.
Monitoring
Monitor hemoglobin and reticulocyte counts during therapy.
Observe stools, check for constipation.
MECHANISM OF ACTION/PHARMACOKINETICS
Pharmacology
Well absorbed from stomach.

Special Considerations/Preparation
Drops: Ferrous sulfate drops available as 15 mg elemental iron per 1 mL (0.2% alcohol).
Confirm product concentration.
Elixir: Contains 44 mg elemental iron per 5 mL (some with 5% alcohol).

Flecainide
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
Begin at 2 mg/kg per dose every 12 hours orally.
Adjust dose based on response and serum concentrations to a maximum of 4 mg/kg per dose every 12 hours. Correct preexisting hypokalemia or hyperkalemia before administration.
Optimal effect may take 2 to 3 days of

therapy to achieve, and steady-state plasma levels may not be reached until 3 to 5 days at a given dosage in patients with normal renal and hepatic function. Therefore, do not increase dosage more frequently than approximately once every 4 days.

Uses

Treatment of supraventricular arrhythmias not responsive to conventional therapies. Not recommended in patients with structurally abnormal hearts.

Administration

Infant formulas and milk may decrease absorption. If milk is removed from the infants diet, a reduction in dose should be considered [1][2][3].

MEDICATION SAFETY

Contraindications/Precautions

Contraindicated in patients with preexisting second- or third-degree AV block, or with right bundle branch block when associated with a left hemiblock, unless a pacemaker is present. Also contraindicated in the presence of cardiogenic shock [1].

Adverse Effects

Flecainide can cause new or worsened arrhythmias, including AV block, bradycardia, ventricular tachycardia, torsades de pointes. There is also a negative inotropic effect.

Dizziness, blurred vision, and headache have been reported in children.

Black Box Warning

An excessive mortality or non-fatal cardiac arrest rate was seen in patients (adults) with asymptomatic non-life-threatening ventricular arrhythmias and a history of myocardial infarction treated with flecainide compared with that seen in patients assigned to a carefully matched placebo-treated group in the Cardiac Arrhythmia Suppression Trial (CAST). It is prudent to consider the risks of Class IC agents (including flecainide), coupled with the lack of any evidence of improved survival, generally unacceptable in patients without lifethreatening ventricular arrhythmias, even if the patients are experiencing unpleasant, but not life-threatening, symptoms or signs. Flecainide is not recommended for use in patients with chronic atrial fibrillation. Case reports of ventricular proarrhythmic effects in patients treated with flecainide for atrial fibrillation/flutter have included increased PVCs, VT, ventricular fibrillation (VF), and death.

Monitoring

Continuous EKG during initiation of therapy, as this is the most common time to see druginduced arrhythmias. Follow trough serum concentrations closely at initiation, 3 to 5 days after any dose change, and with any significant change in clinical status or diet. Therapeutic trough levels are 200 to 800 nanograms/mL.
MECHANISM OF ACTION/PHARMACOKINETICS
Pharmacology
Flecainide is a class IC antiarrhythmic that produces a dose-related decrease in intracardiac conduction in all parts of the heart, thereby increasing PR, QRS and QT intervals. Effects upon atrioventricular (AV) nodal conduction time and intra-atrial conduction times are less pronounced than those on the ventricle. Peak serum concentrations occur 2 to 3 hours after an oral dose. Infant formula and milk products interfere with drug absorption. Plasma protein binding is about 40% in adults and is independent of plasma drug level. Children under 1 year of age have elimination half-life values of 11 to 12 hours. Elimination half-life in newborns after maternal administration is as long as 29 hours.
ABOUT
Special Considerations/Preparation
Available: 50-mg, 100-mg, and 150-mg tablets.
Extemporaneous Compounds
5 mg/mL Oral Suspension: An oral suspension with a final concentration of 5 mg/mL can be made as follows: crush 6 (six) 100-mg tablets, slowly mix in 20 mL of a 1:1 mixture of Ora-Sweet and Ora-Plus, or cherry syrup (cherry syrup concentrate diluted 1:4 with simple syrup) to form a uniform paste, then add to this mixture enough vehicle to make a

final volume of 120 mL. Shake well and protect from light. Stable for 45 days refrigerated and at room temperature when stored in amber glass or plastic [4].
20 mg/mL Oral Solution: [5].
Add 2000 mg of pure pharmaceutical grade flecainide powder to a 250 mL beaker
Add 50 mL of purified water that has been heated to 37C to the beaker
While maintaining temperature at 37C, mix the solution, using magnetic stirring, until the solution is transparent (10 minutes). Temperature should not exceed 37C.
Transfer to a 100 mL graduated cylinder.
Wash the beaker with approximately 10 mL of simple syrup and transfer to the

graduated cylinder.
Add sufficient volume of simple syrup to the graduated cylinder for a final volume of 100 mL.
Transfer back to the beaker for 10 minutes to homogenize the mixture using magnetic stirring.
Transfer to an amber bottle.
Stable for 30 days at 25C
20 mg/mL Oral Suspension: An oral suspension with a final concentration of 20 mg/mL may also be compounded. Extemporaneously compounded flecainide acetate 20 mg/mL prepared in either a 1:1 mixture of Ora-Sweet and Ora-Plus, a 1:1 mixture of Ora-Sweet SF and Ora-Plus, or cherry syrup (cherry syrup concentrate diluted 1:4 with simple syrup) and placed in a 120-mL amber polyethylene terephthalate bottle is stable, retaining a mean of at least 92% of the initial drug concentration, for up to 60 days when stored without light at 5 and 25 degrees C [6].

Fluconazole
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
Coccidioidomycosis: 6 to 12 mg/kg/day IV or orally; continue empiric therapy until infection can be ruled out [1].
Invasive Candidiasis: 12 to 25 mg/kg loading dose, then 6 to 12 mg/kg per dose IV, or orally [2][3][4][5]. In neonates and children, a dose of 12 mg/kg/day is recommended.
Duration of therapy for candidemia, without metastatic complications, is 2 weeks after documented clearance of Candida from the bloodstream and resolution of symptoms [6].
Consider the higher doses for treating severe infections or Candida strains with higher MICs (4 to 8 mcg/mL). Extended dosing intervals should be considered for neonates with renal insufficiency (serum creatinine greater than 1.3 mg/dL).
Higher doses may be required in patients receiving extracorporeal membrane oxygenation (ECMO) [7].
Note: The higher loading and maintenance doses are based on pharmacokinetic/pharmacodynamic data but have not been prospectively tested for efficacy or safety.
Antibiotic Dosing Chart:

Invasive Candidiasis Dosing Interval Chart
Gest. Age
(weeks)
PostNatal
(days)
Interval
(hours)
?29 0 to 14
>14
48
24
30 and older 0 to 7
>7
48
24
Invasive Candidiasis; Prophylaxis (birth weight less than 1000 g [6]or less than
1500 g):[8] 3 to 6 mg/kg/dose IV or orally twice weekly for 6 weeks in neonatal intensive
care units with high incidence rates of Candida infections [8][6].
Thrush: 6 mg/kg on Day 1, then 3 mg/kg per dose every 24 hours orally.
Dose Adjustments
There are no data available for neonates with renal impairment; however, the following dose
adjustments are based on recommendations for adults with renal impairment [9]:
For patients with renal impairment: The normal loading dose should be given, followed
by a reduced daily dose [10].
For patients with a CrCl of 50 mL/min or less (no dialysis): The daily dose should be
reduced by 50% [10].
For patients receiving dialysis: 100% of the usual dose should be given after each
dialysis session; on non-dialysis days, patients should receive a reduced dose according to
creatinine clearance [9].

Uses
Treatment of systemic infections, meningitis, and severe superficial mycoses
caused by Candida species. Resistance has been reported with C glabrata and C krusei and in
patients receiving long-term suppressive therapy.
Neonatal Candidiasis, Including CNS Infection[6]
Invasive candidiasis and candidemia, or very low-birth weigh infants with asymptomatic
candiduria .
Amphotericin B deoxycholate is recommended.
Fluconazole IV or oral is an alternative for those who have not been receiving
prophylaxis with fluconazole.

Lipid formulation amphotericin B agent is an alternative; however use with caution, especially in the presence of urinary tract involvement.
Echinocandins (caspofungin, anidulafungin, or micafungin) should be limited to salvage therapy or scenarios of resistance or toxicity to amphotericin B deoxycholate or fluconazole
Central nervous system infections
Amphotericin B deoxycholate is recommended.
Liposomal amphotericin B is an alternative.
Salvage therapy with flucytosine may be added in those patients who have not responded to initial therapy.
Fluconazole may be used as step-down therapy for fluconazole-susceptible isolates in those patients who respond to initial therapy
Neonatal intensive care unit (with greater than 10% rate of invasive candidiasis)[6]
Prophylaxis with IV or oral fluconazole for 6 weeks is recommended for neonates with birth weights of less than 1000 g
Prophylaxis with oral nystatin is an alternative in neonates with birth weights of less than 1500 g when fluconazole is unavailable or fluconazole resistance is present
Prophylaxis of invasive candidiasis: One recommendation is to limit the use of prophylactic fluconazole to high-risk premature infants when the rate of invasive candidiasis is greater than 2% to 5% [12]. The odds of invasive candidiasis (OR 0.2 (95% CI, 0.08 to 0.51) and Candida colonization (OR 0.28 (95% CI, 0.18 to 0.41) occurred less often in the fluconazole compared with placebo group in an evaluation of 4 trials of prophylaxis in premature infants in the United States. Mortality was not different (11% for fluconazole and 14% for placebo). There was no difference between groups in adverse events (ALT, AST, alkaline phosphatase, or conjugated bilirubin levels). Resistance to Candida isolates were not different between the groups [8].
Further evidence suggest prophylactic fluconazole be limited to when the incidence is moderate to high (specific incidence not identified). Although fluconazole prophylaxis reduced the rates of invasive candidiasis (3% vs 9% (p=0.02)), it did not reduce the primary outcome of incidence of death or invasive candidiasis in infants weighing less than 750 g (median, 25 weeks gestation and 120 hours or younger) compared with placebo in a multicenter study (n=361). The dose of oral or IV fluconazole was 6 mg/kg/dose twice weekly for 42 days [13]. The duration of treatment is important; the overall combined

relative risks of invasive fungal infection were 0.8 (95% CI, 0.48 to 1.35) with a 28-day treatment and 0.3 (95% CI, 0.15 to 0.58) with a 42-day treatment of prophylactic

fluconazole in a meta-analysis (5 studies; 1006 preterm neonates with birthweight less than 1500 g) [14].

Coccidioidomycosis: Empiric fluconazole is recommended for neonates born to mothers with coccidioidomycosis. Discontinue fluconazole once coccidioidomycosis has been ruled out [1].

Administration

Intravenous: Infuse at concentration of 2 mg/mL over 1 to 2 hours (maximum rate 200 mg/hour). Solutions for intravenous infusion are supplied premade (glass bottle or Viaflex plastic bag) in a concentration of 2 mg/mL [10].

In the preparation and administration of injections, National Institute for Occupational Safety and Health (NIOSH) recommends the use of double gloves and a protective gown. Prepare in a biological safety cabinet or a compounding aseptic containment isolator; eye/face and respiratory protection may be needed. Prepare compounds in a closed system drug transfer device. During administration, if there is a potential that the substance could splash or if the patient may resist, use eye/face protection. Administer certain dosage forms via a closed system drug transfer device [11].

Oral: May be given with or without food [10].

The National Institute for Occupational Safety and Health (NIOSH) recommends the use of single gloves by anyone handling intact tablets or capsules or administering from a unit-dose package [11].

In the preparation of tablets or capsules, including cutting, crushing, or manipulating, or the handling of uncoated tablets, NIOSH recommends the use of double gloves and a protective gown. Prepare in a ventilated control device, if possible. Use respiratory protection if not prepared in a control device. During administration, wear single gloves, and wear eye/face protection if the formulation is hard to swallow or if the patient may resist, vomit, or spit up [11].

NIOSH recommends the use of double gloves and a protective gown by anyone handling a hazardous oral liquid or preparing any hazardous drug for administration via a feeding tube.

Prepare in a control device, if possible. Use respiratory, eye, and face protection if not done in a control device. During administration, eye/face protection is needed if the patient may resist, or if there is potential to vomit or spit up [11].

MEDICATION SAFETY

Contraindications/Precautions

Contraindicated in patients receiving cisapride, due to precipitation of life-threatening arrhythmias [10][16]; terfenadine, in patients receiving multiple doses of fluconazole 400 mg or higher; and QT-prolonging drugs metabolized by CYP3A4 (eg, astemizole, cisapride, erythromycin, pimozide, or quinidine) [17].

Cardiovascular: QT prolongation and torsade de pointes have been reported rarely,

primarily in seriously ill patients with multiple confounding risk factors such as structural heart disease, electrolyte abnormalities, and concomitant medications; additional caution advised with use in patients with potentially proarrhythmic conditions [18]

Cardiovascular: Increased risk of life-threatening ventricular arrhythmias and torsades de pointes in patients with hypokalemia and advanced cardiac failure [18]

Concomitant use: Narrow therapeutic index drugs that are metabolized by CYP2C9 or CYP3A4; monitoring recommended [17]

Concomitant use: Avoid voriconazole [17]

Dermatologic: Exfoliative skin disorders have been reported rarely with some fatal cases reported in patients with serious underlying diseases [17]

Endocrine and metabolic: Adrenal insufficiency, including reversible cases, have been reported [15]

Hepatic: Hepatic toxicity, including fatalities, has been reported rarely; monitoring recommended and discontinue if signs of liver disease develop [17]

Hepatic: Use caution in patients with liver dysfunction due to increased risk of hepatic toxicity; monitoring recommended and discontinue if condition worsens [17]

Immunologic: Use caution in patients with hypersensitivity to other azole antifungal agents; cross-hypersensitivity not yet determined [17]

Immunologic: Anaphylaxis has been reported rarely [17]

Immunologic: Deep seated fungal infection and presence of rash; monitoring recommended and discontinue if lesions progress [17]

Immunologic: Superficial fungal infection; discontinue if rash occurs and is attributed to drug [17]
Renal: Preexisting renal dysfunction [17]
Special populations: Sucrase-isomaltase deficiency or heredity fructose or glucose/galactose malabsorption; avoid powder for oral suspension as it contains sucrose [17]
Adverse Effects
Common: Vomiting (5%), abdominal pain (3%), nausea (2%), and diarrhea (2%) with fluconazole in doses up to 15 mg/kg/day for a maximum of 1616 days (n=577; age range, 1 day to 17 years) [15].
Hepatic Mean AST at 4 weeks was significantly greater with fluconazole prophylaxis (16.8 units/L) compared with placebo (13.1 units/L) while mean ALT was not significantly different between fluconazole and placebo groups (22.8 units/L vs 19.5 units/L), in a randomized, double-blind trial of 322 very-low-birth-weight infants. No clinical signs of hepatotoxicity or cholestasis were observed. No treatment for cholestasis or phototherapy for hyperbilirubinemia was required. Prophylactic fluconazole doses were 3 or 6 mg/kg/dose every third day for the first 2 weeks, then every other day for a total duration of 6 weeks for extremely-low-birth-weight infants and for a total duration of 4 weeks for neonates weighing 1000 to 1500 g [19].
Conjugated hyperbilirubinemia (greater than 2 mg/dL) occurred significantly more frequently in extremely-low-birth-weight (ELBW) infants with fluconazole prophylaxis (42.9%; n=140) compared with that of ELBW infants not given fluconazole prophylaxis (8.8%; n=137), in a retrospective study with historical controls. Prolonged duration of conjugated hyperbilirubinemia and treatment with ursodeoxycholic acid was performed more often in the fluconazole group. At discharge, the rate of conjugated hyperbilirubinemia was similar between groups. Fluconazole dosage was 3 mg/kg/dose every 72 hours for 2 weeks, then

every 48 hours for 2 weeks, then every day for 2 weeks [20].
Solution Compatibility
D5W and D10W.
Terminal Injection Site Compatibility
Acyclovir, amikacin, aminophylline, amiodarone, aztreonam, caspofungin, cefazolin,

cefepime, cefoxitin, cimetidine, dexamethasone, dobutamine, dopamine, famotidine, ganciclovir, gentamicin, heparin, hydrocortisone succinate, intravenous immune globulin (human), linezolid, lorazepam, meropenem, metoclopramide, metronidazole, midazolam, morphine, nafcillin, nitroglycerin, oxacillin, pancuronium bromide, penicillin G, phenytoin, piperacillin/tazobactam, potassium chloride, propofol, quinupristin/dalfopristin, ranitidine, remifentanil, ticarcillin/clavulanate, tobramycin, vancomycin, vecuronium, and zidovudine.

Terminal Injection Site Incompatibility

Amphotericin B, ampicillin, calcium gluconate, cefotaxime, ceftazidime, ceftriaxone, chloramphenicol, clindamycin, digoxin, erythromycin lactobionate, furosemide, imipenem, piperacillin, ticarcillin, and trimethoprim/sulfamethoxazole.

Monitoring

Monitor for more serious hepatic injury in patients who develop abnormal liver function tests during therapy [15].

For candidemia, monitor blood cultures daily or every other day until Candida is cleared [6].

MECHANISM OF ACTION/PHARMACOKINETICS

Pharmacology

Water-soluble triazole antifungal agent. Inhibits cytochrome P-450-dependent ergosterol synthesis. Well absorbed after oral administration, with peak serum concentrations reached within 1 to 2 hours. Less than 12% protein binding. Good penetration into CSF after both oral and IV administration. Serum half-life is 30 to 180 hours in severely ill VLBW infants in the first 2 weeks of life and approximately 17 hours in children. Primarily excreted unchanged in the urine.

Fluconazole is a potent inhibitor of CYP2C9 and CYP2C19, and is a moderate inhibitor of

CYP3A4 [9].

ABOUT

Special Considerations/Preparation

Injection

Available as a premixed solution for IV injection in concentrations of 200 mg/100 mL and 400 mg/200 mL in Viaflex bags or glass bottles (2 mg/mL). Do not remove overwrap from Viaflex bag until ready for use. Store at room temperature.Do not freeze.

Oral

Oral dosage form is available as a powder for suspension in concentrations of 10 mg/mL and

40 mg/mL. Prepare both concentrations by adding 24 mL distilled water to bottle of powder and shaking vigorously. Each bottle will deliver 35 mL of suspension. Suspension is stable at room temperature for 2 weeks. Do not freeze.
Extemporaneous compound: For a 1 mg/mL suspension, pulverize 5 100-mg tablets in a mortar and add deionized water to make a suspension. Transfer liquid to a graduate and add sufficient additional water to final volume of 500 mL. May store at room temperature or under refrigeration (preferable); stable for 15 days. Shake well before using [21][22].
Safe handling: The National Institute for Occupational Safety and Health (NIOSH) recommends the use of double gloves and a protective gown by anyone compounding a hazardous oral liquid or preparing any hazardous drug for administration by feeding tube. If possible, prepare in a control device. Respiratory, eye, and face protection are needed if not done in a control device [11].

Flucytosine
NeoFax Drug Monograph Summary - MICROMEDEX
DOSING/ADMINISTRATION
Dose
12.5 to 37.5 mg/kg per dose every 6 hours orally. Increase dosing interval if renal dysfunction is present.
Uses
Antifungal agent used in combination with amphotericin B or fluconazole for treatment of infections caused by Candida, Cryptococcus, and other sensitive fungi.
MEDICATION SAFETY
Adverse Effects
Toxicities are related to serum concentration above 100 mcg/mL, and are usually reversible if the drug is stopped or the dose is reduced. Fatal bone marrow depression (related to fluorouracil production), hepatitis, severe diarrhea, rash. Amphotericin B may increase toxicity by decreasing renal excretion.
Black Box Warning
According to the manufacturer's black box warning, extreme caution is recommended in patients with impaired renal function. Close monitoring of hematologic, renal, and hepatic status of all patients is essential.
Monitoring
Desired peak serum concentration ranges from 50 to 80 mcg/mL. Assess renal function.