JOURNAL OF CLINICAL MICROBIOLOGY, Nov. 2006, p. 4290–4291 Vol. 44, No. 11
0095-1137/06/$08.00+0 doi:10.1128/JCM.01903-06

Emergence of Non-Ceftriaxone-Susceptible *Neisseria meningitidis* in India

Meningococcal disease is endemic in Delhi, and there has been an increase in the number of cases of meningococcal disease occurring in Delhi in recent years (4). Antimicrobial therapy is the cornerstone of meningococcal disease management. Expanded-spectrum cephalosporins (ceftriaxone and cefotaxime) are widely accepted antimicrobials for the treatment of patients suspected of having meningococcal disease (1, 5). In India, there has been a paucity of studies on the antimicrobial sensitivity of *Neisseria meningitidis*. Drug susceptibility testing on the isolates obtained from a recent spurt of cases in and around Delhi in early 2005 revealed increased resistance to ciprofloxacin while all isolates were susceptible to ceftriaxone (4). We report on the emergence of clinical isolates of *N. meningitidis* that were found to be nonsusceptible to ceftriaxone and cefotaxime and were associated with potential therapeutic failure to ceftriaxone therapy.

Six cases of meningococcal disease (five cases of meningococcemia and one case of meningococcal meningitis) were identified during March to April 2006 from patients admitted to Chacha Nehru Children Hospital, Delhi, India (a 250-bed pediatric hospital in East Delhi). Two more cases of meningococcemia were diagnosed in September 2006. All eight isolates were identified as *N. meningitidis* on the basis of Gram staining and a latex agglutination test (Wellcogen bacterial antigen kit [Remel] and BD Directigen meningitis combo test [Becton Dickinson]). Serogrouping was done using a latex agglutination kit (Pastorex meningitis kit; Bio-Rad). All of the isolates were identified as group A *N. meningitidis*.

Antimicrobial susceptibility testing of the isolates was performed using Etest and the disk diffusion method, using Mueller-Hinton agar (Himedia, Mumbai India) with 5% sheep blood. Etest strips (AB Biodisk, Solna, Sweden) of penicillin, ceftriaxone, cefotaxime, nalidixic acid, ciprofloxacin, and chloramphenicol were employed. Pure growth from chocolate agar was used, with the inoculum adjusted to a 0.5 McFarland standard. Testing conditions were as recommended by the Clinical and Laboratory Standards Institute (CLSI) (2). Quality control was achieved by using *Streptococcus pneumoniae* ATCC 49619 and *Escherichia coli* ATCC 25922 with different antimicrobials as recommended by the CLSI. All MIC tests were repeated three times. MIC breakpoints were used for interpretation of results as recommended by the CLSI (2). For disk diffusion testing interpretation, the recommendations of Jorgensen et al. were used (3).

MIC data revealed that six isolates (75%) of *N. meningitidis* were resistant to penicillin and nonsusceptible to ceftriaxone and cefotaxime (Table 1). Only one isolate was found to be susceptible to ciprofloxacin. In all eight cases, a nalidixic acid MIC of ≥ 8 μg/ml was found to be a good predictor of ciprofloxacin resistance. Five isolates (62.5%) were additionally resistant to chloramphenicol. The MIC results revealed the emergence of non-ceftriaxone-susceptible *N. meningitidis* in India, with most of the isolates being multidrug resistant (resistant to three or more antimicrobials).

Disk diffusion testing results are summarized in Table 1. Susceptibility data obtained from disk diffusion testing did not correlate with the MIC results. Like Jorgensen and colleagues, we also observed a larger zone diameter than expected because of the use of a candle jar (3).

Empirical therapy with expanded-spectrum cephalosporins, such as ceftriaxone and cefotaxime, for 2 to 5 days is an ideal approach for management in patients suspected of having meningococcal disease (1, 5). In the present study, patients were labeled as having a partial/delayed response to the antimicrobial (potential therapeutic failure) if they did not become afebrile within 5 days of antimicrobial therapy. Clinical and therapeutic details of six patients who were admitted to the emergency department were obtained from the medical records department of the hospital and are summarized in Table 1. The data for two outpatients (CNBC2 and CNBC7) who subsequently did not turn up to the hospital are not known. Ceftriaxone therapy of >5 days was administered in four patients (range, 6 to 15 days) to make them afebrile, indicating a partial/delayed therapeutic response. Two patients (CNBC1 and CNBC5) were additionally administered chloramphenicol intravenously after 4 to 5 days of ceftriaxone therapy, indicating potential therapeutic failure.

Although no contact cases were observed in the study, the susceptibility data highlight the alarming situation of depleting the arsenal of antibiotics for management of the patients and prophylaxis of their contacts.

The emergence of such resistant strains exposes the effects of the indiscriminate use of antimicrobial agents in both private and government hospitals in the country. The results reveal an urgent need for putting up surveillance for antimicrobial resistance of meningococci.

This is the first study in the world to report on non-ceftriaxone-susceptible clinical isolates of *N. meningitidis*. Also, this is the first study to demonstrate a partial/delayed response to ceftriaxone therapy for meningococcal disease.

REFERENCES

1. **Baines, P. B., and C. A. Hart.** 2003. Severe meningococcal disease in childhood. Br. J. Anaesth. **90:**72–83.
2. **Clinical and Laboratory Standards Institute.** 2005. Performance standards for antimicrobial susceptibility testing; 15th informational supplement. CLSI/NCCLS M100-S15. Clinical and Laboratory Standards Institute, Wayne, Pa.
3. **Jorgensen, J. H., S. A. Crawford, L. C. Fulcher, A. Glennen, S. M. Harrington, J. Swenson, R. Lynfield, P. R. Murray, and F. C. Tenover.** 2006. Multilaboratory evaluation of disk diffusion antimicrobial susceptibility testing of *Neisseria meningitidis* isolates. J. Clin. Microbiol. **44**:1744–1754.
4. **Manchanda, V., S. Gupta, and P. Bhalla.** 2006. Meningococcal disease: history, epidemiology, pathogenesis, clinical manifestations, diagnosis, antimicrobial susceptibility and prevention. Indian J. Med. Microbiol. **24**:7–19.
5. **Sachdeva, A., S. Kukreja, V. Jain, and A. K. Dutta.** 2005. Meningococcal disease—outbreak in Delhi. Indian Pediatr. **47:**547–556.

Vikas Manchanda*
P. Bhalla
Maulana Azad Medical College and Associated Chacha Nehru Children Hospital
Geeta Colony
Delhi 110031, India

*Phone: 91-11-27472222
Fax: 91-11-26899362
E-mail: manchandavikas@hotmail.com

Continued on following page

TABLE 1. Susceptibility testing results of *N. meningitidis* isolates[a]

Bacterial isolate/site of isolation	Symptom(s)	Age/sex	Penicillin		Ceftriaxone		Cefotaxime		Nalidixic acid		Ciprofloxacin		Chloramphenicol		Antibiotic therapy	No. of days[b]
			MIC	ZD	MIC	ZD	MIC	ZD	MIC	ZD	MIC	ZD	MIC	ZD		
CNBC1/blood	Fever for 4 days with rash, altered sensorium	5 yr/M	**1.5**	35	**1.5**	47	**1.5**	48	**128**	**6**	**0.125**	40	0.50	37	Ceftriaxone given at admission (day 0), chloramphenicol added on day 4	7
CNBC2/blood	Not known	5 mo/F	**2.0**	**6**	**8**	**19**	**>32**	**20**	**64**	**6**	**1.5**	33	0.75	33	Patient refused to be admitted, no antibiotic history available	History not available
CNBC3/blood	Fever for 5 days with rash	12 yr/M	0.125	36	**1.5**	47	**4**	47	**64**	**6**	**1.0**	38	1.5	29	Ceftriaxone given at admission (for 10 days)	3
CNBC4/blood	Fever with diarrhea and dehydration	4.5 yr/M	**>32**	**6**	**0.25**	46	**0.50**	48	**64**	**6**	**1.5**	34	**8**	**12**	Ceftriaxone given at admission (for 6 days)	6
CNBC5/CSF	Neck stiffness for 4 days with fever and vomiting	6 yr/M	**>32**	**6**	**6**	**19**	**>32**	**15**	0.047	**18**	0.094	**30**	**>256**	**6**	Ceftriaxone given at admission (day 0), chloramphenicol added on day 5	15
CNBC6/blood	Fever for 2 days with rash, vomiting for 1 day	4.5 yr/F	**0.094**	ND	**1.5**	ND	**16**	ND	>256	ND	1.5	ND	**12**	ND	Crystalline penicillin given at admission (day 0), ceftriaxone added on day 4	14
CNBC7/blood	Not known	7 mo/M	**6.0**	ND	**3**	ND	**8**	ND	**>256**	ND	**6**	ND	**128**	ND	Patient refused to be admitted, no antibiotic history available	History not available
CNBC8/blood	Fever for 2 days with rash for 1 day	10 mo/M	**0.25**	ND	**1.0**	ND	**4**	ND	**>256**	ND	**2**	ND	**12**	ND	Ceftriaxone given at admission	5

[a] CSF, cerebrospinal fluid; ZD, zone diameter; ND, not determined; M, male; F, female. MIC values are given in micrograms per milliliter. Zone diameters are given in millimeters. Resistant/nonsusceptible readings are in boldface.

[b] Number of days after starting antibiotic treatment to become afebrile.

Continued from preceding page