Practice Patterns of Infectious Disease Physicians for Management of Meningococcal Disease

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Background: Although empiric treatment regimens for acute bacterial meningitis are well established, there are many uncertainties regarding management of meningococcal disease. A survey was conducted among infectious disease specialists to assess meningococcal disease practice patterns and availability of antimicrobial susceptibility testing for *Neisseria menigitidis*.

Methods: An online survey was distributed to 1342 pediatric and adult infectious disease specialists to assess common practices and opinions regarding the diagnosis, treatment and prevention of meningococcal disease. Specialists were also asked about the availability of antimicrobial susceptibility testing for *Neisseria meningitidis* at their clinical microbiology laboratory.

Results: Six hundred fifty members responded to the survey (48%). Pediatric infectious disease specialists were more likely than adult specialists to use penicillin as definitive therapy for meningococcal disease (56% versus 46%; $P = 0.038$). Most pediatric specialists who would narrow therapy report that they would only switch to penicillin upon confirmation of penicillin susceptibility (55%), although 44% would narrow therapy based on a *N. meningitidis* species confirmation alone. More than one third of respondents reported that susceptibility testing for *N. meningitidis* is not routinely performed. There was also wide variation in complement deficiency screening criteria and meningococcal disease chemoprophylaxis practices among respondents.

Conclusions: Infectious disease specialists vary significantly in their practices regarding several aspects of meningococcal disease diagnosis, treatment and prevention. Antimicrobial susceptibility testing for *N. meningitidis* is not routinely performed in many practices. Consideration of these variations would be useful when developing treatment and prevention recommendations.

Key Words: meningococcal disease, *Neisseria meningitidis*, antimicrobial resistance, meningitis

(*Pediatr Infect Dis J* 2012;31: e208–e212)

Although rates of meningococcal disease have decreased in the United States, *Neisseria meningitidis* remains a serious cause of bacterial meningitis and sepsis in children and young adults, with a case fatality rate of 10%.[1] In addition, outbreaks and even sporadic cases can cause significant concern in communities.[1] Empiric antibiotic treatment regimens for meningococcal disease are well established[2,3]; however, opinions on other aspects of diagnosis and treatment differ among experts. Various age criteria for routine lumbar puncture in febrile infants have been proposed.[4,5] Recommendations regarding the definitive treatment of meningococcal disease also vary, with some guidelines recommending penicillin G upon confirmation of *N. meningitidis*,[2] whereas others recommend regimen narrowing based on the results of antimicrobial susceptibility testing.[3] Similarly, expert opinions differ regarding screening criteria for complement deficiency among patients with meningococcal disease.[6–8]

The objective of this study was to investigate diagnostic and treatment practice patterns among infectious disease physicians. Better understanding of current treatment practices and antibiotic susceptibility testing availability could inform the development of future treatment and prevention guidelines.

MATERIALS AND METHODS

An online survey to assess typical physician practices in meningococcal disease management and prevention was distributed to 1342 pediatric and adult infectious disease physician members of the Emerging Infections Network (EIN) in June and July 2010 (copy of surveys available from author, upon request). The Infectious Diseases Society of America EIN is a voluntary sentinel network of infectious disease physicians who regularly engage in clinical activity. The network has been funded by the Centers for Disease Control and Prevention since 1995.[9] The surveys were sent electronically to most members; a paper version was used for members who receive surveys by facsimile. Nonrespondents were sent 2 reminders approximately 10 days apart. Two surveys were distributed, 1 for pediatric infectious disease physicians and the other for adult infectious disease physicians. Medicine-pediatric specialists were sent the adult specialist survey, and their responses were included with the adult specialists for all analyses.

Each survey included several multiple-choice questions relating to meningococcal disease, treatment practices, antimicrobial susceptibility testing availability, complement screening and chemoprophylaxis practices. Pediatric specialists were also asked about their age criteria for routine lumbar puncture for healthy infants presenting with fever ≥38°C. Respondents who reported that *N. meningitidis* had no relevance to their practice were excluded from the final analysis. Statistical tests were performed using SAS, version 9.2 (SAS Institute, Cary, NC). We used the χ^2 test or Fischer exact test to compare proportions. $P < 0.05$ was considered to be statistically significant.

RESULTS

Of the 1342 EIN members, 650 members (48%) responded to the survey invitation, including 163 pediatric specialists (25%) and 32 medicine-pediatrics specialists (5%). Pediatric specialists responded in significantly greater proportion than adult specialists (62% versus 45%; $P < 0.0001$), and were more likely to report that

Accepted for publication June 05, 2012.

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This publication was supported by Grant/Cooperative Agreement Number U50 CI 00358 from the Centers for Disease Control and Prevention. The authors have no other funding or conflicts of interest to disclose.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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ISSN: 0891-3668/12/3111-e208
DOI: 10.1097/INF.0b013e31826323a4

N. meningitidis carriage or infections were relevant to their practice (98% versus 74%; $P < 0.0001$). Respondents and nonrespondents were similar in terms of their employment type, hospital type and teaching responsibilities. Respondents were more likely to be involved in research (56% versus 37%; $P < 0.0001$); however, time spent in clinic did not differ (10.4 versus 10.7 months). Twenty-four percent of respondents had less than 5 years' experience, 24% had between 4 and less than 15 years' experience and 52% had ≥15 years' experience ($P < 0.0001$).

A total of 131 respondents reported that *N. meningitidis* infections were not relevant to their practice and were excluded from analysis. The remaining 519 completed surveys represented 39% of all EIN members. Among these respondents, 75% of pediatric specialists reported managing 2 or more cases of meningococcal disease in the last 2 years, whereas only 56% of adult specialists reported managing 2 or more cases ($P < 0.0001$). Managing 4 or more cases was reported by 27% of pediatric specialists and 10% of adult specialists.

Preferences regarding definitive treatment of meningococcal disease among pediatric and adult infectious disease specialists are presented in Table 1. Forty-nine percent of respondents would change antibiotic treatment to penicillin G with laboratory confirmation of meningococcal disease. Adult specialists, however, were less likely than pediatric specialists to change antibiotics (46% versus 56%; $P = 0.038$) and were less likely to switch upon culture confirmation alone (29% versus 44%; $P = 0.016$). Of specialists who would change antibiotics, 89% reported narrow-spectrum antibiotics as preferable for treatment of meningococcal disease and 64% reported penicillin as the treatment of choice. Approximately half (44%) of specialists cite rare penicillin resistance as an important reason for their treatment choice. Primary reasons for not changing antibiotics included concerns about cerebrospinal fluid penetration (63%), a desire to not alter working treatments (33%), cost-effectiveness of cephalosporins (72%), concerns about antibiotic resistance (16%) and unavailability of antimicrobial susceptibility testing (18%).

Responses to questions on antimicrobial susceptibility testing for *N. meningitidis* and the methods used are summarized in Table 2. Among respondents who reported that testing was routinely performed (42%), antibiotic gradient strip (Etest) was the most commonly reported method (25%). Nearly half were unsure of the method used. Susceptibility results most commonly reported are those to penicillin (80%), ceftriaxone (74%), ciprofloxacin (45%) and rifampin (34%).

Responses regarding complement deficiency screening indications are summarized in Table 3. Most respondents would screen patients with a family history of *N. meningitidis* infection or a history of repeat infections. Twenty-eight percent of infectious disease specialists, however, routinely screen all patients with meningococcal disease.

Table 4 summarizes provider responses to questions about groups to which they would offer close-contact chemoprophylaxis to prevent meningococcal disease. Nearly all infectious disease specialists reported that they would offer chemoprophylaxis to household contacts of meningococcal disease patients and contacts with direct exposure to oral secretions, and three quarters would offer chemoprophylaxis to childcare contacts.

Regarding routine lumbar puncture for febrile infants (≥38°C), 15% of pediatric infectious disease specialists recommend an age criteria of ≤12 weeks of age, 32% recommend ≤8 weeks and 45% recommend ≤4 weeks. There was no association between age thresholds and the physician's years in practice, employer type, hospital type or number of meningococcal patients seen in past 2 years.

TABLE 1. Meningococcal Disease Treatment Practices of Pediatric and Adult Infectious Disease Specialists

Treatment Practices	Pediatric Specialists N = 159 (%)*	Adult Specialists N = 360 (%)*	P†
Would you change antibiotics to IV Penicillin G?‡			0.038
Yes	89 (56)	166 (46)	
No	70 (44)	194 (54)	
If yes, when?			
Gram (–) diplococci on Gram stain	0 (0)	7 (4)	
Culture confirmation of *N. meningitidis*	39 (44)	47 (29)	0.016
Penicillin susceptibility confirmation	48 (55)	105 (65)	
Other	1 (1)	2 (1)	
If yes, why?§			
Narrow spectrum preferable	80 (95)	143 (86)	0.029
Penicillin is the treatment of choice	54 (64)	107 (64)	
Significant Penicillin resistance is rare	43 (51)	66 (40)	
Other	6 (7)	5 (3)	
If no, why?§			
Excellent CSF penetration of cephalosporins	39 (76)	115 (60)	0.029
Continue using working treatment	12 (23)	67 (35)	
Susceptibility testing not available	11 (22)	32 (17)	
Susceptibility testing not available soon enough	6 (12)	30 (16)	
Concern about resistance	11 (22)	28 (15)	
Prefer broad-spectrum coverage in severely ill patients	4 (8)	7 (4)	
More cost-effective or feasible	3 (6)	173 (90)	<0.0001
Other	10 (20)	7 (4)	
If no, would you consider penicillin in absence of meningitis?			0.004
Yes	22 (33)	88 (54)	
No	44 (67)	74 (46)	

*Not all respondents answered all questions.

†All P comparing adult and pediatric specialist responses > 0.05 unless stated otherwise.

‡Respondents were asked: "Would you consider recommending changing the antibiotic to IV penicillin G (or ampicillin) in a patient with confirmed meningococcal meningitis and no allergies who is given an empiric antibiotic regimen containing a 3rd generation cephalosporin?"

§Total is greater than 100% as multiple responses were allowed.

CSF indicates cerebrospinal fluid.

TABLE 2. Antimicrobial Susceptibility Testing of *N. meningitidis* in Survey Respondents' Hospital or Laboratory

Susceptibility Testing	Number of Respondents N = 519 (%)
Is antimicrobial susceptibility testing routinely performed?	
Yes	218 (42)
No	187 (36)
Unknown	114 (22)
If performed, method(s) used*	
Broth microdilution	42 (20)
Antibiotic gradient strip (Etest)	51 (25)
Disk diffusion	24 (12)
Other	7 (3)
Not sure	95 (46)

*Total is greater than 100% as multiple responses were allowed.

TABLE 3. Screening Criteria Used to Identify Complement Deficiency in Patients With History of Meningococcal Disease*

Screening Criteria	Pediatric Specialists N = 159 (%)	Adult Specialists N = 360 (%)	$P^{\dagger}$
History of repeat infections	127 (80)	312 (87)	0.048
Family history of *Neisseria* infections	120 (75)	253 (70)	
Vaccine failure	81 (51)	147 (41)	0.032
Chronic meningococcemia	79 (50)	185 (51)	
Screen all patients	70 (44)	76 (21)	<0.0001
Serogroups other than A, B, C‡	30 (19)	28 (8)	0.0002
Age criteria	4 (3)	7 (2)	
Other	5 (3)	5 (1)	

*Total is greater than 100% as multiple responses were allowed.
†All $P > 0.05$ unless stated otherwise.
‡Serogroup W-135, Y, X or other.

DISCUSSION

This survey demonstrates that management of meningococcal infections varies among infectious disease physicians, particularly between adult and pediatric specialists. Respondents reported differences in definitive antibiotic treatment choices, availability and use of antimicrobial susceptibility testing and chemoprophylaxis prescription practices. Reasons cited by respondents for their decisions also varied. In this survey, almost three quarters of pediatric specialists, and 90% of adult specialists, reported managing or consulting on 3 or fewer cases of meningococcal disease in the past 2 years. Because cases are rare, physician experience is limited and many may rely on several different published guidelines for treatment recommendations.

Given the different approaches offered in published guidelines and the variable capacity for susceptibility testing among practices and laboratories, differences in the treatment approaches for meningococcal disease among infectious disease specialists are not surprising. The American Academy of Pediatrics *Red Book* recommends treatment of meningococcal disease with penicillin G without regard to antimicrobial susceptibility.[2] The Infectious Diseases Society of America meningitis treatment guidelines recommend susceptibility testing of *N. meningitidis* isolates before changing to penicillin therapy.[3] Antimicrobial susceptibility testing, however, is not routinely performed in many practice settings. Where testing is performed, commonly used methods include Etest and disk diffusion. Etest, widely used in Europe, is not FDA-approved for use in antimicrobial susceptibility testing in the United States and the minimum inhibitory concentration breakpoints are not well defined. Disk diffusion is not recommended for penicillin susceptibility testing of *N. meningitidis* by the Clinical and Laboratory Standards Institute.[10] Alternatively, commonly used automated systems are not able to test *N. meningitidis*,[11] and the broth microdilution and agar diffusion reference methods are impractical for clinical laboratories that do not regularly isolate *N. meningitidis*. With such varying capacity, adherence to recommendations for universal susceptibility testing is difficult.

The clinical and public health implications of physicians' varied use of antimicrobial susceptibility testing are not established. Regular susceptibility testing may allow surveillance for emerging resistance patterns, and tailoring antibiotic use to the

TABLE 4. Contact Chemoprophylaxis Criteria of Those Potentially Exposed to Meningococcal Infection*

Chemoprophylaxis Criteria	Pediatric Specialists N = 159 (%)	Adult Specialists N = 360 (%)	$P^{\dagger}$
Direct exposure to oral secretions	159 (100)	354 (98)	
Household members	154 (97)	326 (97)	0.012
Shared cups/utensil	127 (80)	221 (61)	<0.0001
Childcare contacts	121 (76)	262 (78)	
Defer to health department	32 (20)	55 (15)	
Classroom contacts	24 (15)	116 (32)	<0.0001
Healthcare workers without exposure to oral secretions	7 (4)	48 (13)	0.002
Nonroommates in same dormitory	0 (0)	27 (8)	0.0004
Not sure	0 (0)	5 (1)	
Close contacts of person with isolation in culture of *N. meningitidis* from nonsterile sites‡			
Pneumonia with only positive sputum	—	138 (38)	
Asymptomatic throat culture	—	55 (15)	
Genital or anorectal infection	—	26 (7)	
Conjunctivitis	—	71 (20)	
None	—	138 (38)	
Not sure	—	72 (20)	

*Total is greater than 100% as multiple responses were allowed.
†All $P > 0.05$ unless stated otherwise.
‡This question was only asked in the adult infectious diseases specialist survey.

organism's susceptibility may limit the development of antibiotic resistance. For example, wide-spectrum antibiotics has contributed to widely resistant *Neisseria gonorrhea* that is difficult to treat.[12] For *N. menigitidis*, the implications are less clear. A majority of *N. meningitidis* isolates in the United States are susceptible to penicillin, with 3–13% of isolates with minimum inhibitory concentrations in the intermediate susceptible range.[13–16] Although the clinical significance of *N. meningitidis* with intermediate susceptibility to penicillin has not been demonstrated, reports of treatment failure in patients infected with these strains are rare, particularly when high-dose penicillin is preceded by 24 hours of empiric treatment with third generation cephalosporins.[17–20]

Besides antimicrobial resistance concerns, the most often indicated reason given by pediatric specialists was the "excellent CSF penetration" of third generation cephalosporins, reflecting concerns about the need to achieve adequate cerebrospinal fluid drug concentrations when treating central nervous system infections. In contrast, the most commonly cited reason among adult specialists who would maintain third generation cephalosporins was cost and feasibility of administration. Ceftriaxone is 10–50% less expensive per dose than penicillin G or ampicillin,[21] and the twice daily dosing regimen is less frequent than the typical dosing schedule for penicillin. Given the ease of administration of broader-spectrum antibiotics, continued treatment with third generation cephalosporins should be considered in the absence of antimicrobial susceptibility testing.

Other areas of meningococcal management where specialists differ significantly are testing for conditions that increase patients' risk of meningococcal disease, and proper contact chemoprophylaxis for high-risk contacts of patients with meningococcal disease. Because patients with terminal complement component or properidin deficiencies are at high risk of recurrent infection,[22] The Centers for Disease Control and Prevention recommends meningococcal vaccination with routine boosters.[23] No guidelines exist, however, for screening meningococcal patients with potential risk factors for complement component deficiencies including a family history of meningococcal disease, repeat infection or infection with unusual serogroups, vaccine failures and chronic meningococcemia. Most physicians surveyed screen patients with a family history of meningococcal infection and repeat infections; however, screening of patients with other potential risk factors is less consistent. In contrast, nearly half of pediatric specialists reported that they would screen all patients. Our data reflect the wide range of opinions on complement deficiency screening, with some experts recommending routine screening for all patients after their first meningococcal disease episode,[8] and others who propose targeted screening of specific higher-risk groups, including patients with disease caused by unusual serogroups.[24] Incidence of complement deficiency among patients with meningococcal diseases is generally low,[6,24–26] but has been reported to be as high as 30–48% among patients infected with unusual serogroups.[27] These studies, however, are more than a decade old and may not reflect the current low-disease incidence in the United States. As the incidence of meningococcal disease declines, an increasing proportion of cases may occur in high-risk patients. Although no definitive guidance on screening currently exists, more frequent screening of patients with meningococcal disease might be prudent.

Persons with close household contact and those with direct exposure to oral secretions of patients are at substantially increased risk for disease; therefore, the Centers for Disease Control and Prevention recommends chemoprophylaxis for household contacts, childcare center contacts and persons in direct exposure with oral secretions from the index patient (eg, mouth-to-mouth resuscitation, endotracheal intubation or endotracheal tube management).[28] Some guidelines also recommend prophylaxis of contacts sharing cups or utensils, a practice frequently reported in our survey.[2] However, there are no data documenting increased risk of disease following sharing of utensils, and it is better interpreted as a marker of close contact. We also found variation among adult specialists in their opinions regarding the need to give chemoprophylaxis to close contacts of healthy patients from whom *N. meningitidis* is isolated in culture from nonsterile sites such as sputum, throat, the genitourinary tract or conjunctiva. The Centers for Disease Control and Prevention guidelines do not recommend chemoprophylaxis of close contacts if the patient has no evidence of a sterile site infection,[28] although some experts recommend chemoprophylaxis of close contacts of patients with meningococcal conjunctivitis.[29] Despite variations in guidelines, data do not support widespread antibiotic chemoprophylaxis beyond close patient contacts (as described earlier) and this practice should be limited.

Nonresponse might have biased the results; however, we believe this bias to be small. Respondents and nonrespondents were similar in most respects except for their involvement in research activities. Although respondents were more likely to be researchers, time devoted to clinical practice did not differ from nonrespondents. A second limitation is that overall experience with meningococcal disease among respondents was low. Twenty percent of respondents did not complete the survey because meningococcal disease was not relevant to their practice, and most completing the survey manage less than 2 cases per year. Relatively infrequent contact with meningococcal disease among respondents and unfamiliarity with guidelines and antimicrobial testing procedures might account for variations presented here.

In summary, infectious disease specialists have a wide range of opinions and practices in several aspects of meningococcal disease and bacterial meningitis management. There are likely several reasons for this, including limitations in the medical literature, differences in expert recommendations, changing disease epidemiology and inconsistent availability of *N. meningitidis* antimicrobial susceptibility testing. Consideration of these practice differences will be important when revising and communicating management guidelines. Efforts to harmonize pediatric and adult practice guidelines should consider these practice differences.

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