SPECIAL THEME – MENINGOCOCCAL DISEASE

Review of the evidence for prehospital administration of benzyl penicillin in meningococcal septicaemia – experience in Queensland.

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Vivienne Tippet BA, GradDipPsych, MPH
Director, Australian Centre for Prehospital Research,
Ambulance Service and Queensland University
Richard Bonham MBChB, DipObst, FANCA, FACEM
Medical Director, Queensland Ambulance Service

Abstract

Meningococcal disease is a rare but potential killer in both adults and children. Community acquired meningococcal disease is caused by a variety of serogroups of *Neisseria meningitides*. Of the five main subgroups, A, B, C, W135 and Y, serogroups, A and Y are rarely identified in Australia. Alternatively, Serogroup B accounts for the highest number of cases followed by serogroup C strains. Meningococcal infection causes two distinct clinical profiles, though dual presentations are not uncommon. The first, meningitis presenting alone, is the more common form of infection and requires urgent but not immediate medical treatment. Conversely the second presentation, meningococcal septicaemia, is considered a medical emergency. In Queensland, careful and detailed consideration of the evidence for introduction of benzyl penicillin for the prehospital treatment of meningococcal septicaemia has been conducted. Notwithstanding the seriousness of the septicaemic presentation, these reviews have resulted in the decision not to introduce this drug in the ambulance service at the time. This paper describes the reasoning behind these decisions.

Keywords: *benzyl penicillin; meningococcal disease; meningococcal septicaemia; prehospital care*

INTRODUCTION

In Queensland, careful examination of a variety of factors, including national and state-based epidemiology of meningococcal septicaemia and the published evidence base, were taken into consideration in determining the utility and efficacy of introducing benzyl penicillin into the emergency pre-hospital environment. In addition to the known national epidemiology, these factors included consideration of:

- transmission;
- chemoprophylaxis; and
- antibacterial anaphylaxis.

In Queensland, the most instructive data has been gleaned from routine disease surveillance sources. Routinely collected prehospital data unfortunately provides little evidence on which

Author(s): Vivienne Tippet and Richard Bonham

to calculate incidence and prevalence of meningococcal septicaemia. Invasive meningococcal disease is notifiable to Queensland Health by both laboratories and clinicians and data has been collected on the Notifiable Conditions database (NOCS) since 1993. In 1999, enhanced surveillance systems were implemented and Queensland Health published the first detailed report on the epidemiology, trends and implications for surveillance and control of the disease in June 2000.

Epidemiology

Meningococcal disease is a rare but potential killer in both adults and children. Community acquired meningococcal disease is caused by a variety of serogroups of *Neisseria meningitidis* [1]. Of the five main subgroups, A, B, C, W135 and Y, serogroups, A and Y are rarely identified in Australia. Alternatively, Serogroup B accounts for the highest number of cases followed by serogroup C strains. Meningococcal infection causes two distinct clinical profiles, though dual presentations are not uncommon. In Australia, serogroups A and Y are rarely identified. Group B accounts for the highest number of cases, followed by serogroup C strains. These two strains are believed to be the main cause of disease clusters. In recent years W135 has been known to cause a small number of cases. In this country, meningococcal disease is considered an endemic infection with cyclical peaks of incidence. Key features of the Australian experience with the disease over the last ten years include:

- a known seasonal peak in winter-spring;
- age groups 0-4 and 15-25 years have the highest incidence;
- diverse serogroup B phenotypes have predominated in all States and there have been no reports of hyperendemic disease;
- an increase in serogroup C disease occurred during the 1990's, particularly in NSW and in 1999 in Victoria. Cases of serogroup C infection were more common in adolescents and young adults; and
- phenotype C:2a:P1.5 was associated with outbreaks of cases in urban NSW affecting adolescents and young adults disproportionately. The increase in Victoria in 1999-2000 is associated with a new phenotype C:2a:P1.4,7 [2].

Mortality and Morbidity

Morbidity and mortality depend on pathogen, the patient's age and condition and the severity of the acute condition. The case fatality rate for meningococcal disease has remained relatively static in the post-antibiotic era. Twenty to fifty percent (20-50%) of patients who develop shock die from the disease [3]. *N. meningitidis* is reported to have a case fatality risk of around 9% [4]. Meningococcal septicaemia appears to have a case fatality rate ranging between 19 and 25%. Meningococcal meningitis plus septicaemia, from 10 – 12%, and in meningitis alone, less than 1% [5,6,7]. In Queensland, there were four (4) deaths were reported in 2000, a case fatality rate of 6.0%. Case fatality rates in Australia in 1999 and 2000 were 7.2% and 4.7% respectively [8].

International Prehospital Protocols

The prehospital diagnosis of meningococcal septicaemia is usually dependent on recognition of the characteristic non-blanching purpuric rash. However, up to 30% of cases start with a blanching pink rash which fades with pressure and then subsequently becomes haemorrhagic. Some patients do not exhibit the characteristic rash. Most clinical protocols stress that if there is a non-blanching rash in an unwell person, meningococcal septicaemia should be assumed and immediate treatment instituted since these patients may deteriorate rapidly, develop shock and circulatory collapse (e.g. Joint Royal Colleges Ambulance Liaison Committee Identification and Management for Ambulance Personnel [9]).

While there is some evidence of conflicting outcomes on the efficacy of prehospital antibiotic treatment for meningococcal disease, the bulk of the literature supports prehospital administration of penicillin. The PHLS Meningococcal Infections Working Group and Public Medicine Environmental Group in the United Kingdom “*strongly recommend that all GP’s should carry benzyl penicillin in their emergency bags*” [10] and this approach is mirrored by the Australian Guidelines. Despite this, studies have demonstrated that the administration of prehospital antibiotics by GPs in the United Kingdom is not as frequent as might be expected [11].

Several studies have demonstrated that patients with suspected meningococcal septicaemia who are given parenteral benzyl penicillin by general practitioners are 2.5 times less likely to die than those not given penicillin [12, 13]. It does appear that the greatest benefit of parenteral penicillin is seen in those who are the most ill, that is, those patients presenting with a haemorrhagic rash [14].

A large urban population-based study conducted in Spain [15] demonstrated that pre-admission antibiotic therapy had a significant protective effect (OR 0.2; 95% CI, 0.04-0.4). A Danish population-based cohort study [16] published in 2002 found that the efficacy of prehospital antibiotic treatment appeared to be:

- dependent on the quality of acute hospital care; and
- may vary with the serogroup.

Though there has been some debate in the literature about the potential of empirical benzyl penicillin obscuring microbial diagnosis [17], it is still generally recommended that antibiotics be commenced immediately where clinical suspicion of meningococcal disease is high. While giving penicillin before blood and CSF specimens have been taken is known to reduce the proportion of positive cultures, it is still possible to isolate meningococci from nasopharyngeal swabs to detect meningococcal DNA by polymerase chain reaction [18].

In late 2002 in the United Kingdom, the Ambulance Service Association (ASA) in collaboration with the Meningitis Research Foundation developed a resource for ambulance personnel to facilitate early recognition of meningococcal septicaemia. The resource document supported the prehospital protocol for administering benzyl penicillin to these patients [19]. The resource materials include advice about assessment, signs and symptoms, time-critical management and infection control.

The following benzyl penicillin dose regime is recommended by the UK Guidelines:

Table 1: Benzyl penicillin administration for meningococcal septicaemia

AGE	DOSE	VOLUME	
		IV	IM
		600mg/10ml	600mg/2ml
< 1 year	300mg	5ml	1ml
1-9 years	600mg	10ml	2ml
> 9 years	1200mg	20ml	4ml

However, the UK protocols *do not* include authorisation for paramedics to administer benzyl penicillin solely for meningococcal meningitis. Benzyl penicillin is only cleared for prehospital administration by paramedics in the presence of a non-blanching purpuric rash indicative of septicaemia.

No US prehospital protocols for ambulance administration of antibiotics could be located, however recommended prehospital management includes:

- evaluation and treatment for shock and hypertension with crystalloid infusion until euvolemic;
- consider seizure precautions and treat seizures according to the standard protocols;
- consider airway protection in patients with altered mental status; and
- for alert patients in a stable condition with normal vital signs, administer oxygen, establish IV access and transport rapidly to an Emergency Department.

MENINGOCOCCAL DISEASE IN QUEENSLAND

Case Definition

Queensland Health applies the following case definitions. Confirmed cases:

- isolation of *N. Meningitides* from an otherwise sterile body site; or
- detection of gram-negative intracellular diplococci in CSF or petechiae; or
- a positive meningococcal antigen test on CSF; or
- a positive polymerase chain reaction (PCR) test on CSF, blood or serum; or
- detection of meningococcal IgM in serum; or
- isolation of *N. Meningitides* from the conjunctiva in a patient with conjunctivitis.

Probable cases are defined by the presence of a clinically compatible illness with at least one of the following:

- a petechial or purpuric rash; or
- isolation of *N. Meningitides* from a throat swab; or
- close contact with a confirmed case.

Incidence and clinical presentation

In Queensland, the annual incidence of invasive meningococcal disease has remained between 1.9 and 3.2/100,000 population since 1993. This annual incidence translates to less than 100 cases per year and is comparable to that in the US, where rates range between 2-3 per 100,000 [20]. In 2000, there were 67 cases reported in the state. Of these cases, 88% were laboratory confirmed and 12% were deemed probable. In the same year, 40% of all cases occurred in children below the age of 10. The clinical presentation of these patients is described in Table 2 [21].

Table 2: Clinical presentation of invasive meningococcal disease in Queensland (2000)

CLINICAL PRESENTATION	NUMBER	PERCENT
Meningitis	23	34.3
Septicaemia	24	38.8
Meningitis + septicaemia	4	6.0
Unstated	6	9.0
Conjunctivitis	2	3.0
Bacteraemia	1	1.5
TOTAL	67	100

Prehospital intervention

In 2000, information from general practitioners was able to be retrieved by Queensland Health for sixty-one (61) of the 67 patients. Of the 2000 cohort, 42 (68.9%) were seen by a general practitioner prior to hospital admission and of this group, 7 (26%) were given antibiotics. The majority of cases seen in general practice settings reached hospital within 24 hours of the consultations, but six cases did not present to hospital until two or more days had elapsed.

No data is available from the Queensland Ambulance Service Ambulance Information Management System database on the number of patients with meningococcal disease who were seen by ambulance officers. Consequently, no estimate of the likely frequency of exposure to these cases where Queensland Ambulance Service is the primary provider can be made.

Community Vaccination Strategies

Queensland Health is currently rolling out a community vaccination initiative for Queenslanders aged 1 to 19. Over a three-year period, a staged vaccination program will involve vaccinating children aged 1 to 5 and secondary school students as a priority (2003), followed by primary school children (2004) [22].

OTHER FACTORS AFFECTING DECISION MAKING

Transmission and chemoprophylaxis

N. Meningitidis infection is thought to be transmitted by large droplets. The incubation period is between 2 to 10 days and patients with *N. Meningitidis* are rendered noninfectious by 24 hours of effective therapy. Risk of transmission is reportedly greatest in the first week of contact [23]. Contrary to popular belief, patients with meningococcal disease are not efficient transmitters of the meningococcus. Rather, the carrier who transmitted the organism to the patient in the first instance is more likely to transmit the meningococcus again [24]. Nosocomial transmission is reported to be uncommon. Lower respiratory tract infections

caused by *N. Meningitidis* may however present a greater risk of transmission than either meningococemia or meningitis, especially if the patient has an active, productive cough. Personnel who care for patients with a suspected *N. Meningitidis* infection can decrease their risk of infection by adhering to droplet precautions [25].

The quadrivalent A, C, Y, W-135 polysaccharide vaccine has been successfully used to control community outbreaks caused by serogroup C, however vaccines for serogroup B infections are thought to be several years away.

The level of variance in guidelines on chemoprophylaxis reflect uncertainty about the risk of meningococcal disease in health care workers. In a retrospective risk survey of health care workers in England and Wales [26], three pairs of primary cases plus health-care workers with secondary infections, were identified between 1982 and 1996. The authors estimated an attack rate of 0.8 per 100,000 health-care workers at risk which would constitute a risk 25 times greater than that reported in the general community. However, the authors conclude that the excess risk is small and inappropriate use of prophylactic antibiotics should be avoided.

While secondary cases of meningococcal disease are rare in Australia [27], secondary cases of *N. meningitidis* occur rapidly and the CDC advises post-exposure antimicrobial prophylaxis for personnel who have had intensive, unprotected contact with infected patients e.g. mouth-to-mouth resuscitation, ETI, ET management or close examination of the oropharynx. Prophylaxis administered later than 14 days after exposure is probably of limited or no value. The CDC recommends [28] either:

- rifampin 600mg orally every 12 hours for 2 days is effective in eradicating nasopharyngeal carriage of *N. meningitidis*; or
- when infections are caused by rifampin-resistant meningococci, or rifampin is contraindicated, ciprofloxacin 500mg orally and ceftriaxone 250mg intramuscularly in single-dose regimens.

Antibacterial anaphylaxis

No specific reports of anaphylaxis following prehospital benzyl penicillin administration for suspected meningococcal septicaemia could be located in the literature. However, MIMs notes that anaphylaxis is more frequent following parenteral therapy, though it has been reported in patients on oral therapy. MIMs recommends:

“Before commencing therapy with any beta-lactam antibiotic, careful enquiries should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other allergens. If a hypersensitivity reaction occurs, appropriate therapy should be instituted and benzyl penicillin therapy discontinued. Serious anaphylactoid reactions require emergency treatment with adrenaline. Oxygen, intravenous steroids and airway management including intubation, should also be administered as indicated.” [29]

In patients with a known hypersensitivity to penicillin or a previous anaphylactic response, Australian Meningococcal Disease Guidelines recommend that:

“Benzyl penicillin should be withheld only if an individual has a clear history of either an anaphylactic or an immediate hypersensitivity reaction ... Most people with a penicillin allergy do not have such a history and they can safely be given benzyl

penicillin... some general practitioners have access to ceftriaxone. Ceftriaxone is an acceptable alternative to benzyl penicillin for the empirical treatment of suspected meningococcal disease prior to transfer to hospital.” [30]

CONCLUSION

The general consensus that pre-admission benzyl penicillin improves the outcome of *N. Meningitis* infection is acknowledged. However, the number of annual incident cases in Queensland has remained relatively static over time. Queensland reports less than 100 cases annually (67 in 2000). It is known that in 2000, 38.8% of patients presented to acute care with septicaemia. These patients are most at risk of adverse outcomes without the earliest possible administration of antibiotics. However, in the same year, approximately 70% of all incident cases were seen by GP's prior to hospital admission. State statistics do not differentiate the numbers of patients who presented directly to Emergency Departments and no specific data is available on cases who had a primary response from Queensland Ambulance Service. However, it was deemed reasonable to assume that only a small number of cases would be seen by Queensland Ambulance Service without prior medical attention.

It is probably equally reasonable to assume that most cases in which Queensland Ambulance Service has been the sole prehospital provider, would reside in rural or remote locations without immediate access to medical attention. Were this able to be demonstrated, then the case for administration of antibiotics by ambulance officers could be argued on the basis of equitable and timely access to treatment. However, the inabilities of current routine ambulance data collections to report suspected meningococcal septicaemia make this argument difficult to sustain.

Data currently collected on the Queensland Ambulance Service Ambulance Report Form does not generate information of relevance to determining the frequency of Queensland Ambulance Service exposure to cases of meningococcal disease. Determining the incidence of cases which could benefit from prehospital antibiotics would therefore have to be generated by the conduct of a specific longitudinal study. Given the number of incident cases in the State, such a study would be likely to be protracted and would require ethical clearance to follow these patients through their acute hospital experience to determine outcomes.

Notwithstanding the severity of septicaemic meningococcal disease and the fact that these patients are in acute need of antibiotic therapy and medical attention, for the small number of cases in which Queensland Ambulance Service would be likely to be the primary provider, the cost-benefit of securing the drug for administration by ambulance officers¹; shelf-life of the agent (once reconstituted these agents must be used immediately and in dry form would be expected to have a shelf life of up to thirty-six (36) months); and development and delivery of an education package to support implementation, makes introduction of antibiotics in Queensland contraindicated at this time. The inability to identify cases from routine prehospital data collection methods also hinders accurate calculation of the Services likely primary exposure to these cases.

Of particular concern for the prehospital sector is the lack of frequency with which established protocols and guidelines for the identification, management and control of meningococcal septicaemia fail to provide specific guidance for prehospital practice and infection control. The development of ambulance protocols for antibiotics in the UK reflects

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¹ At the time of writing benzyl penicillin 600mg box of 5 vials \$8.15 plus GST; Ceftriaxone 1g vial \$4.99 plus GST

both the epidemiology of the disease (2,500 cases and 246 deaths in 1997) as well as the nature and configuration of the National Health System (NHS). These factors are demonstrably different in Queensland where the prevalence has remained static at around 65 cases per year, 39% of which have a septicaemic presentation.

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