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Treatment and prevention of meningococcal infection

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INTRODUCTION

Neisseria meningitidis is a common cause of community-acquired bacterial meningitis in children and adults in the United States and in many other countries. (See "Epidemiology of Neisseria meningitidis infection" and "Bacterial meningitis in children older than one month: Clinical features and diagnosis", section on 'Causative organisms' and "Epidemiology of bacterial meningitis in adults".)

The clinical manifestations of meningococcal disease can be quite varied, ranging from transient fever and bacteremia to fulminant disease with death ensuing within hours of the onset of clinical symptoms. (See "Clinical manifestations of meningococcal infection".)

The treatment and prevention of meningococcal infection will be reviewed here [1-3]. The microbiology, pathobiology, epidemiology, and diagnosis of *N. meningitidis* infection are discussed separately. (See "Microbiology and pathobiology of Neisseria meningitidis" and "Epidemiology of Neisseria meningitidis infection" and "Diagnosis of meningococcal infection".)

TREATMENT OF MENINGITIS AND SEPSIS

The treatment of meningococcal sepsis is a complex medical problem, requiring a team approach by physicians skilled in intensive care medicine, infectious diseases, and the management of coagulopathies. Whenever possible, treatment should be given in a facility capable of administering the full range of medical care.

Antibiotic therapy

Importance of early administration — For patients with known or suspected invasive meningococcal infection, all attempts should be made to initiate parenteral antibiotics as quickly as possible. Prompt administration of appropriate antibiotics as early in the disease as possible is key to a successful outcome of life-threatening meningococcal infection. It is warranted in patients with severe sepsis syndrome, fever with petechiae and/or ecchymoses, or suspected bacterial meningitis. The

optimal timing of antibiotic administration is uncertain, given variability in clinical presentation [4,5]; some European advisory groups have suggested as soon as one hour from presentation [6,7].

Blood cultures should be drawn prior to initiation of antibiotic therapy, but antibiotic therapy should **not** be delayed while waiting for lumbar puncture to be performed. Although administration of antibiotic therapy prior to lumbar puncture can substantially diminish the probability of a positive cerebrospinal fluid (CSF) culture, the diagnosis can often be established from the pretreatment blood cultures and/or molecular tools. (See "Diagnosis of meningococcal infection".)

If meningococcal infection is suspected in a physician's office or outpatient clinic, the patient should be stabilized and transported promptly to an appropriate hospital facility. Some experts also suggest giving antibiotics (eg, intramuscular or intravenous [IV] penicillin G or ceftriaxone) in the outpatient setting if a patient cannot be transferred within an hour to a hospital (but they do not delay transfer for antibiotic administration) [6,7]. The data on the efficacy of antibiotic administration prior to hospital transfer are variable. Some studies performed during epidemics in the 1990s suggested that administration of antibiotics prior to transfer was associated with improved outcome [8,9], but in another study, it was associated with higher mortality [10].

If patients have symptoms possibly suggestive of meningococcal infection (such as fever, prostration, muscle aches), but it is thought to be unlikely after a thorough history and physical examination, they should be advised to monitor themselves carefully with instructions to return for follow-up evaluation in the setting of clinical deterioration (including persistent fever, mental status changes, and rash). Additional care should be taken with infants, for whom an adequate history may not be obtainable. In such situations, direct observation in a controlled setting (eg, emergency room or hospital admission) with empiric treatment until the diagnosis can be excluded is appropriate. (See "Bacterial meningitis in the neonate: Clinical features and diagnosis" and "Bacterial meningitis in children older than one month: Clinical features and diagnosis".)

Early and appropriate antibiotic treatment markedly improves the outcome of invasive meningococcal infections [8,9,11]. In one prospective study that included 907 patients with proven meningococcal disease in Barcelona, Spain, the overall mortality rate was 5.6 percent [9]. In patients who were already receiving antibiotics for another indication prior to hospital admission, there was a marked reduction in mortality (odds ratio 0.09, 95% CI 0.02-0.4), suggesting that antibiotics are effective in controlling proliferation of the organism in the bloodstream and should be started as soon as possible.

Patients with meningococcal sepsis have extremely high bacterial loads, and increasing bacterial loads have been associated with an increased odds of death [12,13]. Given the rapid division time of meningococcus in vitro, a delay of 70 minutes would result in such an increase and a higher risk of a poor outcome. Appropriate parenteral therapy can clear the CSF of meningococci in less than six hours [14].

Regimen selection — In cases of suspected bacterial meningitis, patients should be treated empirically to cover the most likely pathogens while awaiting culture results. The following discussion will focus on the treatment of presumed meningococcal infection. Topic reviews that provide a more general overview of initial therapy for bacterial meningitis are presented separately. (See "Initial

therapy and prognosis of bacterial meningitis in adults" and "Bacterial meningitis in children older than one month: Treatment and prognosis" and "Bacterial meningitis in the neonate: Treatment and outcome".)

Preferred regimens — For treatment of meningococcal meningitis or sepsis prior to the availability of susceptibility testing, ceftriaxone is the agent of choice. Cefotaxime can be used instead of ceftriaxone, but this agent is not available in many settings and must be administered more frequently than ceftriaxone.

If susceptibility testing indicates that the isolate is penicillin susceptible (minimum inhibitory concentration [MIC] <0.1 mcg/mL), either ceftriaxone or penicillin can be used [15-17]. Ceftriaxone has the advantage of more convenient dosing, but penicillin may be less costly in some cases. If the penicillin MIC is between 0.1 and 1.0 mcg/mL, we still favor ceftriaxone; high-dose penicillin is effective in this MIC range but not preferred.

- Ceftriaxone is administered as a 2 g IV dose every 12 hours or, for children, an IV dose of 50 mg/kg (maximum 2 g) every 12 hours.

- Penicillin can be administered IV or intramuscularly. A typical regimen of penicillin G in adults is 4 million units IV every four hours. For children, the dose is 300,000 units/kg per day in a divided dose every six hours; the usual maximum dose is 12 million units/day [18]. Penicillin should **never** be administered intrathecally because of the danger of severe neurotoxicity and is not necessary since both penicillins and cephalosporins readily cross the blood-brain barrier.

  If penicillin is selected, patients should undergo subsequent eradication therapy for presumed nasopharyngeal carriage. (See 'Subsequent eradication therapy for select patients' below.)

Both penicillin and ceftriaxone are bactericidal and have been shown to clear the CSF of viable organisms quickly. They reach levels in the CSF in excess of those needed to treat meningococcus, and the duration of antibiotic activity is prolonged, resulting in stable levels [19,20]. However, there are limited clinical data comparing outcomes with penicillin or ceftriaxone [15-17]. In an observational study in which most patients received penicillin for four or seven days or ceftriaxone for four days, the overall case-fatality rate was approximately 6 to 7 percent, and the rate of chronic neurologic sequelae was also 6 to 7 percent [21]. These are greatly improved over historical mortality rates prior to the availability of antibiotics. (See 'Prognosis' below.)

Resistance to penicillin and cephalosporins has been reported but is generally uncommon.

- Meningococcal strains with decreased sensitivity to third-generation cephalosporins have been observed. In one study, approximately 2 percent of invasive meningococcal isolates between 2012 and 2015 in France demonstrated reduced susceptibility to third-generation cephalosporins [22].

- The first reports of *N. meningitidis* resistant to penicillin appeared in 1988 [23,24]. Relative resistance to penicillin is caused by a reduced binding affinity to specific penicillin-binding proteins [25]. Although such resistant meningococcal strains have been infrequently reported,

clinicians should be alerted to the possibility of their occurrence in unexplained treatment failures or in cases of slowly resolving meningitis. (See "Beta-lactam antibiotics: Mechanisms of action and resistance and adverse effects", section on 'Mechanisms of bacterial resistance'.)

In the unlikely event that the isolate is resistant to both penicillin and ceftriaxone, chloramphenicol can be used if locally available, similar to patients who cannot receive a beta-lactam. This and other potential alternative treatment options are discussed below. (See 'Patients intolerant of beta-lactams' below.)

Patients intolerant of beta-lactams — Systemic meningococcal infection has a high mortality unless treated appropriately, and use of the most effective antibiotics is paramount. Patients who are intolerant to beta-lactams should be managed in consultation with an infectious diseases specialist.

For such patients, it is important to evaluate the nature of the beta-lactam allergy, since the approach to treatment in these critically ill patients depends upon the type of reaction (algorithm 1).

- **Patients with mild reaction without features of an immunoglobulin (Ig)E-mediated reaction** – In general, most patients who are labeled as allergic to penicillin who do not report a history of severe immediate allergy (eg anaphylaxis) are able to receive a third-generation cephalosporin such as ceftriaxone. (See "Choice of antibiotics in penicillin-allergic hospitalized patients".)

- **Patients with IgE-mediated reactions** – Patients with a severe immediate allergy (eg, anaphylaxis) to a penicillin can usually be treated with a third-generation cephalosporin, such as ceftriaxone, given with a test-dose procedure. (See "Choice of antibiotics in penicillin-allergic hospitalized patients", section on 'Test dose procedure (graded challenge)'.)

  If there is also a history of a severe immediate allergy to ceftriaxone, most patients can tolerate carbapenems because cross-reactivity rates between penicillins or cephalosporins and carbapenems for patients with proven immediate allergy are <1 percent, although several reactions have been reported [26]. In such patients, meropenem should be administered using a test-dose procedure. Carbapenems have been used for bacterial meningitis with meningococcus and other gram-negative organisms, although the experience with meningococcal meningitis is limited [27]. The dose of meropenem recommended for treatment of meningitis is 2 g IV every 8 hours for adults or 40 mg/kg every 8 hours for children (up to a maximum of 6 g/day) [27]. Imipenem should not be administered, as seizures have been reported with this combination in children [28].

- **Patients with serious delayed reactions** – When there is concern for a severe delayed allergy to a penicillin or a cephalosporin (Stevens Johnson syndrome/toxic epidermal necrolysis [SJS/TEN], drug reaction with eosinophilia and systemic symptoms [DRESS], acute generalized exanthematous pustulosis [AGEP]), all beta-lactams and carbapenems should generally be avoided. In this case, chloramphenicol (100 mg/kg per day IV in divided doses every 6 hours, up to a maximum dose of 4 g/day) is an acceptable alternative antibiotic choice, although its availability is limited, particularly in resource-rich settings. Resistance of meningococcal strains to chloramphenicol has rarely been described [29].

Fluoroquinolones are also a potential alternative in patients with meningococcal infection who cannot use beta-lactams or carbapenems. Clinical experience is extremely limited for systemic infection, and the optimal dosing is unclear. As an example, one pharmacokinetic study suggested that in adults, levofloxacin 500 mg IV every 12 hours would be sufficient to treat *N. meningitidis* if the MICs are <0.1 to 0.2 mcg/mL [30]; however, other experts would consider a higher dose of levofloxacin (eg, 750 mg every 12 hours). In either case, the dose may need to be adjusted in patients with known renal insufficiency because of an increased risk of toxicity [31]. Information on renal dosing can be found in the drug information topic within UpToDate.

Although fluoroquinolones may be suitable for some patients, resistance to fluoroquinolones is widespread, and use of this class of antibiotics should be avoided in areas with known resistance to these agents. Additional information on fluoroquinolone resistance is found below. (See 'Regimens' below.)

If an agent other than a third-generation cephalosporin is used, patients should undergo subsequent eradication therapy for presumed nasopharyngeal carriage. (See 'Subsequent eradication therapy for select patients' below.)

Duration of therapy — An adequate response to therapy includes clearing of fever, stability of blood pressure, improving mental status, and stabilizing of hematologic parameters. A repeat lumbar puncture is not typically required, since the expected clinical improvement is rapid.

The precise duration of antibiotic therapy will vary based upon the patient's age, the severity of initial illness, and the response to therapy:

- **Adults** – For adults, we suggest a minimum of four days of total therapy for meningococcal meningitis. For patients with a severe presentation and/or delayed response to therapy, extending treatment to seven days is appropriate.
- **Children** – For children, we generally treat for five to seven days; this recommendation is consistent with guidelines from the American Academy of Pediatrics [18].

Treatment for longer than seven days has not proven necessary, unless a secondary infection complicates meningococcal disease.

Data informing the optimal duration of therapy are limited. In an observational study of 527 cases of invasive meningococcal infection that occurred over a time period when the recommended duration changed from seven to four days, mortality rates and rates of complications were comparable with both durations [21]. Short courses have also been studied in epidemic settings and appear comparably effective to longer courses. (See 'Considerations during epidemics in resource-limited settings' below.)

Previous studies had suggested that seven days was comparable with longer durations, and seven days had been the previously preferred duration [15,32].

Subsequent eradication therapy for select patients — Patients with invasive meningococcal disease who were treated with an agent other than a third-generation cephalosporin should receive chemoprophylaxis for eradication of presumed nasopharyngeal carriage prior to discharge from the

hospital to prevent subsequent transmission to close contacts [33-35]. Treatment with antimicrobial agents other than third-generation cephalosporins does not reliably eradicate nasopharyngeal carriage of *N. meningitidis*. Chemoprophylaxis regimens for such patients are the same as for post-exposure prophylaxis (table 1). (See 'Regimens' below.)

Considerations during epidemics in resource-limited settings — Epidemics of meningitis due to *N. meningitidis* are reported almost every year in sub-Saharan Africa (figure 1) [36]. Since 1995, the World Health Organization (WHO) has recommended empiric treatment of suspected cases of meningococcal infection with one or two intramuscular injections of long-acting chloramphenicol (oily suspension); however, the continued production of this drug is uncertain. Although alternative drugs with proven efficacy against *N. meningitidis* are available (eg, benzylpenicillin, ampicillin, and IV or intramuscular chloramphenicol or ceftriaxone), protocols requiring multiple injections are impractical during an epidemic. Shorter regimens of beta-lactams may be reasonable alternatives [36-38].

A single intramuscular dose of ceftriaxone is an alternative first-line treatment to chloramphenicol for epidemic meningococcal meningitis. In a randomized trial of 510 patients (441 under the age of 15 years) with suspected disease during a meningococcal meningitis epidemic in Niger, a single dose of intramuscular ceftriaxone was as effective as a single dose of long-acting chloramphenicol in oil [36]. The treatment failure rate was 9 percent at three days in both groups and the mortality rate was 5 to 6 percent.

Results were similar among patients with confirmed meningitis caused by *N. meningitidis*.

A short course of penicillin may also be an option. In a prospective study of adults in New Zealand, three days of 12 million units of benzylpenicillin was an effective regimen [38].

Discontinuing glucocorticoids — Empiric dexamethasone may be administered in adults and children with bacterial meningitis while awaiting microbiologic data. (See "Dexamethasone to prevent neurologic complications of bacterial meningitis in adults" and "Bacterial meningitis in children: Dexamethasone and other measures to prevent neurologic complications".)

Dexamethasone has **not** been shown to be of benefit in meningococcal meningitis and should be discontinued once this diagnosis is established [39-41].

The possible role of pharmacologic doses of glucocorticoids in septic shock and of dexamethasone in bacterial meningitis is discussed separately. (See "Evaluation and management of suspected sepsis and septic shock in adults" and "Dexamethasone to prevent neurologic complications of bacterial meningitis in adults" and "Bacterial meningitis in children: Dexamethasone and other measures to prevent neurologic complications", section on 'Dexamethasone'.)

Treatment of shock — Vascular collapse and shock are frequent early manifestations of meningococcal disease caused largely by the bacterial product, lipooligosaccharide, which is a potent toxin. Details of resuscitative efforts for septic shock are discussed in detail elsewhere. (See "Evaluation and management of suspected sepsis and septic shock in adults".)

Protein C concentrate — In severe meningococcal sepsis, protein C activation is impaired [42]. In severe meningococcal sepsis, we suggest use of protein C concentrate, although it has not been approved by the US Food and Drug Administration for this indication. The suggested dose of protein C is 100 to 120 international units/kg initially followed every six hours for three subsequent doses of 60 to 80 international units/kg. (See "Clinical manifestations of meningococcal infection".)

Limited data suggest that protein C concentrate might be beneficial in patients with meningococcal sepsis and purpura fulminans [43]:

- In a randomized trial including 40 children with purpura fulminans and meningococcal sepsis, treatment with protein C concentrate was associated with resolution of coagulopathy with no adverse effects; there was no significant difference in amputation rate or mortality [44].

- In an open-label study of protein C replacement in 36 patients (mean age 12 years) with purpura fulminans, survival was improved and there were fewer amputations than predicted from historical controls [45]. However, because of the limited data supporting the use of protein C concentrate, it has not been used commonly in the therapy of meningococcal infections.

Supportive care — Since the occurrence of shock is frequent in patients with meningococcal infection, therapy should be provided in a tertiary care medical facility whenever possible. If patients with meningococcal sepsis arrive at hospitals without such capabilities, they should be treated with appropriate antimicrobial therapy and promptly transferred to a facility with a fully staffed intensive care unit. Vasopressor and aggressive fluid replacement are integral components in the management of septic shock. (See "Initial management of shock in children" and "Evaluation and management of suspected sepsis and septic shock in adults".)

Treatment of complications

Disseminated intravascular coagulation and purpura fulminans — Purpura fulminans is a thrombotic disorder characterized by extravasation of blood into the tissues producing ecchymoses and petechiae and is often accompanied by disseminated intravascular coagulation (DIC). While petechiae are common in meningococcal infection, increasing numbers of petechiae, confluent ecchymoses, persistently bleeding venipuncture sites, and bleeding gums despite adequate antimicrobial therapy and supportive care are suggestive of DIC. (See "Clinical manifestations of meningococcal infection".)

Early and aggressive interventions with antimicrobials and support of vascular perfusion are keys to prevention of DIC and purpura fulminans. Once purpura fulminans has developed, surgical debridement of lesions and skin grafting may be necessary in some cases. Deep necrosis of limbs or digits may necessitate amputation [46]. Other possible therapies of DIC and purpura fulminans are discussed separately. (See "Evaluation and management of disseminated intravascular coagulation (DIC) in adults".)

Other life-threatening complications — Other major life-threatening complications necessitating therapy include acute respiratory distress syndrome (ARDS), neurologic sequelae ranging from coma to diabetes insipidus, nosocomial pneumonia due to superinfection or aspiration during the obtunded

state, and pericarditis. (See "Acute respiratory distress syndrome: Supportive care and oxygenation in adults".)

Pericarditis can be particularly insidious and appears as a manifestation during convalescence. Pericardiocentesis is indicated in some cases for improved hemodynamic function. (See "Clinical manifestations of meningococcal infection", section on 'Pericarditis' and "Purulent pericarditis".)

PROGNOSIS

Before antibiotics and immune serum were available, the mortality of meningococcal infection was 70 to 90 percent [47]. The prognosis of meningococcal disease was dramatically improved by the introduction of sulfonamides in the late 1930s, followed by penicillin a decade later. Current reported mortality rates in the United States, as reported by the Centers for Disease Control and Prevention, are 10 to 15 percent [48]. This mortality rate is similar to that in the late 1960s despite major advancements in supportive care [49-51].

Several studies have attempted to establish prognostic criteria for the outcome of meningococcal sepsis [9,52]. In a Spanish study, the major significant independent predictors of death were a hemorrhagic diathesis, focal neurologic signs, and age ≥60 years (odds ratio [OR] 101, 25, and 10, respectively) [9]. Early antibiotic therapy was associated with good outcomes. (See 'Importance of early administration' above.)

An increased case-fatality rate is associated with outbreaks compared with sporadic meningococcal disease. The magnitude of this difference was illustrated in a retrospective analysis of cases in the United States from 1994 to 2002 [53]. Active surveillance identified 668 cases, of which 229 patients (69 clusters) met the criteria of either a community-based or organizational outbreak. After controlling for age, serogroup, and clinical presentation, outbreak-associated cases were associated with a significantly higher case-fatality rate than were sporadic cases (21 versus 11 percent; OR 3.3; 95% CI 2.0-5.5).

Gender may influence prognosis. In one study from New York including 151 cases of invasive meningococcal disease between 2008 and 2016, a higher case-fatality rate was observed among women (adjusted relative risk 2.1, 95% CI 1.2-3.8); among patients with meningitis, the relative risk was 13.7 (95% CI 3.2-58.1) [54]. The basis for these differences is not understood.

PREVENTION

The methods for the prevention of meningococcal infection include antimicrobial chemoprophylaxis following identification of an index case, use of droplet precautions, vaccination prior to exposure, and avoidance of exposure [2]. (See "Epidemiology of Neisseria meningitidis infection", section on 'Risk factors for acquisition of infection'.)

Droplet precautions — Droplet precautions should be continued for 24 hours after institution of effective antibiotics in patients with suspected or confirmed *N. meningitidis* infection [2]. After 24

hours, viable organisms can no longer be isolated from treated patients. (See "Infection prevention: Precautions for preventing transmission of infection", section on 'Droplet precautions'.)

Antimicrobial chemoprophylaxis

Following exposure — Antimicrobial chemoprophylaxis was first used successfully to abort the spread of meningococcal infection in the 1930s [55]. The reported attack rate for close contacts of patients with sporadic meningococcal disease is approximately 4 in 1000 persons exposed (0.4 percent), which is 500 to 800 times higher than that of the general population [48,56].

Indications — Chemoprophylaxis is indicated in close contacts of patients with meningococcal infection and should be given as early as possible following the exposure [48,57]. Although "close contact" has not been clearly defined, it generally refers to individuals who have had prolonged (>8 hours) contact while in close proximity (<3 feet) to the patient or who have been directly exposed to the patient's oral secretions during the seven days before the onset of the patient's symptoms and until 24 hours after initiation of appropriate antibiotic therapy [2].

Close contacts may include individuals exposed in the following ways [2,48]:

- Household members, roommates, intimate contacts, contacts at a childcare center, young adults exposed in dormitories, military recruits exposed in training centers
- Travelers who had direct contact with respiratory secretions from an index patient or who were seated directly next to an index patient on a prolonged flight (ie, one lasting ≥8 hours)
- Individuals who have been exposed to oral secretions (eg, intimate kissing, mouth-to-mouth resuscitation, endotracheal intubation, or endotracheal tube management)

Prophylaxis is **not** indicated if exposure to the index case is brief. This includes the majority of health care workers unless there is direct exposure to respiratory secretions (as with suctioning or intubation). The attack rate in health care workers at risk is increased compared with that of the general population, but the absolute increase in risk is very small, and antimicrobial prophylaxis is therefore not recommended for health care workers who have not had direct exposure to respiratory secretions [48,58].

Oropharyngeal or nasopharyngeal cultures are not helpful in determining the need for chemoprophylaxis and might unnecessarily delay institution of this preventive measure [48].

Evidence supporting chemoprophylaxis is limited, but we favor it because of the potential severity of meningococcal infection in individuals with high-risk exposure. Evidence informing chemoprophylaxis is discussed elsewhere. (See 'Regimens' below.)

Timing of prophylaxis — Antimicrobial chemoprophylaxis should be administered as early as possible (ideally <24 hours after identification of the index patient). Chemoprophylaxis administered >14 days after exposure to the index case is probably of limited or no value and is therefore **not** recommended by the United States Centers for Disease Control and Prevention (CDC) [48].

The rate of secondary disease in contacts is highest immediately after the onset of disease in the index patient. Secondary cases usually occur within 10 days of the primary case, but longer intervals have been described in rare case reports [59].

In the setting of a suspected meningococcal disease outbreak in which confirmed cases have occurred, it is not necessary to wait for confirmation of *N. meningitidis* in subsequent cases to initiate chemoprophylaxis of close contacts when meningococcal disease is strongly suspected (eg, identification of gram-negative diplococci, detection of *N. meningitidis* antigen from cerebrospinal fluid by latex or from formalin-fixed tissue by immunohistochemistry, or when there are clinical signs such as purpura) [57].

Regimens — To help inform regimen selection for chemoprophylaxis, clinicians should consult with local public health authorities. In the United States, information can also be found on the CDC website.

- **Preferred regimens** – Preferred regimens for antimicrobial prophylaxis include rifampin, ciprofloxacin, and ceftriaxone (table 1) [48,60]. The choice of agent depends in part upon antimicrobial susceptibility within a community. As an example, ciprofloxacin should not be used for chemoprophylaxis of close contacts of individuals with meningococcal disease when ciprofloxacin-resistant *N. meningitidis* has been identified in the local community [48].

  Although quinolone resistance is rare, it has been detected worldwide. Ciprofloxacin-resistant *N. meningitidis* isolates were detected in three patients in North Dakota and Minnesota in 2007 [61,62]. In 2008, a case of pneumonia caused by ciprofloxacin-resistant *N. meningitidis* was detected in California as part of the United States Active Bacterial Core surveillance system [62]. From 2019 to 2020, 11 ciprofloxacin-resistant, beta-lactamase-producing isolates of *N. meningitidis* were detected in eight states [63]. Isolated ciprofloxacin-resistant isolates have also been reported from a variety of other countries around the world [61,64,65]. In Spain, 10 of 5300 isolates of *N. meningitidis* that were collected between 1999 and 2006 had reduced susceptibility to ciprofloxacin [64].

- **Alternative regimens** – Azithromycin is an alternative agent for prophylaxis if one of the preferred agents cannot be used (eg, if rifampin or ceftriaxone are contraindicated in the setting of a ciprofloxacin-resistant *N. meningitidis* exposure). In adults, the dose of azithromycin is 500 mg orally as a single dose; in children, the dose is 10 mg/kg orally as a single dose (max dose 500 mg). Although azithromycin has significant activity against meningococcus, it is not recommended as a first-line agent for chemoprophylaxis, since it has not been well studied for this indication.

  Evidence informing the clinical effectiveness of antimicrobial prophylaxis in preventing disease is limited. The potential clinical benefit of prophylaxis is inferred from studies that demonstrate eradication of nasopharyngeal carriage with antimicrobials.

Specifically, a 2013 meta-analysis of 24 randomized or quasi-randomized clinical trials evaluated the effectiveness of antibiotic treatments for eradication of nasopharyngeal carriage at one to two weeks

after treatment [66]. The following findings were noted:

- Rifampin (relative risk [RR] 0.20, 95% CI 0.14-0.29) and ciprofloxacin (RR 0.03, 95% CI 0.00-0.42) were significantly effective at eradicating *N. meningitidis* carriage compared with placebo at one to two weeks. Rifampin continued to be effective for up to four weeks after therapy, but resistant isolates were seen.

- Based on the results of a single study, ceftriaxone was more effective than rifampin (RR 5.93, 95% CI 1.22-28.68) at eradicating *N. meningitidis* carriage after one to two weeks of follow-up. No trials have evaluated ceftriaxone against placebo, and the drug must be administered parenterally.

- Clinical efficacy of eradication could not be assessed, since there were no cases of disease following antibiotics or placebo.

Follow-up of close contacts — Surveillance of close contacts receiving prophylaxis for at least 10 days following exposure as well as counseling about the signs and symptoms of meningococcal infection ensure prompt treatment of any secondary cases that might arise.

Patients receiving C5 inhibitors — C5 inhibitors such as eculizumab and ravulizumab are monoclonal antibody terminal complement inhibitors used for treatment of complement-mediated hemolytic uremic syndrome and paroxysmal nocturnal hemoglobinuria. Administration of C5 inhibitors has been associated with a 1000- to 2000-fold increased risk of meningococcal infection [67], and life-threatening and fatal meningococcal infections have been reported [68].

We suggest patients treated with C5 inhibitors receive antimicrobial prophylaxis for the duration of C5 inhibitor administration, in addition to meningococcal vaccination. Although there is a lack of evidence supporting this approach, invasive meningococcal disease has occurred in patients receiving C5 inhibitors despite receipt of meningococcal vaccine, including infections caused by non-typeable strains not included in the vaccines [67]. A detailed discussion of meningococcal vaccination is presented elsewhere. (See "Meningococcal vaccination in children and adults", section on 'Immunization of persons at increased risk'.)

Antimicrobial prophylaxis for prevention of meningococcal infection consists of penicillin V (for adults 500 mg orally twice daily; for children ≥3 years of age 250 mg orally twice daily; for children <3 years of age 125 mg orally twice daily). In the presence of penicillin allergy, a macrolide such as azithromycin (in adults 500 mg orally once daily; in children 5 mg/kg orally once daily [maximum dose 500 mg]) can be substituted, based on the relatively narrow spectrum and efficacy against meningococcus.

Because neither vaccination nor antimicrobial prophylaxis can be expected to prevent all cases of meningococcal disease, patients on C5 inhibitors should be educated about the risk of infection and encouraged to seek medical care immediately if any symptoms of meningococcal disease occur.

Vaccination — Meningococcal vaccines and the indications for immunization are discussed separately. (See "Meningococcal vaccination in children and adults" and "Patient education: Vaccines for adults (Beyond the Basics)" and "Patient education: Vaccines for infants and children age 0 to 6 years (Beyond the Basics)" and "Patient education: Vaccines for children age 7 to 18 years (Beyond the Basics)".)

MANAGEMENT OF N. MENINGITIDIS FROM OTHER SITES

Urethritis — Meningococcal urethritis can be indistinguishable from acute gonococcal urethritis (a more common cause of genitourinary infection) based on clinical features and Gram stain [69,70]. Both pathogens are susceptible to similar antibacterial agents (eg, ceftriaxone), so the treatment of presumed gonorrhea infections will typically be effective for patients with meningococcal infections of the genitourinary tract (including urethritis, epididymitis, and pelvic inflammatory disease). (See "Treatment of uncomplicated Neisseria gonorrhoeae infections" and "Approach to infectious causes of dysuria in the adult man", section on 'Treatment' and "Pelvic inflammatory disease: Treatment in adults and adolescents".)

Other rare sites of infection — Antimicrobial regimens used for treatment of other rare sites of infection (eg, arthritis, pericarditis, pneumonia) include ceftriaxone (2 g every 24 hours for adults, or 50 mg/kg [maximum 2 g] every 12 to 24 hours for children) or high-dose penicillin G (for adults 4 million units IV every four hours; for children 300,000 units/kg per day in a divided dose every six hours [usual maximum dose 12 million units/day]). There are limited data to guide the duration of treatment; regimens are typically administered for five to seven days, but may be extended up to two weeks in patients with pericarditis.

In addition to antimicrobial therapy, some infections (such as arthritis and pericarditis) warrant drainage of fluid from the site of infection.

Incidental nasopharyngeal isolation — Occasionally, *N. meningitidis* is detected on throat or nasopharyngeal culture obtained for some other reason. The most common indication is pharyngitis, which is not caused by *N. meningitidis*. Although nasopharyngeal carriage with *N. meningitidis* plays an important role in the transmission and the development of invasive disease, there is no role for treatment of patients with detection of *N. meningitidis* on throat or nasopharyngeal culture in the absence of invasive disease or an ongoing outbreak. (See "Microbiology and pathobiology of Neisseria meningitidis", section on 'Nasopharyngeal carriage'.)

There are three problems with attempting to eliminate nasopharyngeal carriage in the community:

- Spontaneous loss and acquisition of carriage is common. This was illustrated in a study in military recruits in which 34 percent experienced one or more change in carrier status over time [71].
- Recurrent colonization may occur after prophylaxis. In a community-wide prophylaxis program in a semi-closed kibbutz population in Israel, the colonization rate of serogroup B meningococcus dropped from 4.6 percent at baseline to 0 percent at three weeks; it then rose to 0.5 percent at six months and 3.9 percent (similar to the baseline level) at one year [72].
- Antimicrobial prophylaxis has no proven clinical efficacy outside an outbreak. The meta-analysis cited above included trials in healthy carriers [66]. Clinical efficacy of eradication could not be assessed since there were no cases of disease following antibiotics or placebo.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Bacterial meningitis in adults" and "Society guideline links: Meningococcal infection" and "Society guideline links: Bacterial meningitis in infants and children".)

SUMMARY AND RECOMMENDATIONS

Treatment of meningitis and sepsis

- Prompt administration of appropriate antibiotics early in the disease is key to a successful outcome of life-threatening meningococcal infection. Empiric coverage for meningococcal infection is warranted in patients with severe sepsis syndrome, fever with petechiae and/or ecchymoses, and suspected bacterial meningitis. (See 'Importance of early administration' above.)

  Other aspects of empiric treatment for suspected bacterial meningitis are discussed in detail elsewhere. (See "Initial therapy and prognosis of bacterial meningitis in adults".)

- For initial therapy of patients with suspected meningococcal meningitis or sepsis, we suggest ceftriaxone rather than an alternative regimen (**Grade 2C**). The dose of ceftriaxone is 2 g intravenous [IV] every 12 hours for adults, or 50 mg/kg [maximum 2 g] IV every 12 hours for children. Third-generation cephalosporins, such as ceftriaxone, have very low rates of resistance, are easy to dose, and are also effective for eradication of nasopharyngeal carriage of meningococcus. (See 'Preferred regimens' above.)

- If susceptibility testing indicates that the isolate is penicillin susceptible (minimum inhibitory concentration [MIC] <0.1 mcg/mL), either ceftriaxone or high-dose penicillin G (for adults 4 million units IV every four hours; for children 300,000 units/kg per day in a divided dose every six hours [usual maximum dose 12 million units/day]) can be used. (See 'Preferred regimens' above.)

- For patients who are intolerant of beta-lactams, the approach to treatment depends upon the nature of the allergy. For those who cannot use beta-lactams, chloramphenicol (100 mg/kg per day IV in divided doses every six hours, up to a maximum dose of 4 g/day) is an effective substitute in areas where it is available. Meropenem and levofloxacin are also alternatives, although clinical experience and data on their use are limited. (See 'Patients intolerant of beta-lactams' above.)

- If an antibiotic other than ceftriaxone is used for treatment, we suggest adding a second agent for eradication of presumed nasopharyngeal carriage to prevent subsequent transmission to close contacts (**Grade 2C**). Options for a second agent are the same as those used for chemoprophylaxis (table 1). (See 'Subsequent eradication therapy for select patients' above.)

- For patients with severe meningococcal sepsis, including those with purpura fulminans, we suggest protein C concentrate (**Grade 2C**). Patients with severe meningococcal sepsis have impaired activation of protein C, which contributes to coagulopathic complications. (See 'Protein C concentrate' above.)

- Other components of septic shock management are supportive and are discussed in detail elsewhere. (See "Evaluation and management of suspected sepsis and septic shock in adults".)

Prevention

- Inpatient infection control includes droplet precautions for 24 hours after institution of effective antibiotics in patients with suspected or confirmed *Neisseria meningitidis* infection. (See 'Droplet precautions' above.)

- For close contacts of patients with meningococcal meningitis or sepsis, we suggest antimicrobial chemoprophylaxis (**Grade 2C**). Antimicrobial chemoprophylaxis should be administered as early as possible (ideally <24 hours after identification of the index patient and not >14 days after exposure). Regimens for antimicrobial prophylaxis include rifampin, ciprofloxacin, and ceftriaxone (table 1). (See 'Antimicrobial chemoprophylaxis' above.)

- In patients receiving C5 inhibitors, we suggest administration of daily antimicrobial prophylaxis with penicillin for the duration of C5 inhibitor administration (**Grade 2C**). Administration of C5 inhibitors has been associated with increased incidence of meningococcal disease. Use of C5 inhibitors is also an indication for meningococcal vaccination. (See 'Patients receiving C5 inhibitors' above.)

- Meningococcal vaccines are discussed separately. (See "Meningococcal vaccination in children and adults".)

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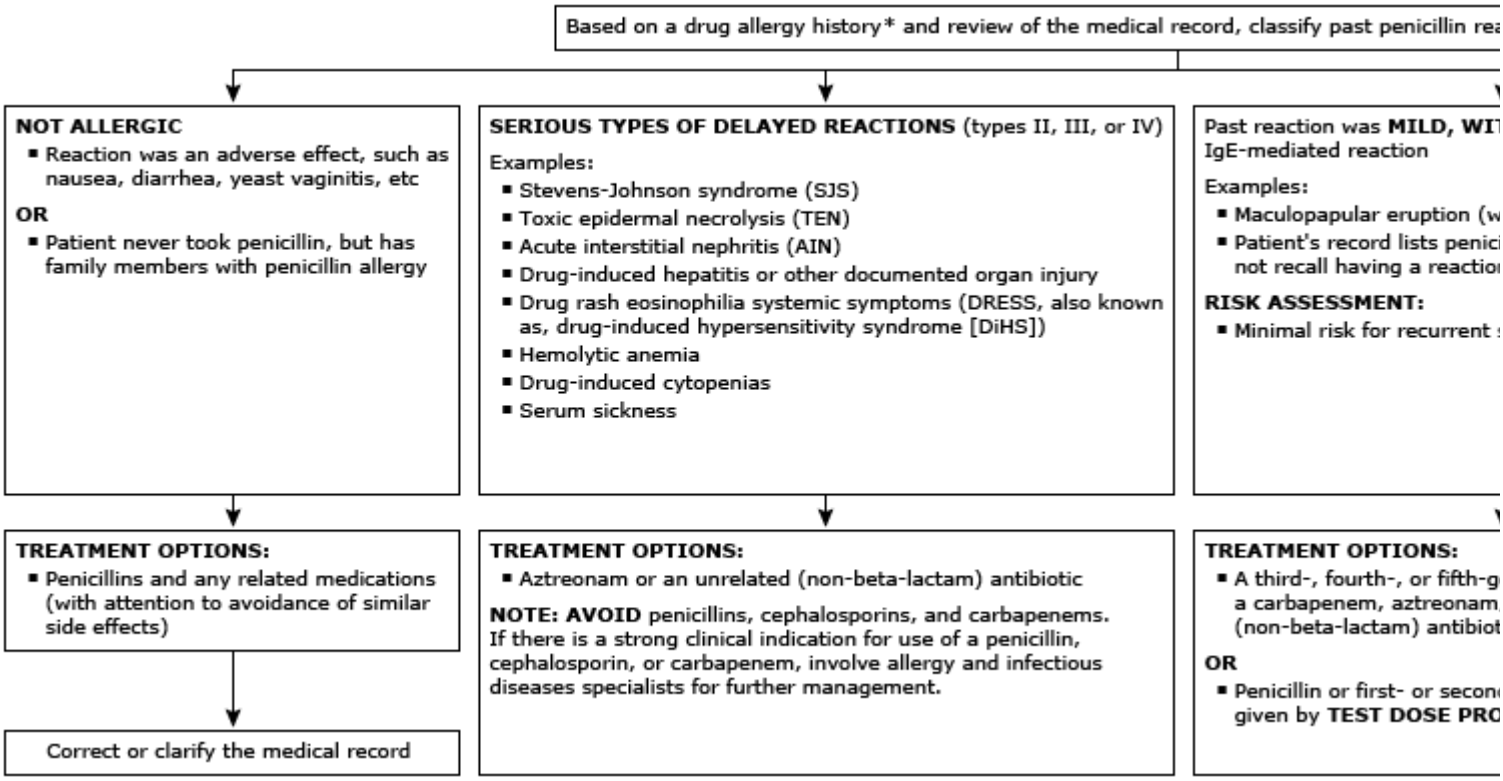
GRAPHICS

Approach to the patient with a past penicillin reaction who requires antibiotics



This algorithm is intended for use in conjunction with the UpToDate content on choice of antibiotics in penicillin-alle
but also applies to outpatients if test dose procedures can be performed in an appropriately monitored setting with
including anaphylaxis.

IgE: immunoglobulin E.

* Ask the following:

1. What exactly were the symptoms?
    - Raised, red, itchy spots with each lesion lasting less than 24 hours (hives/urticaria)?
    - Swelling of the mouth, eyes, lips, or tongue (angioedema)?
    - Blisters or ulcers involving the lips, mouth, eyes, urethra, vagina, or peeling skin (seen in SJS, TEN, othe
    - Respiratory or hemodynamic changes (anaphylaxis)?
    - Joint pains (seen in serum sickness)?
    - Did the reaction involve organs like the kidneys, lungs, or liver (seen in DRESS, other severe type IV rea
2. What was the timing of the reaction after taking penicillin: Minutes, hours, or days later? Was it after the first
3. How long ago did the reaction happen? (After 10 years of avoidance, only 20% of patients with IgE-mediated
4. How was the reaction treated? Was there a need for urgent care or was adrenaline/epinephrine administered
5. Has the patient tolerated similar medications, such as ampicillin, amoxicillin, or cephalexin since the penicillin

¶ Isolated mild hives, without other symptoms of an IgE-mediated reaction, can often occur in the setting of an infe
or >10 years ago, may also be considered to be at minimal risk for a recurrent serious reaction.

Δ This algorithm is intended for use in conjunction with additional UpToDate content. For a description of how to sa
on choice of antibiotics in penicillin-allergic hospitalized patients.

◇ Consult allergist to perform skin testing. If skin testing is not possible, patient may still be able to receive penicilli
desensitization (also known as tolerance induction) procedure. Refer to the UpToDate topic on rapid drug desensitiz

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Graphic 112936 Version 5.0

Chemoprophylaxis regimens for protection against meningococcal disease[1-3]

Drug	Age group	Dose	Duration and route of administration
Preferred regimens			
Rifampin*	Infants age <1 month	5 mg/kg/**dose** every 12 hours	2 days (4 doses) of oral therapy
	Infants and children age ≥1 month	10 mg/kg/**dose** (maximum: 600 mg) every 12 hours	2 days (4 doses) of oral therapy
	Adults	600 mg every 12 hours	2 days (4 doses) of oral therapy
Ciprofloxacin¶	Infants and children age ≥1 month	20 mg/kg (maximum 500 mg)	Single oral dose
	Adults	500 mg	Single oral dose
Ceftriaxone	Children age <15 years	125 mg	Single IM dose
	Adults and adolescents age ≥15 years	250 mg	Single IM dose
Alternative regimen (eg, if rifampin or ceftriaxone cannot be used in the setting of ciprofloxacin-resistant *Neisseria meningitidis* exposure)			
Azithromycin$^{\Delta}$	Infants and children	10 mg/kg (maximum 500 mg)	Single oral dose
	Adults	500 mg	Single oral dose

IM: intramuscular.

* Rifampin is not recommended for pregnant women because the drug is teratogenic in laboratory animals. Because the reliability of oral contraceptives might be affected by rifampin therapy, consideration should be given to using alternative contraceptive measures while rifampin is being administered. For additional information on drug interactions, refer to the Lexicomp drug interaction program within UpToDate.

¶ Ciprofloxacin should not be used if fluoroquinolone-resistant strains of *N. meningitidis* have been identified in the community. In addition, ciprofloxacin is not recommended for pregnant women. Although systemic fluoroquinolones are not routinely used as a first-line agent in children less than 18 years of age, it is reasonable to use a single dose of ciprofloxacin for chemoprophylaxis for meningococcal disease.

Δ Although azithromycin has activity against meningococcus, it has not been well studied for this indication.

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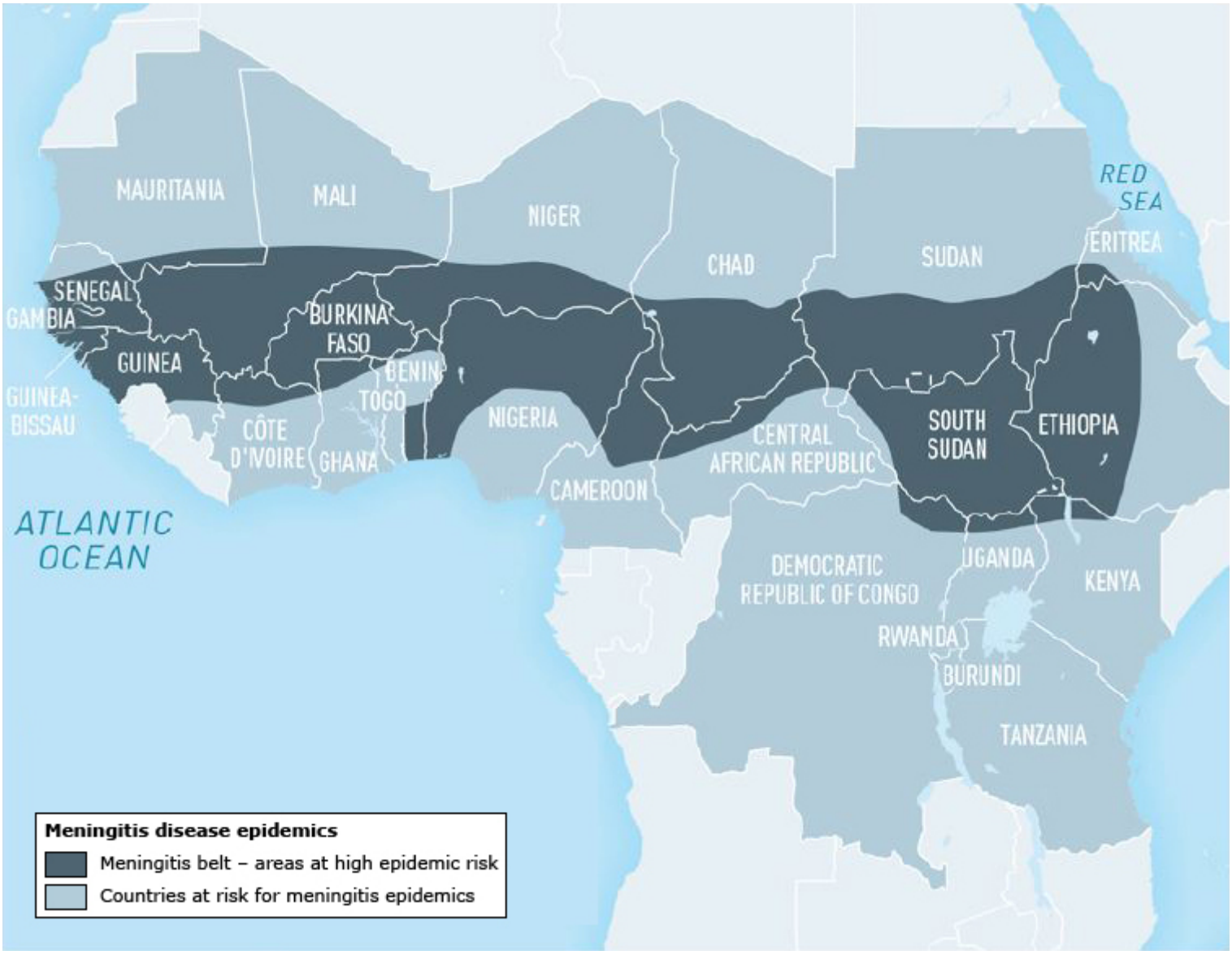
Graphic 51944 Version 8.0

Areas with frequent epidemics of meningococcal meningitis



Disease data source: World Health Organization. International Travel and Health. Geneva, Switzerland: 2012.

Reproduced from: Mbaeyi SA, McNamara LA. Travel-Related Infectious Diseases: Meningococcal Disease. In: CDC Yellow Book 2020, Brunette GW, Nemhauser JB (Eds), Oxford University Press, New York 2019. Available at: https://wwwnc.cdc.gov/travel/yellowbook/2020/table-of-contents (Accessed on August 2, 2019).

Graphic 63287 Version 7.0

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Conflict of interest policy

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