Mortality in meningococcal disease: please report the figures accurately

We read with great interest the two recent articles on mortality in meningococcal disease.1,2 While we would agree with the message contained in both articles, namely that the mortality associated with this condition has decreased with time, we have serious concerns regarding the presentation of the data in the paper from the St Mary’s group.

Booy and colleagues report a crude mortality of 2% for the year 1997,3 a figure that has generated considerable media interest. Several reasons are cited for this falling mortality: the provision of mobile intensive care, meticulous attention to stabilising the patient prior to arrival in the district hospital, and the existence of a specialist “sepsis” intensive care unit. However the way in which the mortality data are presented and the statistics are computed are misleading and provide an inaccurate picture of the outcome for severe meningococcal disease. The figures were calculated without applying the well established mortality prediction model (PRISM) on their data. Furthermore, mortality rates from individual intensive care units or time periods are difficult to compare even using mortality prediction models.

Mary’s group present their data in a similar manner. In 1997 2% of deaths occurred before PICU retrieval, prior to admission to the PICU. Mary’s series includes mortality rates determined by the use of mortality prediction models, without reassurance that the same threshold for admission was applied. Second, has this trend continued in subsequent years? This question cannot be answered by the surveillance data included in the paper. It is our impression that the St Mary’s retrieval team has occasionally admitted patients who die before admission to the PICU. This is quite misleading and potentially dangerous for the management of the severely ill infant.

Table 1 Mortality data for severe meningococcal patients retrieved to Guy’s Hospital January 1998 to November 2001

<table>
<thead>
<tr>
<th>Time to death from retrieval</th>
<th>1998</th>
<th>1999</th>
<th>2001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths prior to team arrival</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Time to death from PICU team arrival</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 6 hours</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>6 to 12 hours</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>12 to 24 hours</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Greater than 24 hours</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total PICU deaths</td>
<td>4</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Total survivors</td>
<td>40</td>
<td>45</td>
<td>56</td>
</tr>
</tbody>
</table>

It is our impression that the St Mary’s retrieval team is hailing their improved survival rates as a potential cause of decreased mortality. The paper by Booy et al contains no reassurance on this issue and no information is given about the performance of the mortality prediction model (PRISM) on their data. Furthermore, their series includes mortality rates from individual intensive care units or time periods that appear to exclude the deaths occurring during retrieval. This despite the fact that the quality of retrieval is haled as a potential cause of decreased mortality. Booy et al provide reassurance by quoting a consistently high rate of ventilation in the reported cases and detailed information on the performance of the mortality prediction model. Hence if there has been a decrease in the threshold for admission it has been accompanied by an increased use of ventilation and perhaps other interventions. It is not clear whether the data from the north west include deaths during retrieval, prior to admission to the PICU.

Both series significantly outperform the expected mortality predicted by PRISM which is not surprising and calls into question the use of the model. Convincing evidence of a fall in mortality for meningococcal septic shock however requires a uniform definition of the illness and “all cause” mortality data from a geographically defined resident population. The regional arrangement for delivery of paediatric intensive care in the north west of England combined with the factors mentioned above make it far more likely that Booy et al have indeed detected a true improvement in survival for this condition. Since 1996 there has been a trend for more
children to receive intensive care in lead centres\(^1\) and this might be expected to reduce mortality across the board.

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References

Improved outcome in severe meningococcal disease

We thank Tibby et al and Pearson for their interest in our paper.\(^1\) We agree with Pearson that evidence for a fall in overall mortality in meningococcal septic shock would require a geographical community based study. We described mortality in severe meningococcal disease in a paediatric intensive care unit (PICU).

In our multispecialty PICU in the north west, we have observed a continued decrease in both actual PICU mortality and mortality attributable to disease severity since the original study period (table 1). Paediatric index of mortality (PIM) is a more contemporary scoring system than PRISM (paediatric risk of mortality score), and so has been calibrated to the PICU population. PIM gives a score at point of first PICU contact.

This general trend of improving meningococcal outcome is also reflected in other PICUs. As shown by the results from St Mary’s PICU in London, where in a group with an overall actual mortality of 18.7% (PICU mortality for the study period being 10%), and an additional 8.7% mortality for the “untreatable”, they encouraged and managed to reduce the meningococcal PICU mortality in their “specialist PICU” from 23% to 2% (1992–97).\(^2\) Tibby et al, from Guy’s Hospital PICU in London (1998–2001), in their letter report a similar very low mortality rate.

There has been continued improvement in outcome from severe meningococcal disease throughout the UK. Early recognition and early institution of treatment are of paramount importance. No single centre holds the monopoly on the improved outcome in meningococcal disease. Although improved intensive care has undoubtedly contributed to this fall in mortality, there should be more recognition of the role of those in the community, parents and carers, general practitioners, and district general hospitals who have significantly contributed (and continue to contribute) to the survival of these critically ill children.

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Table 1

<table>
<thead>
<tr>
<th>Year</th>
<th>Actual mortality/PICU admissions</th>
<th>Mortality per year</th>
<th>PIM predicted SMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995–1998</td>
<td>11/123 (8.9%)</td>
<td>3/95 (3%)</td>
<td>0.16</td>
</tr>
<tr>
<td>1999–2001</td>
<td>3/5</td>
<td>1.5</td>
<td>0.24</td>
</tr>
</tbody>
</table>

SMR = paediatric index of mortality (PIM) predicted mortality/actual mortality.

Genuine reduction in meningococcal deaths results from teamwork

As paediatric intensivists in lead centres accredited for paediatric intensive care (PIC) training and responsible for the care of approximately 7000 cases per year, we read with concern the report from St Mary’s Hospital which reported improved outcome of meningococcal disease (MD) in 1997 compared with previous years.\(^1\)

Their reported reduction in mortality must be seen in the context of an overall reduction in childhood mortality of a wide nature and improvement in the outcome for many conditions requiring PIC such as acute respiratory failure,\(^3\) persistent pulmonary hypertension\(^4\) and complex congenital heart defects.\(^5\) Overall UK PIC mortality rates have fallen to a standardised mortality ratio (SMR) of 0.87 as assessed by the Paediatric Index of Mortality\(^6\) compared with the model generated in 1994.\(^7\)

Their application of the severity of illness score (PRISM) is incorrect. No patient has a 100% predicted risk of mortality and therefore all deaths observed in any such study must increase the SMR. The exclusion of nearly half of the total deaths (29/62, 47%) who did not survive the long stabilisation and overall retrieval times must reduce SMR regardless of any other intervention. Whilst inclusion of these cases does not alter the direction of the relationship between SMR and year, it raises the overall mortality in the series towards 20% and more than doubles the headline mortality in 1997. Data from the last 4 years would be of interest. In addition, the lack of any data relating to the performance of the model in different risk groups fails to address the potential confounding factor of disease severity. Since all survivors will reduce SMR, one cause of apparent improvement in risk-adjusted survival is increased admission of low risk cases.\(^8\)

Figure

Actual and predicted annual case fatality rates

References
Recent series from other institutions have followed the convention of presenting data by level of predicted risk. The claim that their “Mobile Intensive Care” service is the key element in improved survival is confusing when all the cases that died under the care of this service were excluded from both the analysis and the “headline” figure of 2% mortality for MD. However, our greatest concern is the claim that these data support their particular “model” of care of critically ill children. This is not consistent with their report, as St Mary’s had been performing transports since 1992 but the fall in mortality occurred some 4–5 years later. It should be remembered that PICU retrievals have been performed in Liverpool and Glasgow since the late 1970s. Their claim that this “model” has reduced mortality of meningococcal disease is also inconsistent with the similar improvements in outcome presented by other PICUs.

We feel the narrow focus of the paper on the ICU care of MD is misleading. It ignores the important contribution of many others including parents, charities, and healthcare workers. Their role in education, early identification, treatment, and immediate high quality resuscitation is discounted. To imply that ICU management after the initial resuscitation is the key factor in improved survival undermines the vital contributions of these groups.

We read with disappointment the response of Dr Peters and colleagues1 to our article “Reduction in case fatality rate from meningococcal disease associated with improved healthcare delivery. The key factor in improved survival is the increased experience in meningococcal disease into clinical trials. As a large number of critically ill children were referred to our unit, we were able to record high-quality data regarding clinical status, severity of illness and outcome. We began to demonstrate a reduction in mortality from 1994 onwards, as it takes time to establish the clinical experience which can have a significant impact on the disease process.

The unit at St Mary’s has been greatly involved in the development of a model of care involving “genuine teamwork” with the aim of improving the healthcare of children with MD. To this end we have been working with the meningitis charities which are acknowledged on the paper for their early involvement. We have applauded our efforts. We believe, and have repeatedly stated, that what has been achieved by multidisciplinary effort involving “genuine teamwork” with the aim of improving the healthcare of children with MD, could only have been achieved by multidisciplinary effort involving all sectors of health care delivery.

References


Why do infants being treated for acute lymphoblastic leukaemia fail to thrive?

Figure 1 shows the weight gain of five infants treated for acute lymphoblastic leukaemia (ALL) in relation to centile charts, which were treated at the Yorkshire Regional Centre for Paediatric Oncology and Haematology from 1996 until the present. Patients 1–4 were treated in accordance with the MRC UKALL Infant 1 chemotherapy protocol, and patient 5 in accordance with Infant 99.

The most striking aspect is that from diagnosis to end of intensive therapy (approximately week 40 of treatment), the first four patients, despite aggressive nutritional support, failed to thrive, with two requiring long term total parenteral nutrition (TPN) during maintenance therapy in order to rectify this. Patient 5, in contrast, thrived during treatment.

The infants treated on the MRC UKALL Infant 1 protocol all had grade III/IV gut toxicity following intensive therapy, resulting in the infants being highly catabolic; although some weight gain was achieved with TPN, it was difficult to sustain this increase with enteral feeding.

It became apparent that patients not fully weaned at diagnosis showed a severe delay in feeding skills, becoming orally defensive, resulting in a grossly inadequate solid intake throughout intensive treatment, which continued into maintenance therapy. The only patient to continue normal feeding development was patient 4, who was 36 weeks at diagnosis, and fully weaned.

Patient 5, like the others diagnosed under 30 weeks old, had delayed feeding skills, taking virtually no solids or feed orally. However, she did not show such severe gut toxicity. She was fed an amino acid based formula (Neocate, ShS International Ltd, UK) since induction therapy.

The failure of infants with ALL to thrive may be consequent on severe gut toxicity, length of treatment, and failure of weaning. The improved outcome of patient 5 may be the result of use of a different chemotherapy protocol, which included dexaxomesamine.

A second possibility is the early introduction of an amino acid based formula, which is a source of L-glutamine, an important nitrogen source for enterocytes, which plays a key role in maintaining mucosal cell integrity and gut barrier function. It may be that exposure to a continuous low dose of glutamine throughout intensive chemotherapy helped to reduce the severity of mucositis.

References
Growth charts for height and weight—statement

The recent review by Professor Noel Cameron was, at least in our view, the most balanced of a number of reports published in recent times.

The fact that Cameron is a regular contributor to this journal, and that he has turned his attention to the subject of growth charts, is the latest in a series of articles, reviews, and publications stretching back over a number of years which uses either one or both of the above stated charts as references when discussing as being widely used in hospitals, departments of paediatrics, community health departments, and academic institutions.

We say “once again surprised”, as Professor Cameron’s review, despite being so well balanced, is the latest in a series of articles, reviews, and publications stretching back over a number of years which uses either one or other, or both, of the above stated charts as references when discussing or comparing growth charts. Indeed, one or two of these previously published articles have been wholly misleading, comparing as they did the British 1990 reference with the above, while at the same time failing to mention the introduction of the updated Buckler–Tanner (1995) (Castlemead Reference 11B and 12B) charts still appear to be readily available is indeed a source for concern, as none of the former have been produced or sold by ourselves for an absolute minimum of 15 years (our sales records go no further back), while the latter has neither been produced or sold for a period of some seven years. In short, Castlemead fully accept that the Tanner Whitehouse Takiishi (1966) and Tanner Whitehouse (1976) charts are long since obsolete, and should play no part in any considerations respecting growth charts for height and weight. Given the above, we are at a loss to understand why these two charts continue to appear as subjects for review.

In an attempt to draw this particular issue to a close, Castlemead is prepared to offer any hospital, department of paediatrics, community health department, or academic institution still holding stocks of either the Tanner Whitehouse Takiishi (1966) or Tanner Whitehouse (1976) (Castlemead Reference 11A and 12A) a “new” for “old” replacement of their stock with the updated Buckler Tanner (1995) growth charts (Castlemead Reference 11B and 12B).

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References

Juvenile dermatomyositis associated with hereditary angioneurotic oedema

Juvenile Dermatomyositis (JDM) is a chronic inflammatory disease probably of an autoimmune nature. Hereditary angioneurotic oedema (HANE) is an enzyme deficiency that results in the loss of inhibition of the classical complement pathway. This results in the consumption of classical pathway factors particularly C4. It is associated with some autoimmune diseases such as SLE. We report for the first time the occurrence of JDM in a child with HANE.

A 6 year old Caucasian boy with a family history of type 2 HANE presented with a 4 month history of a red, scaly rash on the back of his fingers and hands, on the dorsum of his feet and toes, on his knees, and above both eyelids. The rash appeared characteristic of JDM. He had difficulty in climbing stairs. Clinical examination revealed some weakness of the proximal muscles. Investigations included a raised creatine kinase of 3000 U/L (normal 50–150), a muscle biopsy typical of JDM, very low levels of C4 and C30, and confirmation of type 2 HANE with absent functional C1 inhibitor activity but raised immunochromatochemical levels. Complement C4 returned to normal levels after 2 months treatment with danazol but there was no change in the clinical or laboratory signs of dermatomyositis. Complete resolution of the clinical and biochemical signs of myositis occurred a short time after the introduction of prednisolone. The danazol was stopped but the prednisolone was continued. The reduction in serum complement C4 returned but there has been no clinical deterioration. Subsequently the prednisolone was stopped and there has been no flare of his JDM.

Interestingly the administration of danazol to patients with SLE and HANE has led to the reduction in complement consumption and thus normalisation of C4 levels in the classical pathway accompanied by resolution of the SLE. However no such effect was seen in our patient. The failure to alter the course of our patient’s JDM by restoration of the classical pathway components is interesting. It does not suggest that the aetiology of JDM is due to failure of clearance of immune complexes. However, it is possible that the uncontrolled classical pathway activation or acquired C4 deficiency may have contributed to the initiation of the disease.

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References