Mortality in severe meningococcal disease

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Abstract

Aim—To evaluate mortality of critically ill children admitted with meningococcal disease.

Methods—Prospective study of all children admitted to a regional paediatric intensive care unit (PICU) between January 1995 and March 1998 with meningococcal disease. Outcome measures were actual overall mortality, predicted mortality (by PRISM), and standardised mortality ratio.

Results—A total of 123 children were admitted with meningococcal disease. There was an overall PICU mortality of 11 children (8.9%). The total mortality predicted by PRISM was 24.9. The standardised mortality ratio (SMR) was 0.44. Results were compared with those from four previously published meningococcal PICU studies (USA, Australia, UK, Netherlands) in which PRISM scores were calculated. The overall PICU mortality and SMR were lower than those in the previously published studies.

Conclusion—Compared with older studies and calibrating for disease severity, this study found a decrease in the mortality of critically ill children with meningococcal disease.

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Meningococcal disease (caused by *Neisseria meningitidis*) has long been a feared killer of previously well children. In population based studies, including all ages, the overall mortality for meningococcal disease was found to be around 7%.^{1,2} In a recent review of hospital admissions, a hospital mortality of 20% in children with meningococcal disease was reported.³ The reported mortality of children who are admitted to intensive care with meningococcal disease varies between 14.5% and 35%.⁴⁻⁸ As a result of regional variations in incidence of meningococcal disease, its role as a cause of death within a paediatric intensive care unit (PICU) varies between units.

Quantitative, unbiased methods of assessing risk of mortality have important applications in paediatric intensive care. They can be used to discriminate between different levels of disease severity, or to separate patients into different groups for treatment when determining the effects of treatment regimes. Standardised severity scores allow comparison of clinical outcomes between two or more groups of patients differing in time or in place. PRISM (paediatric risk of mortality score), developed

more than 10 years ago, is such a scoring system for predicting risk of mortality and can be used to assess the severity of disease in the paediatric intensive care population.⁹ It uses 14 physiological variables to prognosticate a risk of mortality/death. Its reliability in predicting mortality and severity of illness has been evaluated and validated in a large number of intensive care units in Europe and the USA.⁹⁻¹¹

A retrospective review of meningococcal disease between 1957 and 1987 found the mortality rate rose from 10% to 16%, though when allowance was made for disease severity the fatality rate was unchanged with time.¹² To evaluate whether there has been a recent improvement in mortality from this disease, we studied all children presenting to a regional intensive care unit with meningococcal disease over a 38 month period.

Methods

All children presenting consecutively with meningococcal disease to a regional PICU at an academic children's hospital over a 38 month period (January 1995 to March 1998) were studied prospectively. This study was reviewed and approved by our local research ethics committee. The diagnosis of meningococcal disease was made on the basis of microbiological confirmation of meningococcal disease (positive blood culture or polymerase chain reaction test), or clinically (features of infection with characteristic meningococcal purpuric rash, in absence of microbiological evidence of other infecting organisms).

The PRISM predicted mortality for each patient was calculated according to the original description by Pollack and colleagues,⁹ after conversion to the locally used SI units.

We compared our PRISM predicted mortality and actual mortality results with those from four other previously published studies in which PRISM scores or PRISM predicted mortality had been calculated.^{4,6,7,13} We calculated the standardised mortality ratio (actual mortality/PRISM predicted mortality) for these four published studies as well as our own study.

STATISTICAL ANALYSIS

Results are given as mean and range or 95% confidence interval (95% CI).¹⁴ A receiver operating characteristic (ROC) curve was constructed to relate the sensitivity (correct prediction of death) of the mortality prediction model to its specificity (correct prediction of survival). The area under the ROC curve (A_c) was calculated.¹⁵

Results

A total of 123 children (61 girls) were admitted to the PICU with a diagnosis of meningococcal

Table 1 Predicted and actual mortality stratified by PRISM (paediatric risk of mortality) for subsets of predicted risk of mortality

Predicted risk of death	Number of patients	PRISM predicted mortality	Actual mortality	Standardised mortality ratio*
<5%	54	1.26	1	0.79
5–10%	18	1.36	0	0
10–30%	22	4.15	1	0.24
30–50%	10	3.99	1	0.25
>50%	19	14.12	8	0.57
Total	123	24.88	11	0.44†

*Actual mortality/PRISM predicted mortality.

†95% CI: 0.17–0.71.

disease between January 1995 and March 1998. The median age of the children was 28 months (range 2 months to 16.9 years), though there was a bimodal distribution, with the highest peak at 6 months of age and a smaller secondary peak of incidence at 14 to 15 years. Three children had meningococcal meningitis alone (one of these presenting late to the intensive care for management of subdural effusions), 60 had meningococcal sepsis without meningitis, 59 had meningococcal sepsis and meningococcal meningitis (clinical signs of meningism, lumbar punctures not done), and one child had meningococcal pericarditis alone.

Of the the 123 children, 100 (95% CI: 92 to 109) or 81.3% were ventilated, and 89 (95% CI: 79 to 99) or 72.4% were treated with inotropes. Fifty nine children (48%) had microbiologically confirmed meningococcal disease (definite); the remainder were diagnosed on strict clinical criteria. The length of PICU stay ranged from discharge on the day of admission up to 27 days, with a median of 4 days and a mean of 4.9 days. One child was sent for extracorporeal membrane oxygenation as a consequence of severe acute respiratory distress syndrome.

Overall PICU mortality for meningococcal disease was 11 (95% CI: 4.7 to 18.4) of the 123 children (8.9%). The total mortality predicted for the group, by PRISM,⁹ was 24.9 (95% CI: 18.3 to 31.5). The standardised mortality ratio for our 123 PICU patients with meningococcal disease was 0.44 (95% CI: 0.17 to 0.71).

Table 1 shows the predicted and actual mortality when stratified by PRISM for subsets of predicted risk of mortality. The area under the ROC curve for the PRISM score in the 123 patients with meningococcal disease was 0.87 (95% CI: 0.76 to 0.97). Table 2 shows the PRISM predicted mortality, actual mortality,

Table 2 PRISM (paediatric risk of mortality) predicted mortality, actual mortality, and standardised mortality ratio (PRISM predicted mortality/actual mortality) contrasted with previously published series

Author	Years of study	Total number of patients	PRISM predicted mortality	Actual mortality	Standardised mortality ratio
Algren <i>et al</i> ⁸	1979–1984	62	9.1	9	1.00
Kentucky, USA	1988–1991				
Mok and Butt ⁶	1985–1992	35	14.4	12	0.83
Melbourne, Australia					
Nadel <i>et al</i> ¹³	Published 1996	98	23	18	0.78
London, UK	Over two years				
Van Brakel <i>et al</i> ⁷	1988–1993	53	15.4	10	0.65
Utrecht, Netherlands					
Current series	1995–1998	123	24.9	11	0.44
Merseyside, UK					

and standardised mortality ratios contrasted with previously published series.^{4 6 7 13}

Discussion

In studying 123 children with meningococcal disease admitted to the regional intensive care unit, we found an overall PICU mortality of 8.9% and a standardised mortality ratio of 0.44, which is lower than in previously published studies.

Scoring systems are used to discriminate between different levels of disease severity. Severity scores allow comparison of clinical outcomes between chronologically or geographically different groups of patients. Many different scoring systems are available. Numerous disease specific scores have been developed for meningococcal disease.³ PRISM and the more recently developed PIM (paediatric index of mortality)¹⁶ were both developed to predict the risk of death of children during intensive care admission. Both PIM and PRISM give a risk of mortality. This contrasts with meningococcal disease specific scores (for example, Glasgow meningococcal sepsis prognostic score,¹⁷ Stiehm and Damrosch score,¹⁸ Niklasson score¹⁹) which produce an arbitrary number. PIM has an advantage, being a point of first contact score, whereas PRISM uses data from the first 24 hours of PICU admission, when a high proportion of the deaths occur. PIM is a more contemporary scoring system and so during development has been calibrated to the more recent lower mortality rates, whereas the original PRISM was calibrated using children treated during the 1980s. PRISM has subsequently been recalibrated (PRISM III)²⁰ to take more recent changes in mortality into account. In our study PRISM has been chosen, because the past employment of PRISM allows its utilisation for comparison with previously published studies.

Previous studies have shown the reliability of PRISM in predicting the outcome of children admitted to intensive care units.^{4 9 10 21} Although in applying an “all comers” score to selected patients we may be using the score improperly, earlier studies of children with meningococcal disease have shown that PRISM reliably discriminated the severely ill children from those less ill, and that the actual and predicted mortality was the same or very close.^{4 6 10 11} The discriminatory performance of a test is better assessed by the area under the ROC curve.¹⁵ Our finding of an area under the ROC curve of 0.87, close to that of Van Brakel *et al* of 0.94,⁷ indicates the good overall discriminatory performance of the PRISM score for mortality prediction in paediatric patients with meningococcal disease.

Regional differences in the incidence of children with meningococcal disease presenting to the PICU, as well as differences in the severity of illness, confound comparisons between units and studies. To overcome this we used a standardised and validated severity of illness scoring system (PRISM) to predict mortality⁹ and compared it to the actual mortality, giving a standardised mortality ratio. When risk of mortality was calculated using PRISM, we

found that the actual mortality was lower than predicted by PRISM (tables 1 and 2). The suggestion that our overall mortality is low as a consequence of admitting less ill children for observation is refuted by the high proportion (81%) who required ventilation and by their PRISM scores (table 1).

The diagnostic criteria for meningococcal disease varied in the studies we reviewed from only culture or antigen proven,^{6,7} to a combination of culture proven, antigen or antibody positive, or strict clinical criteria.^{4,13} This should not influence comparison, as the PRISM scores and calculated standardised mortality ratios take any variation in the range of disease severity into account.

In some of the reviewed studies the number of meningococcal patients treated per year was relatively small.^{6,7} It can be argued that this relative paucity of exposure within these units could influence the treatment and therefore the mortality. It has been recognised in medical practice that improvement in outcome may reflect a relation between quantity and quality.^{11,21-23}

We used a validated risk of mortality/severity scoring system (PRISM) to assess standardised mortality ratios in studies spanning the past two decades and found a steady decrease in the mortality of critically ill children with meningococcal disease. This supports the proposition that we are seeing a true reduction in mortality from severe meningococcal disease, and not just a change in referral practice or in disease severity.

This study has shown a steady improvement in mortality from severe meningococcal disease with time. In trials of new therapies in meningococcal disease, a reduction in mortality when compared to historical controls does not accurately reflect treatment effect. Historical controls are inappropriate in studies of severe meningococcal disease. This reinforces the requirement for prospective randomised controlled trials. The recent decline in mortality will also make it difficult for current and future trials to show significant decreases in mortality outcomes, a fate suffered by the recent rBPI₂₁ trial.²⁴

Why the mortality should have declined is less obvious. Trials of new therapies in meningococcal disease have proven disappointing so far in that none have produced a significant reduction in mortality.²⁴⁻²⁷ Certainly in the UK over the past 5–10 years there has been heightened public and medical awareness of meningococcal disease. This has most probably impacted on earlier recognition and therefore earlier appropriate management and treatment of the disease. Improved management in accident and emergency departments and referring hospitals undoubtedly enhances the clinical status of this patient group on presentation to the PICU or its retrieval team. However PRISM scores calibrate for disease severity and thus would take this factor into account. Yet there still has been a steady improvement in PRISM derived standardised mortality ratios over recent times, as shown by this study. The reduction of PICU mortality

reflects general improvements in paediatric intensive care and is most probably multifactorial: regionalisation of care, increasing resources, better organisation, experienced paediatric intensivists, trained specialised PICU retrieval teams, closer communication with referring hospitals, and possibly more aggressive treatment regimes.

Although we have shown a reduction in standardised mortality ratios when we compare our results with previously published studies, the mainstay of therapy must be prevention. It is heartening that since the introduction of the conjugated meningococcal C vaccine, the incidence of serogroup C has declined in the groups vaccinated, in the face of an increase in serogroup B disease.²⁸ We await the introduction of an effective meningococcal B vaccine.

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Dummies

There are some aspects of child rearing which are hardy perennials; they include teething, circumcision, thumb sucking, and dummies (pacifiers). Dummies have attracted their fair share of emotion, being regarded by some with disdain or even disgust. The World Health Organisation is against them on the grounds that they lead to early weaning. Observational studies have shown that babies with dummies are weaned earlier but cannot demonstrate cause and effect. Now a randomised trial in Montreal (Michael S Kramer. *Journal of the American Medical Association* 2001; **286**:322–6) has suggested that dummy use does not cause early weaning.

They studied 281 healthy, breast-feeding, mother–singleton infant pairs who were randomised to receive nurse counselling with (experimental) or without (control) advice on avoiding use of a dummy and on the use of alternative comforting methods (breastfeeding, carrying, rocking). Two hundred and fifty eight mother–infant pairs completed the study.

Dummy use was decreased in the experimental group (total avoidance 39% *v* 16%, daily use 41% *v* 56%). The rate of weaning by 3 months, however, was not significantly different between the two groups (18.9% *v* 18.3%) and dummy use had no significant effect on daily duration of crying or fussing at 4, 6, or 9 weeks. When randomised group allocation was ignored, dummy use was strongly associated with earlier weaning (weaning by 3 months: 35% (daily dummy users) *v* 13% (nonusers)).

Counselling can reduce the rate of dummy use but does not affect the rate of early weaning. It seems likely that mothers who use dummies may be more inclined to wean early but that dummy use is a consequence rather than a cause of this inclination.

Parents like dummies. Even in the group counselled against using them, over 60% of mothers used them. This study suggests that dummy use may be a predictor but not a cause of early weaning. The authors write that breastfeeding promotion programmes and international agencies should re-examine their staunch opposition to dummies.

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