

PENICILLIN-RESISTANT *NEISSERIA MENINGITIDIS* BACTERAEMIA, KIMBERLEY REGION, MARCH 2010

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Abstract

A 4-year-old fully immunised male presented to a regional hospital in the West Kimberley with fever and lethargy. Blood cultures yielded serogroup B *Neisseria meningitidis*, resistant to benzylpenicillin (minimum inhibitory concentration (MIC) 1.0 mg/L). The patient was treated with intravenous ceftriaxone and made a complete recovery. Although invasive *N. meningitidis* isolates with reduced penicillin susceptibility are not uncommon in Australia, this is the first report of a benzylpenicillin-resistant isolate (MIC > 0.5 mg/L) causing invasive disease. As benzylpenicillin is currently recommended as first line empiric and definitive therapy for invasive meningococcal disease, the emergence of penicillin-resistant *N. meningitidis* disease is of concern and emphasises the importance of ongoing surveillance for antimicrobial resistance. *Commun Dis Intell* 2010;34(3):324–326.

Keywords: *Neisseria meningitidis*; penicillin resistant; meningococcus; meningococcal disease

Case report

A 4-year-old fully immunised male presented to a regional hospital in the West Kimberley with fever and lethargy. On examination, he was febrile (T = 39.4°C), tachycardic (pulse rate 160 bpm) and tachypnoeic (respiratory rate 26 per minute), however there was no rash or signs of meningism. Blood cultures yielded serogroup B *Neisseria meningitidis*. The patient was treated with intravenous ceftriaxone 900 mg for 5 days and made a complete recovery. A lumbar puncture performed 72 hours after commencing ceftriaxone was negative for *N. meningitidis* on culture and by polymerase chain reaction.

Antimicrobial susceptibility testing was performed in the routine microbiology laboratory by Etest® (AB Biodisk, Solna, Sweden) and results interpreted according to Clinical Laboratory Standards Institute (CLSI) breakpoints.¹ Etest® minimum inhibitory concentration (MIC) results were as follows: benzylpenicillin, 0.5 mg/L (resistant); ceftriaxone, 0.004 mg/L (susceptible); ciprofloxacin, 0.006 mg/L (susceptible); rifampicin

0.012 mg/L (susceptible) and chloramphenicol, 1 mg/L (susceptible). The isolate was beta-lactamase negative by nitrocefin testing.

The isolate was referred to the National Neisseria Network Reference Laboratory, Prince of Wales Hospital, New South Wales for confirmatory susceptibility testing. The identification of the organism was confirmed and susceptibility testing for benzylpenicillin was performed using two alternative methods (Calibrated Dichotomous Susceptibility (CDS) disc testing and MIC determination using agar dilution and CLSI breakpoints). There was no zone to the Pen0.5u disc by the CDS method, indicating resistance, which was confirmed by the MIC method and demonstrated a benzylpenicillin MIC of 1.0 µg/mL (resistant).

Genosubtyping of the *N. meningitidis* isolate was performed by *porA* gene variable region (VR) 1 and 2 DNA sequencing as previously described.² When the deduced amino acid sequences of VR1 and VR2 were submitted to the *N. meningitidis porA* VR database (<http://neisseria.org/nm/typing/pora>), there were only partial matches to VR1 peptides 5–29 (56%) and 21–14 (60%) and VR2 peptides 2–39 (67%) and 16–107 (46%). When compared to a Western Australian database of 81 *N. meningitidis* isolates strains (including 7 from the Kimberley) collected from 2000–2006³ this genosubtype had not previously been identified.

Discussion

Highly resistant (benzylpenicillin MIC > 256 mg/L), beta-lactamase producing *N. meningitidis* isolates have been sporadically reported from Canada, South Africa, and Spain.⁴ However, beta-lactamase-negative *N. meningitidis* strains with increased benzylpenicillin MICs of > 0.06 mg/L have been isolated more commonly from the United Kingdom, Europe, Greece, South America, South Africa, Asia and the United States of America (USA). These relatively resistant *N. meningitidis* isolates have penicillin MICs ranging from 0.01 mg/L to 1 mg/L.⁴ Reduced susceptibility in these isolates is due to decreased binding of benzylpenicillin due to altered penicillin-binding proteins (PBP2 and PBP3).⁴

In 2008, 108 of 149 (72%) invasive *N. meningitidis* isolates submitted to the Australian National Neisseria Network demonstrated reduced susceptibility to benzylpenicillin (MICs 0.06–0.5 mg/L).⁵ To date, this is the first report of an invasive *N. meningitidis* isolate with a benzylpenicillin MIC >0.5 mg/L from Australia (personal communication, John Tapsall, National Neisseria Network Reference Laboratory).

The clinical significance of reduced penicillin susceptibility in *N. meningitidis* is unclear. Treatment failures and higher rates of complications have been observed, although administration of higher doses of penicillin has been reported as clinically effective.^{4,6,7,8} Several reports indicate that there is no association between invasive meningococcal disease with decreased susceptibility to penicillin and mortality.^{6,8} Current Australian guidelines recommend benzylpenicillin for the treatment of proven meningococcal meningitis, irrespective of penicillin susceptibility.⁹ Current USA recommendations for the treatment of bacterial meningitis¹⁰ recommend therapy with third-generation cephalosporins (ceftriaxone or cefotaxime) for meningococcal meningitis until susceptibilities are available, and recommends penicillin or ampicillin for *N. meningitidis* isolates with penicillin MICs of <0.1 mg/L and third-generation cephalosporins for isolates with MICs of 0.1–1.0 mg/L.^{10,11}

Decreased susceptibility to benzylpenicillin in invasive *N. meningitidis* isolates is now common in Australia,⁵ but fortunately benzylpenicillin resistance appears to be rare. This report highlights the importance of culture and susceptibility testing in invasive meningococcal disease, and of ongoing national surveillance for antimicrobial resistance in *N. meningitidis*.

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References

1. Clinical Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing. Twentieth Informational Supplement (CLSI) M100-S20. 2010;30(1):101.
2. Jelfs J, Munro R, Wedege E, Caugant DA. Sequence variation in the *porA* gene for a clone of *Neisseria meningitidis* during epidemic spread. *Clin Diagn Lab Immunol* 2000;7(3):390–395.
3. Pereira L, Harnett G, Chidlow G, Speers D. Prevalence of genosubtypes (*porA* types) of invasive meningococcal disease in Western Australia from 2000 to 2006. *Pathology* 2008;40(7):728–729.
4. Janda WM, Gaydos CA. *Neisseria*. In: Murray PR, Baron EJ, Tenover JC, Tenover FC, eds. *Manual of Clinical Microbiology*. Washington: ASM press; 2007 pp. 601–620.

5. Australian Meningococcal Surveillance Programme. Annual report of the Australian Meningococcal Surveillance Programme, 2008. *Commun Dis Intell* 2009;33(3):259–267.
6. Plessis M, Gottberg A, Cohen C, Gouveia L, Klugman K. *Neisseria meningitidis* intermediately resistant to penicillin and causing invasive disease in South Africa in 2001–2005. *J Clin Microbiol* 2008;46(10):3208–3214.
7. Hedberg ST, Fredlund H, Nicholas P, Caugant DA, Olcen P, Unemo M. Antibiotic susceptibility and characteristics of *Neisseria meningitidis* isolates from the African meningitis belt, 2000 to 2006: phenotypic and genotypic perspectives. *Antimicrob Agents Chemother* 2009;53(4):1561–1566.
8. Brown EM, Fisman DN, Drews SJ, Dolman S, Rawte P, Brown S, et al. Epidemiology of invasive meningococcal disease with decreased susceptibility to penicillin in Ontario, Canada 2000 to 2006. *Antimicrob Agents Chemother* 2010;54(3):1016–1021.
9. Antibiotic Writing Group. Central nervous system infections. Therapeutic guidelines – Antibiotic. 2006; version 13: pp 55–68.
10. Tunkel AR, Hartman BJ, Kaplan SL, Kaufman BA, Roos KL, Sceld WM, et al. Practice guidelines for the management of bacterial meningitis. *Clin Infect Dis* 2004;39(9):1267–1284.
11. Apicella MA. *Neisseria meningitidis*. In: Mandell GL, Bennett JE, Dolin R eds. Mandell, Douglas and Bennett's. *Principles and Practice of Infectious Disease*. Elsevier Churchill Livingstone 2010; pp. 2737–2752.