VIRGINIA
EPIDEMIOLOGY BULLETIN

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July 1997

Volume 97, Number 7

Control and Prevention of Meningococcal Disease: Recommendations of the Advisory Committee on Immunization Practices (ACIP)

Summary

The following article includes excerpts from the MMWR article with the above title (1997;46[No. RR-5]:1-10). These recommendations update information regarding the polysaccharide vaccine licensed in the United States for use against disease caused by Neisseria meningitidis serogroups A, C, Y and W-135, as well as antimicrobial agents for chemoprophylaxis against meningococcal disease (superseding MMWR 1985;34:255-9). This report provides additional information regarding meningococcal vaccines and the addition of ciprofloxacin and ceftriaxone as acceptable alternatives to rifampin for chemoprophylaxis in selected populations.

If you would like a copy of the entire MMWR article, you may call the Office of Epidemiology at 804/786-6261 or visit the Centers for Disease Control and Prevention web site http://www.cdc.gov.

Introduction

Neisseria meningitidis causes both endemic and epidemic disease, principally meningitis and meningococcemia. As a result of the control of *Haemophilus influenzae* type b infections, *N. meningitidis* has become the leading cause of bacterial meningitis in children and young adults in the United States, with an estimated 2,600 cases each year. The case-fatality rate is 13% for meningitic disease (defined as the isolation of *N. meningitidis* from cerebrospinal fluid) and 11.5% for persons who have *N. meningitidis* isolated from blood, despite therapy with antimicrobial agents (e.g., penicillin) to which U.S. strains remain clinically sensitive.

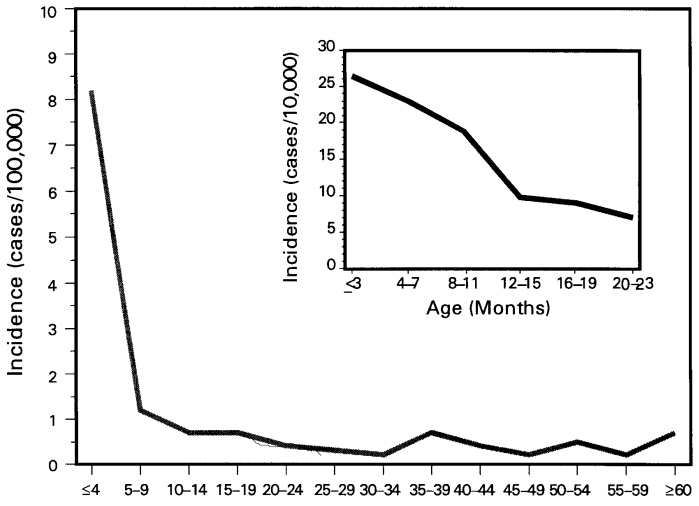

Figure 1. Incidence of meningococcal disease, by age group, selected U.S. areas, 1989-1991

The incidence of meningococcal disease peaks in late winter to early spring. Attack rates are highest among children 3-12 months of age and then steadily decline among older age groups (Figure 1). Based on multistate surveillance conducted during 1989-1991, serogroup B organisms accounted for 46% of all cases and serogroup C for 45%; serogroups W-135 and Y and strains that could not be serotyped accounted for most of the remaining cases. Recent data indicate that the proportion of cases caused by serogroup Y strains is increasing. Serogroup A, which rarely causes disease in the United States, is the most common cause of epidemics in Africa and Asia. In the United States, localized community outbreaks of serogroup C disease and a statewide serogroup B epidemic have recently been reported.

Persons who have certain medical conditions are at increased risk for developing meningococcal infection. Meningococcal disease is particularly common among persons who have component deficiencies in the terminal common complement pathway (C3, C5-C9); many of these persons experience multiple episodes of infection. Asplenic persons also may be at increased risk for acquiring meningococcal disease with particularly severe infections. Persons who have other diseases associated with immunosuppression (e.g., human immunodeficiency virus [HIV] and *Streptococcus pneumoniae*) may be at higher risk for acquiring meningococcal disease and for disease caused by some other encapsulated bacteria. Evidence suggests that HIV-infected persons are not at substantially increased risk for epidemic serogroup A men-

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ingococcal disease; however, such patients may be at increased risk for sporadic meningococcal disease or disease caused by other meningococcal serogroups. Previously, military recruits had high rates of meningococcal disease, particularly serogroup C disease; however, since the initiation of routine vaccination of recruits with the bivalent A/C meningococcal vaccine in 1971, the high rates of meningococcal disease caused by those serogroups have decreased substantially and cases occur infrequently. Military recruits now routinely receive the quadrivalent A,C,Y, W-135 meningococcal vaccine.

Meningococcal Polysaccharide Vaccine

The quadrivalent A,C,Y,W-135 vaccine (Menomune® -A,C,Y,W-135, manufactured by Connaught Laboratories, Inc.) is the formulation currently available in the United States. The recommended dose of vaccine is a single 0.5 mL subcutaneous injection. Each vaccine dose consists of 50 µg each of the purified bacterial capsular polysaccharides. Menomune® is available in single-dose, 10-dose, and 50-dose vials.

Vaccine Efficacy

The immunogenicity and clinical efficacy of the serogroups A and C meningococcal vaccines have been well established. The serogroup A polysaccharide induces antibody in some children as young as 3 months of age, although a response comparable with that among adults is not achieved until 4 or 5 years of age; the serogroup C component is poorly immunogenic in recipients who are <18-24 months of age. The serogroups A and C vaccines have demonstrated estimated clinical efficacies of 85%-100% in older children and adults and are useful in controlling epidemics. Serogroups Y and W-135 polysaccharides are safe and immunogenic in adults and in children >2 years of age; although clinical protection has not been documented, vaccination with these polysaccharides induces bactericidal antibody. The antibody responses to each of the four polysaccharides in the quadrivalent vaccine are serogroup-specific and independent.

Duration of Efficacy

Measurable levels of antibodies against the group A and C polysaccharides decrease markedly during the first 3 years following a single dose of vaccine. This decrease in antibody occurs more rapidly in infants and young children than in adults. Similarly, although vaccine-induced clinical protection probably persists in schoolchildren and adults for at least 3 years, the efficacy of the group A vaccine in young children may decrease markedly with the passage of time: in a 3-year study, efficacy declined from >90% to <10% among children who were <4 years of age at the time of vaccination, whereas among children who were ≥4 years of age when vaccinated, efficacy was 67% three years later.

Recommendations for Use of Meningococcal Vaccine

Routine vaccination of civilians with the quadrivalent meningococcal polysaccharide vaccine is not recommended because of its relative ineffectiveness in children < 2 years of age (among whom risk for endemic disease is highest) and its relatively short duration of protection. However, the polysaccharide meningococcal vaccine is useful for controlling serogroup C meningococcal outbreaks.

Indications for Use

In general, use of polysaccharide meningococcal vaccine should be restricted to persons ≥2 years of age; however, children as young as 3 months of age may be vaccinated to elicit short-term protection against serogroup A meningococcal disease (two doses administered 3 months apart should be considered for children 3-18 months of age).

In general, use of polysaccharide meningococcal vaccine should be restricted to persons ≥2 years of age...

Routine vaccination with the quadrivalent vaccine is recommended for certain high-risk groups, including persons who have terminal complement component deficiencies and those who have anatomic or functional asplenia. Persons whose spleens have been removed because of trauma or nonlymphoid tumors and persons who have inherited complement deficiencies have acceptable antibody responses to meningococcal vaccine; however, the clinical efficacy of vaccination has not been documented for these persons, and they may not be protected by vaccination. Research, industrial, and clinical laboratory personnel who routinely are exposed to *N. meningitidis* in solutions that may be aerosolized should be considered for vaccination.

Vaccination with the quadrivalent vaccine may benefit travelers to and U.S. citizens residing in countries in which *N. meningitidis* is hyperendemic or epidemic, particularly if contact with the local populace will be prolonged. Single-dose vials of the quadrivalent vaccine are now available and may be more convenient than multidose vials for use in international health clinics for travelers. Epidemics of meningococcal disease are recurrent in that part of sub-Saharan Africa known as the "meningitis belt," which extends from Senegal in the west to Ethiopia in the east. Epidemics in the meningitis belt usually occur during the dry season (i.e., from December to June); thus, vaccination is recommended for travelers visiting this region during that time. Epidemics occasionally are identified in other parts of the world and recently have occurred in Saudi Arabia (during a Haj pilgrimage), Kenya, Tanzania, Burundi, and Mongolia. Information concerning geographic areas for which vaccination is recommended can be obtained from international health clinics for travelers, state health departments, and CDC (telephone: [404]332-4559).

Primary Vaccination

For both adults and children, vaccine is administered subcutaneously as a single 0.5 mL dose. The vaccine can be administered at the same time as other vaccines but at a different anatomic site (i.e., deltoid muscle or buttocks). Protective levels of antibody are usually achieved within 7-10 days after vaccination.

Revaccination

Revaccination may be indicated for persons at high risk for infection (e.g., persons remaining in areas in which disease is epidemic), particularly for children who were first vaccinated when they were <4 years of age; such children should be considered for revaccination after 2-3 years if they remain at high risk. Although the need for revaccination of older children and adults has not been determined, antibody levels decline rapidly over 2-3 years, and if indications still exist for immunization, revaccination may be considered within 3-5 years.

Precautions and Contraindications

Reactions to Vaccination

Adverse reactions to meningococcal vaccine are mild and consist principally of pain and redness at the injection site, for 1-2 days. Estimates of incidence of mild-to-moderate local reactions have varied, ranging from in-

frequent to >40% among vaccine recipients. Pain at the site of injection is the most commonly reported adverse reaction, and a transient fever might develop in ≤2% of young children.

Vaccination During Pregnancy

Studies of vaccination during pregnancy have not documented adverse effects among either pregnant women or newborns. In addition, these studies have documented high antibody levels in maternal and umbilical cord blood following vaccination during pregnancy. Antibody levels in the infants decreased during the first few months after birth; subsequent response to meningococcal vaccination was not affected. These observations have been confirmed in more recent studies of other polysaccharide vaccines administered during pregnancy. Based on data from studies involving use of meningococcal vaccines and other polysaccharide vaccines administered during pregnancy, altering meningococcal vaccination recommendations during pregnancy is unnecessary.

Prospects for New Meningococcal Vaccines

To enhance the immunogenicity and protective efficacy of A and C polysaccharides in infants and young children, methods similar to those used for *H. influenzae* type b conjugate vaccines have been applied to produce conjugate serogroups A and C vaccines. Capsular polysaccharides are being covalently linked to carrier proteins to convert the T-cell-independent polysaccharide to a T-cell-dependent antigen. The efficacy of these vaccines has not been evaluated.

Because the serogroup B capsular polysaccharide is poorly immunogenic in humans, vaccine development for serogroup B meningococci has focused on the outer membrane proteins as potential immunogens. The immunogenicity and protective efficacy of several outer membrane protein vaccines against several serogroup B meningococci have been evaluated recently. Evaluation of those vaccines documented estimated efficacies ranging from 57% to 83% in older children and adults. However, a subsequent study of one of these vaccines did not document efficacy in children <4 years of age, the group often at highest risk for disease. None of the currently available serogroup B meningococcal vaccines are licensed for use in the United States.

Antimicrobial Chemoprophylaxis

Antimicrobial chemoprophylaxis of close contacts of sporadic cases of meningococcal disease is the primary means for prevention of meningococcal disease in the United States (Table). Close contacts include a) household members, b) day care center contacts, and c) anyone directly exposed to the patient's oral secretions (e.g., through kissing, mouth-to-mouth resuscitation, endotracheal intubation, or endotracheal tube management). The attack rate for household contacts exposed to patients who have sporadic meningococcal disease has been estimated to be four cases per 1,000 persons exposed, which is 500-800 times greater than for the total population. Because the rate of secondary disease for close contacts is highest during the first few days after onset of disease in the primary patient, antimicrobial chemoprophylaxis should be administered as soon as possible (ideally within 24 hours after the case is identified). Conversely, chemoprophylaxis administered >14 days after onset of illness in the index case-patient is probably of limited or no value. Oropharyngeal or nasopharyngeal cultures are not helpful in determining the need for chemoprophylaxis and may unnecessarily delay institution of this preventive measure.

Antimicrobial chemoprophylaxis of close contacts of sporadic cases of meningococcal disease is the primary means for prevention of meningococcal disease in the United States.

Rifampin is administered twice daily for 2 days (600 mg every 12 hours for adults, 10 mg/kg of body weight every 12 hours for children ≥1 month of age, and 5 mg/kg every 12 hours for infants <1 month of age). Rifampin is effective in eradicating nasopharyngeal carriage of *N. meningitidis*. ***Rifampin is not recommended for pregnant women, because the drug is teratogenic in laboratory animals.*** Rifampin changes the color of urine to reddish-orange and is excreted in tears and other body fluids; it may cause permanent discoloration of soft contact lenses. Because the reliability of oral contraceptives may be affected by rifampin therapy, consideration should be given to using alternate contraceptive measures while rifampin is being administered.

In addition to rifampin, other antimicrobial agents are effective in reducing nasopharyngeal carriage of *N. meningitidis*. Ciprofloxacin in various dosage regimens is >90% effective in eradicating nasopharyngeal carriage. A single 500 mg oral dose of ciprofloxacin is a reasonable alternative to the multidose rifampin regimen. Ciprofloxacin levels in nasal secretions far exceed the MIC_{90} for *N. meningitidis* following oral dosing. Ciprofloxacin is not generally recommended for persons <18 years of age or for pregnant and lactating women because the drug causes cartilage damage in immature laboratory animals. However, a recent international consensus report has concluded that ciprofloxacin can be used for chemoprophylaxis of children when no acceptable alternative therapy is available.

When ceftriaxone was administered in a single parenteral dose (an intramuscular dose

Table. Schedule for administering chemoprophylaxis against meningococcal disease

Drug	Age group	Dosage	Duration and route of administration*
Rifampin	Children <1 mo	5 mg/kg every 12 hrs	2 days
	Children ≥1 mo	10 mg/kg every 12 hrs	2 days
	Adults	600 mg every 12 hrs	2 days
Ciprofloxacin	Adults	500 mg	Single dose
Ceftriaxone	Children <15 yrs	125 mg	Single IM† dose
Ceftriaxone	Adults	250 mg	Single IM dose

*Oral administration unless indicated otherwise.
†Intramuscular.

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of 125 mg for children and 250 mg for adults), it was 97%-100% effective in eradicating pharyngeal carriage of *N. meningitidis*. Thus, ceftriaxone (diluted in 1% lidocaine to reduce local pain after injection) is also a reasonable alternative for chemoprophylaxis.

Systemic antimicrobial therapy of meningococcal disease with agents other than ceftriaxone or other third generation cephalosporins may not reliably eradicate nasopharyngeal carriage of *N. meningitidis.* If other agents have been used for treatment, the index patient should receive chemoprophylactic antibiotics for eradication of nasopharyngeal carriage before being discharged from the hospital.

Conclusions

N. meningitidis is the leading cause of bacterial meningitis in older children and young adults in the United States. The quadrivalent A,C,Y, and W-135 meningococcal vaccine available in the United States is recommended for control of serogroup C meningococcal disease outbreaks and for use among certain high-risk groups, including a) persons who have terminal complement deficiencies, b) persons who have anatomic or functional asplenia, and c) laboratory personnel who routinely are exposed to *N. meningitidis* in solutions that may be aerosolized. Vaccination also may benefit travelers to countries in which disease is hyperendemic or epidemic. Conjugate serogroup A and C meningococcal vaccines are being developed by using methods similar to those used for *H. influenzae* type b conjugate vaccines, and the efficacies of several experimental serogroup B meningococcal vaccines have been documented in older children and young adults.

Antimicrobial chemoprophylaxis of close contacts of patients who have sporadic cases of meningococcal disease is the primary means for prevention of meningococcal disease in the United States. Rifampin has been the drug of choice for chemoprophylaxis; however, data from recent studies document that single doses of ciprofloxacin or ceftriaxone are reasonable alternatives to the multidose rifampin regimen for chemoprophylaxis.

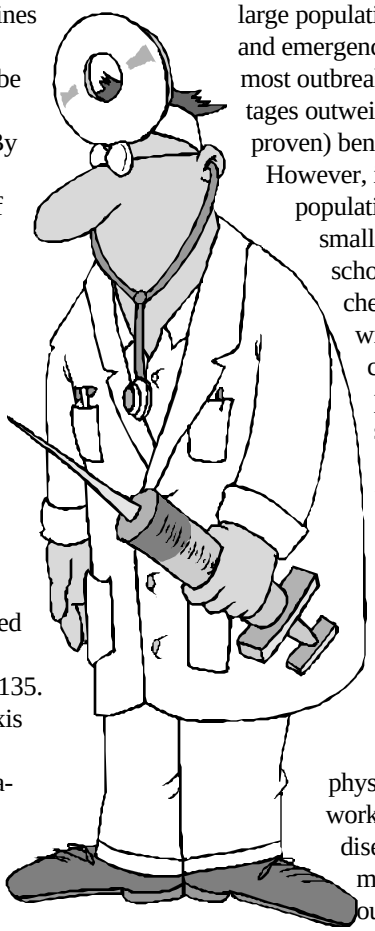
Control and Prevention of Serogroup C Meningococcal Disease: Evaluation and Management of Suspected Outbreaks:

Recommendations of the Advisory Committee on Immunization Practices (ACIP)

The following is a brief summary of a recent MMWR article with the above title (1997;46[No. RR-5]:13-21) that may be of particular interest to public health professionals. To obtain a copy of the complete report, you may call the Office of Epidemiology (804/786-6261) or visit the web site for the Centers for Disease Control and Prevention at http: //www.cdc.gov.

Outbreaks of serogroup C meningococcal disease (SCMD) have been occurring more frequently in the United States since the early 1990s, and the use of vaccine to control these outbreaks has increased. These outbreaks are characterized by increased rates of disease among persons who may have a common organizational affiliation or who live in the same community.

The decision to implement mass vaccination to prevent meningococcal disease depends on whether the occurrence of more than one case of the disease represents an outbreak or an unusual clustering of endemic meningococcal disease. Because the number of cases in outbreaks is usually small, this determination is not easily made without evaluation and analysis of the pattern of disease occurrence. Mass vaccination campaigns are expensive, require a massive public health effort, and can create unwarranted concern among the public. However, mass vaccination can prevent unnecessary morbidity and mortality. This report provides public health professionals (i.e., epidemiologists in state and local health departments) with guidelines for determining whether mass vaccination should be implemented to prevent meningococcal disease. By using surveillance for SCMD and calculation of attack rates, public health officials can identify SCMD outbreaks and determine whether use of meningococcal vaccine is warranted. This MMRW article describes ten steps for evaluation and management of suspected SCMD outbreaks. The principles described also apply to suspected outbreaks caused by meningococcal serogroups A, Y, and W-135.



Mass chemoprophylaxis (i.e., administration of antibiotics to large populations) is not effective in most settings in which community-based or organization-based outbreaks have occurred. Disadvantages of widespread administration of antimicrobial drugs for chemoprophylaxis include cost of the drug and administration, difficulty of ensuring simultaneous administration of chemoprophylactic antimicrobial drugs to large populations, side effects of the drugs, and emergence of resistant organisms. In most outbreak settings, these disadvantages outweigh the possible (and unproven) benefit in disease prevention.

However, in outbreaks involving small populations (e.g., an outbreak in a small organization, such as a single school), administration of chemoprophylaxis to all persons within this population may be considered. If mass chemoprophylaxis is undertaken, it should be administered to all members at the same time. In the United States, measures that have *not* been recommended for control of SCMD outbreaks include restricting travel to areas with a SCMD outbreak, closing schools or universities, or canceling sporting or social events.

Educating communities, physicians, and other health-care workers about meningococcal disease is an important part of managing suspected SCMD outbreaks. Educational efforts should be initiated as soon as a SCMD outbreak is suspected.

CHEMOPROPHYLAXIS OF CONTACTS OF PERSONS WITH MENINGOCOCCAL DISEASE

Editor's note:

When a case of meningococcal disease is identified, close contacts of the patient should receive appropriate chemoprophylaxis. Recently, the Office of Epidemiology was asked to clarify the reason for administering chemoprophylaxis. The specific question was: Is chemoprophylaxis given to eradicate carriage of the organism in an asymptomatic carrier who may have transmitted the organism to the case and who now poses a potential risk to other susceptible persons or, do we give chemoprophylaxis to prevent secondary cases from occurring as a result of exposure to the case?

The importance of the carrier state in meningococcal disease has been known for a long time. It has been hypothesized that meningococcal infection is usually introduced into a household by an asymptomatic adult. Carriage then spreads through the household, reaching infants usually after one or more other household members have been infected.[1] Disease is most likely to occur in infants and young children who lack immunity to the strain of organism circulating and who subsequently acquire carriage of an invasive strain.

An examination of 26 households, each with two cases of meningococcal disease, found that eight (31%) of the successive cases occurred on the same day.[1] The interval between first and second cases for the remaining households was 1-4 days (6 cases, 23%), 5-13 days (8 cases, 31%) and 14-30 days (4 cases, 15%). Given that the incubation period for meningococcal disease ranges from 2 to 10 days (typically 3 to 4 days),[2] this suggests that most of the successive cases were probably co-primary cases.

Other studies of households with more than one case of meningococcal disease have shown that the time between the primary and successive case is highly variable, from less than 24 hours to 39 weeks or more.[3] It is difficult to state definitively whether a successive case that occurs two or more days after the onset of the primary case is secondary to transmission by the case or is co-primary with exposure to the same nasopharyngeal carrier as the case. Some articles use the term secondary to describe any additional cases in a household, but this may be misleading since it doesn't acknowledge the possibility of a common carrier.[4] Certainly, anyone with onset less than 48 hours from onset of the case is more likely to be a co-primary case since the incubation period would be too short for transmission to have occurred from the case.

Because the meningococcal organism is transmitted by respiratory droplets and is susceptible to drying, it has been postulated that close contact is necessary for transmission. Therefore, by eradicating carriage in close contacts, such as household members, transmission to other susceptibles who are not carriers will be reduced, preventing successive

cases of illness. Failure to give chemoprophylaxis to close contacts may lead to additional cases. For example, a healthy father carried a strain identical (by DNA fingerprinting) to that isolated from the blood of a son with meningococcal septicemia as well as to meningococci isolated from the blood of another son admitted to the hospital with meningococcal disease ten months earlier.[5] Presumably, the father was the source of both cases; he had not received chemoprophylaxis after his first child became ill.

We could find little evidence to support the theory that the primary case poses a high risk for transmitting the organism to others.[6] Situations where transmission clearly occurred from the primary case are rarely described.[7] Some studies have examined nasopharyngeal carriage in the case. One such study found only 1 of 14 cases (7%) of post-treatment nasopharyngeal colonization among patients who had not received rifampin prior to discharge.[8] In another study, cultures of the upper respiratory tract were obtained from 14 patients with meningococcal disease.[9] Upon hospital admission, 9/14 (64%) were colonized with the same strain of *Neisseria meningitidis* as cultured from their blood or cerebrospinal fluid. Four of 14 (29%) were still colonized one week after the cessation of parenteral antibiotic treatment. Even with carriage rates as high as found in this study, this does not necessarily mean that the case poses a high risk to others. That is, most patients with meningococcal disease have not had contact with another person with the disease. Instead, cases occur sporadically throughout the year, and since the organism has no known reservoir outside of man, asymptomatic carriers are usually the source of transmission.[10,11]

Several mechanisms have been suggested by which chemoprophylaxis may prevent additional cases once a primary case has occurred:[12]

1. By eliminating meningococcal carriage in household members and other close contacts, therefore reducing transmission to susceptibles who are not carriers. Numerous studies have shown that rifampin, ciprofloxacin and ceftriaxone are effective in eliminating nasopharyngeal meningococci.[13-17]

2. By treating newly acquired infection in contacts who are non-immune and may be incubating the disease. However, the doses of rifampin used for chemoprophylaxis are inadequate to treat incubating meningococcal infection reliably.[12]

3. By preventing susceptible contacts from acquiring infection by directly inhibiting colonization. This approach could only be effective for the two days of prophylaxis.[12]

Finally, rifampin-resistant strains have been reported and the indiscriminate use of antibiotics contributes to this problem. Therefore, chemoprophylaxis should be restricted to those close contacts who are at highest risk of carrying the pathogenic strain. Close contacts are defined as those persons who could have had intimate contact with the patient's oral secretions such as through kissing or sharing of food or drink within the ten days preceding the onset of illness of the case. Close contacts requiring chemoprophylaxis are generally limited to household members and other intimate contacts; day care center classmates; and medical personnel who performed unprotected mouth-to-mouth resuscitation or intubated or suctioned the patient before antibiotic therapy was begun. Routine prophylaxis of medical personnel is not indicated except as noted above. Persons with meningococcal disease should receive chemoprophylaxis prior to hospital discharge unless their infection was treated with ceftriaxone or cefotaxime.[18]

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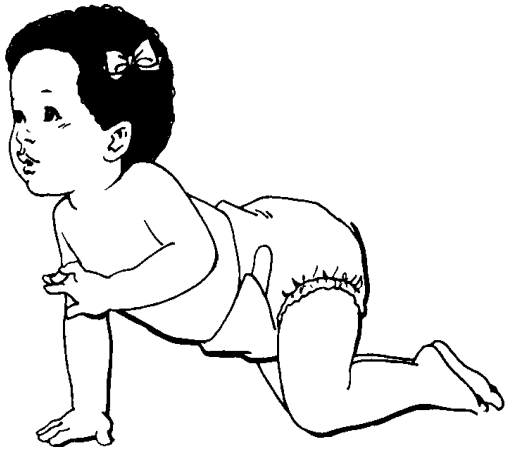
SPECIAL SURVEILLANCE FOR IDIOPATHIC ACUTE PULMONARY HEMORRHAGE AMONG INFANTS



Pediatric idiopathic pulmonary hemorrhage and hemosiderosis has recently been associated with mold growth in water-damaged homes.[1,2] The Centers for Disease Control and Prevention is seeking to identify cases of idiopathic pulmonary hemorrhage among infants under one year of age. For surveillance purposes, the following case definition has been established: pulmonary hemorrhage or pulmonary hemosiderosis or nosebleed in an otherwise healthy infant less than one year of age that is not due to any other known causes of pulmonary hemorrhage in infancy (e.g., cardiac or vascular malformations, infectious processes, trauma, etc.). If you learn of a case of this condition in an infant, please call the Office of Epidemiology (804-786-6029).

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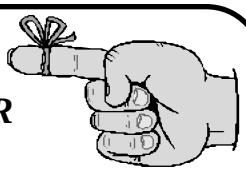
The Office of Epidemiology will be saying a fond farewell to ***Dr. Grayson B. Miller, Jr.*** *on September 9, 1997, as he leaves to become the Health Director of the Crater Health District. His wisdom and experience will surely be missed.*

We are pleased to announce that ***Dr. Suzanne Jenkins*** *has been selected to serve as the Acting Director of the Office of Epidemiology until a permanent director is selected.*

REMINDER



Isolates of *Neisseria meningitidis* from a normally sterile site (e.g., blood or cerebrospinal fluid) should be sent to the Division of Consolidated Laboratory Services for serogrouping. Determination of the serogroup is a critical part of surveillance for meningococcal disease. (The May issue of the *Virginia Epidemiology Bulletin* included a summary of meningococcal disease surveillance in Virginia.)

Letter to the Editor:

To the Editors:

I just received the April *Virginia Epidemiology Bulletin* (VEB) which, over all, I think is an excellent review of tick-borne diseases. However, I must strongly object to your recommendation of chloramphenicol as the secondary preferred treatment of choice for human ehrlichiosis. There is only scant, anecdotal evidence that chloramphenicol might have any usefulness, but a number of studies now exist suggesting its ineffectiveness in ehrlichiosis. This misleading recommendation could result in the mismanagement of an infected patient or even that patient's death from ehrlichiosis.

The recommendation for a secondary drug of choice should be for rifampin or ciprofloxacin, with the notation that while *in vitro* studies suggest their usefulness, these drugs have not yet been adequately studied *in vivo* for the treatment of ehrlichiosis. Use of a secondary drug should be reserved for only those with an absolute contraindication to a tetracycline. Even in young children, a tetracycline should not be withheld in this potentially life threatening infection due to a fear of causing an imperceptible staining of the teeth.

Raymond S. Weinstein, M.D.
Dale City, VA

Dear Dr. Weinstein,

Thank you for bringing to our attention the concerns about the use of chloramphenicol in the treatment of ehrlichiosis for persons for whom tetracycline drugs are contraindicated. While the treatment recommendations printed in the April 1997 issue of the VEB were taken from the *Control of Communicable Diseases Manual*,[1] your letter prompted us to do a more thorough search of the literature, including reading the articles which you referenced. It is clear that members of the tetracycline family, particularly doxycycline, are the most effective drugs in treating ehrlichiosis. Choosing an antibiotic when doxycycline is contraindicated is much more difficult. It is not as clear-cut as stated in the *Control of Communicable Diseases Manual* and subsequently, our VEB article.

What became clear as we reviewed the literature was the efficacy of doxycycline in treating ehrlichiosis. Furthermore, in the case of potentially life-threatening illnesses such as ehrlichiosis and Rocky Mountain spotted fever (RMSF), the use of doxycycline may be warranted in some patients for whom tetracycline drugs are normally contraindicated (i.e., children under 9 years of age). In fact, the American Academy of Pediatrics now acknowledges that tetracyclines are acceptable treatment for ehrlichiosis and RMSF in children of any age because the treatment benefits outweigh the risks.[2,3] Cosmetically perceptible tooth staining is unlikely to occur when tetracyclines are used for a short course of treatment and for a limited number of treatment courses during the years that the permanent teeth are developing.[4] As with any therapeutic intervention, the risks and benefits should be discussed with the patient's parents.

In persons for whom tetracycline drugs are absolutely contraindicated (i.e., pregnant women and persons with a well-defined severe allergy to tetracyclines) choosing an effective antibiotic is not straightforward. While *in vitro* studies showed that chloramphenicol was ineffective against *Ehrlichia chaffeensis* (the agent of human monocytic ehrlichiosis {HME} in the United States), it is possible that chloramphenicol could be effective *in vivo* despite poor *in vitro* performance.[5,6] And indeed, successful outcomes after chloramphenicol treatment have been reported.[7,8] However, given the questions about its clinical efficacy and the fact that oral chloramphenicol is no longer available in the United States, the need for secondary oral agents for the treatment of ehrlichiosis is even more critical. As you pointed out, rifampin may be considered. *In vitro*, *E. chaffeensis* and the unnamed agent of human granulocytic ehrlichiosis (HGE) were both highly susceptible to rifampin.[5,6] We are unaware of *in vivo* studies of the efficacy of this drug. However, some discrepancies have been found in the activities of quinolones against ehrlichiae. *E. chaffeensis* was not susceptible to ciprofloxacin using standard laboratory antibiotic concentrations; at high doses it has been found to be bacteriostatic.[5] The agent of HGE was considered intermediately susceptible to ciprofloxacin *in vitro*.[6] To our knowledge, there is no published evidence of the clinical efficacy of ciprofloxacin in treating HME or HGE. In fact, there was recently a report of a patient for whom ciprofloxacin did not prevent deterioration of his clinical condition and did not inhibit subsequent isolation of ehrlichial morulae from his blood.[9] *In vitro*, trovafloxacin was significantly more active against the agent of HGE and would be worth testing against *E. chaffeensis* as it may hold promise for the treatment of ehrlichiosis when it becomes available.[6] It is possible that the best that can be said at this time is that there is no good recognized secondary agent for treating human ehrlichiosis and that cases for which tetracycline drugs are absolutely contraindicated present a dilemma for the clinician.

We apologize for not delving further into this issue before publishing recommendations in the VEB, and we thank you for taking the time to write and giving us an opportunity to learn more about this issue.

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As indicated by the above letter and response, there is still much to be learned about the treatment of ehrlichiosis and Rocky Mountain spotted fever (RMSF). The Centers for Disease Control and Prevention is interested in hearing from physicians who have treated patients with laboratory-confirmed ehrlichiosis or RMSF to learn more about the antibiotics used and the clinical outcome, particularly if therapies other than doxycycline or tetracyclines have been used. This information may be used to formulate treatment guidelines in the future. For further information, please contact Chris Paddock, M.D. in the Division of Viral and Rickettsial Diseases at (404)639-1309 or you may contact him by E-mail (cdp9@cdc.gov).

Cases of Selected Notifiable Diseases Reported in Virginia*

Disease	Total Cases Reported, June 1997						Total Cases Reported Statewide, January through June		
	State	Regions					This Year	Last Year	5 Yr Avg
		NW	N	SW	C	E			
AIDS	106	13	33	6	10	44	598	566	630
Campylobacteriosis	67	15	14	21	9	8	222	287	258
Giardiasis	32	6	13	2	7	4	204	126	120
Gonorrhea	633	48	63	73	134	315	3975	4797	6082
Hepatitis A	25	5	14	2	4	0	99	81	73
Hepatitis B	13	1	8	1	0	3	63	73	69
Hepatitis NANB	3	1	1	0	0	1	11	8	14
HIV Infection	79	8	21	4	14	32	480	492	572
Influenza	0	0	0	0	0	0	396	371	651
Legionellosis	2	2	0	0	0	0	11	12	7
Lyme Disease	4	0	0	2	1	1	4	7	20
Measles	0	0	0	0	0	0	0	2	3
Meningitis, Aseptic	13	2	4	5	0	2	83	70	82
Meningitis, Bacterial†	9	2	2	1	3	1	45	44	54
Meningococcal Infections	5	1	1	1	0	2	33	34	34
Mumps	2	0	0	2	0	0	6	4	18
Pertussis	6	2	1	1	1	1	25	18	12
Rabies in Animals	43	16	9	8	7	3	304	277	201
Rocky Mountain Spotted Fever	2	0	0	0	0	2	4	5	2
Rubella	0	0	0	0	0	0	1	2	0
Salmonellosis	78	15	21	7	19	16	369	443	389
Shigellosis	38	3	12	15	1	7	258	233	193
Syphilis, Early‡	64	1	5	5	17	36	342	453	634
Tuberculosis	24	2	10	3	2	7	165	149	169

Localities Reporting Animal Rabies: Accomack 1 cat; Albemarle 1 raccoon; Alexandria 3 raccoons; Alleghany 1 raccoon; Amherst 1 raccoon; Appomattox 1 skunk; Arlington 1 raccoon; Augusta 2 skunks; Campbell 2 raccoons; Chesterfield 1 fox, 5 raccoons; Culpeper 3 raccoons; Cumberland 1 raccoon; Fauquier 1 cat; Fluvanna 1 skunk; Franklin County 1 dog; King and Queen 1 raccoon; Loudoun 1 fox, 1 raccoon, 1 skunk; Louisa 1 raccoon; Pittsylvania 1 raccoon; Prince William 1 cat, 1 raccoon; Pulaski 1 fox; Rappahannock 1 raccoon; Rockbridge 1 fox, 1 raccoon; Rockingham 1 cat; Shenandoah 1 raccoon; Warren 2 raccoons; Westmoreland 1 fox.

Occupational Illnesses: Asbestosis 29; Carpal Tunnel Syndrome 46; DeQuervain's Syndrome 1; Hearing Loss 5; Lead Poisoning 3; Pneumoconiosis 20.

*Data for 1997 are provisional.

†Other than meningococcal.

‡Includes primary, secondary, and early latent.

Published monthly by the
VIRGINIA DEPARTMENT OF HEALTH
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