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 transfer to the district hospital and the existence of a specialist “sepsis” intensive care unit. However the way in which the mortality data are presented demonstrate several contradictions. Booy and colleagues purport that intensive care begins from the time the retrieval team is contacted, indeed they calculate PRISM mortality risk from this time, yet mortality is calculated only from those patients who physically arrive back in their own unit. It is well known that mortality from meningococcal disease is greatest in the first 6 hours, primarily from myocardial failure.1 To cull non-survivors before PICU admission thus creates a self-fulfilling prophesy.

To illustrate this, we present data from our own unit (Guy’s Hospital), which cover a similar geographical catchment area to St Mary’s. The table shows mortality data for the period January 1998 to November 2001, illustrating time of death after arrival of the retrieval team. For the sake of completeness we have also included the four deaths that occurred before the arrival of the team. Over this period we have undertaken 183 retrievals on patients with severe meningococcal disease; 147 (80%) of these required mechanical ventilation and/or inotropic support. 12% of these patients presented with meningitis alone, the remainder with septic shock. The overall crude mortality is 8.2% (15/183), which includes four patients who died before arrival of the retrieval team. Our death rate becomes comparable to that of St Mary’s if we exclude patients who die within 6 hours of the arrival time of death after arrival of the retrieval team. Our death rate is 5.4% (10/183), which may artifically reduce PICU mortality. We would therefore ask that the St Mary’s group present their data in a similar fashion, including retrieval times. Specifically, were the 29 deaths before physical admission to the PICU occurring whilst under the management of the retrieval team at the local hospital (and thus under PICU management, by their own definition)? If so, mortality should be adjusted accordingly. Second, has this trend continued in subsequent years? This disease attracts media and public attention and it is therefore vital that outcome data which are accessible to the public and may be used to influence service reorganisation be presented in a transparent manner.

<table>
<thead>
<tr>
<th>Table 1 Mortality data for severe meningococcal patients retrieved to Guy’s Hospital January 1998 to November 2001</th>
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<tbody>
<tr>
<td>1998</td>
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<tr>
<td>---</td>
</tr>
<tr>
<td>Deaths prior to team arrival</td>
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<tr>
<td>Time to death from PICU team arrival</td>
</tr>
<tr>
<td>Less than 6 hours</td>
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<tr>
<td>6 to 12 hours</td>
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<tr>
<td>12 to 24 hours</td>
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<tr>
<td>Greater than 24 hours</td>
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<tr>
<td>Total PICU deaths</td>
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<tr>
<td>Total survivors</td>
</tr>
</tbody>
</table>

Inter-unit comparisons are flawed

Mortality from meningococcal septic shock may be falling; however, it is difficult to be sure. Inter-unit comparisons of the sort precipitated by these articles and correspondence are inevitably distorted by confounding factors. These factors are not entirely removed by the use of mortality prediction models.

Historically, mortality data for meningococcal septicaemia from the UK Public Health Laboratory Service Communicable Disease Surveillance Centre have always shown a lower mortality rate than the many paediatric intensive care units. However, the comparison is regarded as inappropriate because the surveillance data include patients with positive blood cultures (septicaemia) who were not shocked and so would be expected to survive without intensive care. If one admits such patients to intensive care then both crude and standardised mortality are artificially reduced. Furthermore, mortality rates from individual intensive care units or time periods are difficult to compare even using mortality prediction models, without reassuring the same threshold for admission and intervention applies in each case. The paper by Booy et al contains no reassurances 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 which appear to exclude the deaths during retrieval. This despite the fact that the quality of retrieval is hailed as a potential cause of decreased mortality. Thorburn et al provide some 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.

PostScript

If you have a burning desire to respond to a paper published in ADC or FeN, why not write us a letter or an eLetter? Log on to our website (www.archdischild.com), find the paper that interests you, click on “full text” and send your response by email by clicking on “submit a response”. Providing it isn’t libellous or obscene, it will be posted within seven days. You can retrieve it by clicking on “read eLetters” on our homepage. The editors will decide, as before, whether to also publish it in a future paper issue.

References
children to receive intensive care in lead centres 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. 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 multiplicity PICU in the north west, we have observed a continued decrease in both actual PICU mortality and mortality adjusted for 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 study period (table 1). Paediatric index of mortality (PIM) predicted mortality/actual mortality. SMR = paediatric index of mortality (PIM) predicted mortality/actual mortality.

Table 1

<table>
<thead>
<tr>
<th>Year</th>
<th>SMR</th>
<th>PIM predicted SMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1992/93</td>
<td>1.16</td>
<td>0.24</td>
</tr>
<tr>
<td>1994</td>
<td>1.5</td>
<td>0.3</td>
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<tr>
<td>1995</td>
<td>1.5</td>
<td>0.3</td>
</tr>
<tr>
<td>1996</td>
<td>1.5</td>
<td>0.3</td>
</tr>
<tr>
<td>1997</td>
<td>1.5</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Since all survivors will reduce SMR, one cause of apparent improvement in risk-adjusted survival is increased admission of low risk cases.

Mortality in meningococcal disease: please report the figures accurately

We thank Tibby and colleagues for their interest. We believe they and others would be interested in the accompanying figure (see above).

It compares yearly case fatality rates on all referrals to St Mary's PICU, regardless of whether they died before a mobile intensive care team arrived or while the team was assisting with resuscitation. The 29 "outside" deaths are included (3 in 1992/3, 8 in 1994, 10 in 1995, 3 in 1996, 5 in 1997). As stated in our published paper, logistic regression analysis, controlling for disease severity, age and sex, and including these extra deaths, showed no change in the estimated odds ratio for the yearly reduction in death rate, namely 0.41. The overall case fatality rate for 1997 became 6% compared with the PICU admission rate of 2% and a predicted case fatality rate 34% using PRISM scores.

For the 5 deaths in 1997 outside St Mary’s PICU, response times between call to the unit and arrival of a team at the DGH varied between 100 and 185 minutes. One child died as the local hospital were telephoning us; two arrested within 90 minutes of St Mary’s being called and died within minutes of the team arriving, and the other two died between 2 and 7 hours after arrival.

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. Their reported reduction in mortality must be seen in the context of an overall reduction of childhood mortality in a wide range of conditions. Our centre experienced improvement in the outcome for many conditions requiring PIC such as acute respiratory failure, persistent pulmonary hypertension and complex congenital heart defects. Overall UK PIC mortality rates have fallen to a standardised mortality ratio (SMR) of 0.87 as assessed by the Paediatric Index of Mortality compared with the model generated in 1994. 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.
Recent series from other institutions have followed the convention of presenting data by level of predicted risk.1-3

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.1-3

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 did not claim that mobile intensive care is the key element in improved survival. What we stated was “Considerable changes in the management of patients with MD have occurred over the study period. While no single factor alone is likely to explain the reduction in mortality, several factors might have contributed to the improved outcome.” In the past, few centres, including those with PICUs, admitted more than a small number of patients with MD annually. Furthermore, patients were often considered too sick to transfer to a specialist centre and were treated in the A&E department, paediatric ward or adult ICU of the local district general hospital. Establishment of a mobile intensive care team allowed the centralisation of care of children with MD at a specialist clinical and research unit, which in turn enabled extensive experience in the management of MD to be developed; this may be the most important reason for the improved outcome. In other words, it was the increased experience in dealing with meningococcal disease that was the critical factor.

The role of mobile intensive care was more directly addressed when we stated that it “has probably been another important factor in improved outcome”, not the key factor.

The conclusions of our paper clearly state the multiple factors responsible for the results of the study, which have shown that a notable reduction in the case fatality rate for MD has been achieved.

The purpose of presenting our data was to emphasise the improvements in mortality in a particular group of patients brought about by a change in health care delivery. The key point being shared early intervention by a multidisciplinary team with a major research interest in the care of the critically ill child with infectious disease, who have the benefit of a “critical mass” experience.

The PICU at St Mary’s Hospital, London was established in 1992, at the time primarily to facilitate the enrolment of children with 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 as key research partners to develop guidelines, publish treatment algorithms and improve policies. In addition our research unit has played a key role in the design and implementation of clinical trials of adjunctive treatments in meningococcal disease, which has led to the publication of the only two large randomised, double blind, placebo controlled studies in childhood septic shock.

Finally we are humbled by the magnitude of response from many other colleagues who have applauded our efforts. We believe, and have repeatedly stated, that what has been widely accepted as a major advance in the treatment of meningococcal disease is that 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 as key research partners to develop guidelines, publish treatment algorithms and improve policies. In addition our research unit has played a key role in the design and implementation of clinical trials of adjunctive treatments in meningococcal disease, which has led to the publication of the only two large randomised, double blind, placebo controlled studies in childhood septic shock.4

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 chart positions, who 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 Interfant 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 (Necocate, 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 dexachetamine.

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. 1,4 It may be that exposure to a continuous low dose of glutamine throughout intensive chemotherapy helped to reduce the severity of mucositis.

References

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Osteogenesis imperfecta and intravenous pamidronate

Osteogenesis imperfecta (OI) is a chronic, disabling condition in which treatment with cyclical intravenous treatment with pamidronate can be useful for symptom relief, despite questions about long term safety. 1 A recent study 2 in this journal showed a decrease in bone turnover and gradual increase in bone density measurements without significant side effects, following such treatment in children affected with OI.

We wish to report our own experience in 10 children with OI who have received cyclical intravenous pamidronate (1 mg/kg/day for 3 days every three months). The median (range) age at the start of treatment was 9.1 (3.1–12.7) years. Treatment was initiated in the context of symptoms having an adverse effect on the quality of life, associated with evidence of decreased bone density assessed by dual energy x ray absorptiometry (DXA scan, QDR1000/W, Hologic systems, Boston, Massachusetts). 3

Five of these children were at the severe end of the symptom spectrum (requiring pain, multiple fractures, and impaired mobility). Four children were treated for pain and fractures, whereas one received pamidronate for pain only. After 1.8 (0.9 to 3.0) years of treatment, nine children were pain free. Four children had no further fractures and one child had improved mobility. The initial infusion of pamidronate was associated with flu like symptoms, fever, rigors, abdominal pain, or vomiting in six children. Serum calcium levels were low (<2.2 mmol/l) following therapy in six subjects, and three required treatment with calcium and vitamin D supplements.

Repeat DXA scans showed an increase in lumbar spine bone mineral content (BMC) standard deviation score (SDS) (fig 1), from −3.44 (−6.6 to −1.39) to −0.96 (−3.10 to 3.13) SDS following 1.3 (0.7 to 2.7) years of pamidronate treatment. This beneficial response to treatment was similar to that reported elsewhere. 1

In conclusion, our findings add to those of others that intravenous pamidronate infusion improves bone mineral density and reduces symptoms of severe pain, recurrent fractures, and impaired mobility in children with OI. There are minor acute side effects to the treatment, but long term safety needs to be determined.

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References


Growth charts for height and weight—statement

The recent review by Professor Noel Cameron 3 was, at least in our view, the most balanced of a number of reports published in recent times. 

The recent review by Professor Noel Cameron 3 was, at least in our view, the most balanced of a number of reports published in recent times. On reading the introduction and historical background to this article, we were once again surprised to find that the Tanner Whitehouse Takaishi (1966) and the Tanner Whitehouse (1976) height and weight charts (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 Takaishi (1966) and Tanner Whitehouse (1976) charts still appear to be readily available is indeed a source for concern, as none of the former have been produced or sold for 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 Takaishi (1966) and Tanner Whitehouse (1976) 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 Takaishi (1966) or Tanner Whitehouse (1976) (Castlemead Reference 11A and 12A) a “new” or “old” replacement of their stock with the updated Buckler Tanner (1995) growth charts (Castlemead Reference 11B and 12B).

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2 NHS Executive Child Health in the Community. A guide to good practice. 6.27.

Juvenile dermatomyositis associated with hereditary angioneurotic oedema

Juvenile Dermatomyositis (JDM) is a chronic inflammatory disease probably of an autoimmune nature. 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). 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 C3, and confirmation of type 2 HANE with absent functional C1 inhibitor activity but raised immunochromelical 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. 4 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
