Severity of meningococcal infections is related to anthropometrical parameters

N Perez, L Regairaz, J Bustamante, N Osimani, D Bergna, J Morales, M R Agosti, S Gonzalez-Ayala, C Peltzer, A Rodrigo

Arch Dis Child 2007;92:790–794. doi: 10.1136/adc.2006.104885

See end of article for authors' affiliations

Correspondence to: Nestor Perez, Unidad de Inmunología, Hospital de Niños Sor María Ludovica, 14 y 65, La Plata 1900, Argentina; disaper@netverk.com.ar

Accepted 20 April 2007
Published Online First
8 May 2007

Background: Invasive meningococcal infections remain an important cause of death in children. In addition, malnutrition has been classically associated with increased severity of infectious diseases. However, in our experience lethal meningococcaemia in clinically malnourished children is extremely rare. Our purpose was to determine whether there is an association between nutritional status and outcome in children with invasive meningococcal infection.

Methods: We carried out an observational study and prospectively determined anthropometrical parameters in 127 children aged 1 month to 4 years with invasive meningococcal infection seen in our inpatient facilities from August 1999 to May 2004. Severity and survival were the clinical end points analysed.

Results: Children with severe disease had higher weight for age (1.02 vs -0.19) and height for age (1.12 vs -0.58) z scores than those with non-severe disease. Non-survivors had higher weight for age (0.90 vs -0.16) and height for age (0.73 vs -0.57) z scores than survivors. Clinical and biological variables usually accepted as predictors of high mortality or severity in patients with meningococcal infection were not significantly associated with weight for age and height for age z scores.

Conclusion: In the present prospective series of children with invasive meningococcal disease, severity and death were linked to anthropometrical parameters and seemed to be associated with a very good nutritional status, which confirmed our previous uncontrolled observations.

Invasive meningococcal infections remain an important cause of morbidity and death in children, with case-fatality rates ranging from 6% to 15%.^{1,2} The reasons why only some individuals develop the most lethal form of invasive disease (ie, fulminant meningococcaemia) are not fully understood.^{1,3} Some inherited conditions, such as genetic polymorphisms in mannose-binding lectin and tumour necrosis factor (TNF) promoter, and FC- γ IIa heterogeneity and complement deficiencies (reviewed in Emonts *et al*), have been linked to increased frequency or severity of cases.

Malnutrition has been classically associated with increased frequency and severity of infectious diseases, particularly in the 0–4-year-old age group.⁵ However, this was not our clinical impression during many years of work with patients suffering and dying from meningococcal infection.⁶ In our experience, infants and small children dying from meningococcaemia normally had a very good nutritional appearance.

In order to confirm the association between a good nutritional appearance and death from meningococcal infection, we retrospectively reviewed the medical records of 74 children aged 1 month to 4 years with proven meningococcal infections (seven deaths) who were assisted in our hospital during a 2-year period. Children who died were stated as being clinically well-nourished and there were no deaths in five children with a weight for age z score less than -2 . However, in severely ill or dying patients, weight was frequently a rough estimation and heights were rarely obtained. We therefore initiated the present prospective study to examine differences in mortality and severity as clinical end points, as a function of weight and height for age, in 1-month to 4-year-old children with meningococcal infections.

METHODS

Patients aged 1 month to 4 years with a clinical diagnosis of meningococcal meningitis or sepsis² who were assisted in the

Sor María Ludovica Children's Hospital in La Plata, Argentina, since August 1999 were prospectively included in the study and were considered probable cases. The study was stopped in May 2004 because a double blinded, placebo-controlled trial which would modify the treatment of severe cases was initiated. Patients were retained in the study only if the discharge diagnosis was also consistent with meningococcal disease. Efforts directed at demonstrating the aetiology of the infection or isolating the causative organism included blood cultures, cerebrospinal fluid (CSF) cultures, direct staining of CSF and slide tests (Slidex meningite kit, bioMérieux, Marcy l'Etoile, France). Individuals with Gram-negative cocci in CSF staining or meningococcal detection by at least one of these procedures were considered to have proven meningococcal disease.³ Leukocyte and platelet counts in peripheral blood, cellularity of the CSF, blood pressure, inotropics and fluid needs, peripheral blood refill and the presence of petechiae or echymosis were measured on arrival at the inpatient services of the Sor María Ludovica Children's Hospital at La Plata. Need for intensive care and days spent in the intensive care unit (ICU) were recorded.

Patients who died, had amputations or required extensive reparative surgery were considered as having severe meningococcal infection.

Weight, supine length, skinfold thickness and mid-upper arm circumference were obtained. Weight was measured on arrival (before or at the same time that resuscitation fluid administration was initiated) on a standard scale with an accuracy of 100 g. Length was determined by one of us (NP) with a rigid wooden device with an accuracy of 0.5 cm. Skinfold thickness and mid-upper arm circumference were determined by a trained observer (NO) using the standard

Abbreviations: BMI, body mass index; CSF, cerebrospinal fluid; ICU, intensive care unit; LPS, lipopolysaccharide; TNF, tumour necrosis factor

Table 1 Clinical and biological findings in 127 children with meningococcal infection

	Non-severe (n = 112)	Severe (n = 15)	p Value
Age in months*	15.5 (6–31)	18 (12–28)	0.720
Sex (male/female)	61/51	8/7	0.934
Presence of petechiae**	92/111	13/15	0.526
Presence of purpura	56/109	14/15	0.002
Leukocytes $\times 1000/\text{mm}^3$	19.9 (10.2–24)	6.4 (4.2–20.8)	0.006
Platelets $\times 1000/\text{mm}^3$	224.0 (170–285)	69.0 (37–135)	<0.001
CSF cellularity/ mm^3	910 (4–10000)	9 (2–11)	0.002
Positive CSF culture	53/87	8/11	0.447
Positive blood culture	27/52	6/10	0.639
Median blood pressure	77 (69–87)	63 (61–74)	0.016
Heart rate/minute	140 (128–160)	172 (140–188)	0.009
Volume resuscitation	54/100	15/15	0.001
Need for inotropics	22/90	15/15	<0.001
Previous antibiotics	22/78	6/14	0.273

*For continuous variables, median (25–75 centiles) values are shown.

**For dichotomic variables, the number of positive subjects/subjects in whom the variable was obtained is shown.

procedure⁷ before prolonged intensive resuscitation procedures were performed. Results were transferred to a centile table⁷ and expressed as centile values.

Weight for age, height for age, weight for height z scores and body mass index (BMI) were calculated with Siscre software according to international standards.⁸

Statistical procedures were performed using SPSS 9.0 for Windows. Comparisons of continuous data between dichotomised categories were made using the Mann Whitney test. Correlations were calculated using the non-parametric Spearman's correlation coefficient. Proportions were compared by the χ^2 test. Comparisons of outcomes between groups of at-risk individuals were made with Fisher's exact test, using two-by-two tables. The p values obtained were two tailed.

Informed consent was obtained from the children's parents or guardians. Ethical approval was obtained from the local independent ethics committee. Scientific approval was obtained from appropriate local authorities.

RESULTS

A total of 131 white children aged 1 month to 4 years were seen in our inpatient facilities with suspected or proven meningococcal meningitis or sepsis. On arrival, 36 children had a clinical diagnosis of meningococcal infection but without confirmation criteria (probable cases). Four of these patient received another diagnosis during their hospital stay and were excluded from the analysis. A total of 95 children satisfied the criteria of proven meningococcal infection.

Thirteen children died and two children had fingers amputated and needed extensive reparative surgery comprising multiple skin grafts. Fifteen children were therefore considered as having severe infection. Two of the non-survivors died before

any anthropometrical parameters could be obtained and were excluded from the analysis; both were stated to be clinically well-nourished on admission.

Clinical and biological findings at admission in severe and non-severe cases are shown in table 1.

Only clinical and biological variables usually accepted as markers of poor outcome^{9–10} were significantly associated with severe infection in the present series of patients. Clinical and biological variables were identical in children with suspected or proven meningococcal infection (data not shown).

When the anthropometrical data of severe and non-severe patients were compared, patients with severe disease had higher weight for age z scores and were significantly taller than patients with non-severe disease. Children with severe infection had higher mid-upper arm circumference measurements than those with non-severe infection, and a similar but non-significant trend was also present for skinfold thickness (table 2).

When non-survivors and survivors were compared, non-survivors had higher weight for age (0.90 vs -0.16 ; p 0.025) and height for age (0.73 vs -0.57 ; p 0.012) z scores than survivors. As seen in table 2, BMI was significantly higher in those with severe than in those with non-severe disease. Weight for height z scores were also higher in those with severe disease, but differences did not reach statistical significance. The relative scarcity of data on skinfolds and arm circumference should be considered when analysing the results. This shortage is due to the fact that it was difficult for a single trained person to evaluate patients before prolonged intensive resuscitation procedures were begun. The distribution of weight for age and height for age of severe and non-severe cases is shown in fig 1.

In the post hoc analysis, we searched for markers, conditions or other variables related to weight and height for age, that may actually be responsible for the association between weight and height for age and severity. We therefore determined the correlation of weight and height for age and all variables significantly associated with severity listed in table 1. None of the analysed variables was correlated with both weight for age and height for age z scores (data not shown).

We also searched for an association of weight and height for age and the following new variables: need to be transferred to an ICU (an indirect indicator of severity), number of persons living in the house (as an indicator of household crowding) and laboratory confirmation of meningococcal infection (to rule out bias induced by misdiagnoses). Twenty two children needed to be transferred to an ICU. Medians of weight for age z scores appeared to be higher in children who required ICU support compared with medians in children who did not (0.17 vs -0.15 , respectively; p = 0.08). Medians of height for age z scores were higher in children who required ICU support compared with children who did not (0.37 vs -0.58 , respectively; p 0.01). Neither the number of persons living in the house nor laboratory confirmation of meningococcal infection was asso-

Table 2 Anthropometrical parameters of severe and non-severe patients

	Non-severe	Severe	p Value
Weight for age z score*, n = 124	$-0.19 (-0.87/0.59)$	$1.02 (0.14/1.42)$	0.001
Height for age z score, n = 120	$-0.58 (-1.2/0.17)$	$1.12 (-0.22/1.4)$	0.001
Mid-upper arm circumference (centile), n = 70	50 (25/90)	97 (80.5/97)	0.009
Skinfold thickness			
Subscapular (centile), n = 69	10 (8.2/50)	50 (25/75)	0.084
Tricipital (centile), n = 78	25 (3/50)	50 (25/86)	0.148
BMI, n = 118	16.58 (15.5/18)	18 (16.8/19.2)	0.039
Weight for height z score, n = 118	$0.26 (-0.28/1)$	$0.82 (-0.1/1.8)$	0.09

*Results are medians (25/75 centiles).

Figure 1 Weight and height for age z scores in severe and non-severe meningococcal disease.

ciated with either weight or height for age z scores (data not shown).

DISCUSSION

The Sor María Ludovica Children's Hospital in La Plata is a tertiary care hospital and receives more than 50% of patients with invasive meningococcal infections in the province of Buenos Aires. Children with this presumptive diagnosis are frequently referred to us from peripheral centres and, if suitable, receive fluids and parenteral antibiotics (usually a third-generation cephalosporin) before referral.

Death from meningococcal infection, and particularly from meningococcaemia, is usually a brutal event occurring in formerly healthy infants and children. In addition to previous well-being, in our personal clinical experience, an excellent nutritional appearance was the rule in babies who died from meningococcaemia; severe meningococcaemia in clinically malnourished children was extremely rare.

In our series of 127 children with meningococcal infection, we have been able to demonstrate a significant difference in weight and height for age in children with severe compared to those with non-severe disease and between survivors and non-survivors. These results agreed with our anecdotal observation.

A significant association between death from meningococcal infection and high weight for age has been recently reported by Blanco Quiros *et al*, who searched retrospectively for parameters

associated with poor outcome in 71 Spanish children aged 2 months to 13 years.¹¹ In their series they did not find an association between weight for age and scores of severity obtained on arrival at hospital (Glasgow Scale for Meningococcal Sepsis and the Pediatric Risk of Mortality). Children with higher weight for age had increased fatality rates even when they had similar severity scores on arrival. Unfortunately, height was not obtained.

A major concern in our work is the fact that weight can be modified by infection itself or by resuscitation procedures, and it may represent a bias in that the most severely ill children receive earlier and more aggressive fluid therapy and have a higher frequency of renal impairment, fluid retention or liquid sequestration. This reserve, however, does not apply to length.

When in post hoc analysis we examined the correlation of weight or height for age z scores with other variables, including some considered surrogate markers of severe meningococcal infection,^{2-9,10} none was found to be significantly associated simultaneously with both weight and height for age z scores. This is in accordance with the findings of Blanco Quiros,¹¹ and suggests that weight and height for age z scores are independently associated with severity.

Our study was designed to prove the association of increased severity of and mortality from invasive meningococcal infection with a good nutritional status; therefore the causes of the phenomenon we describe remain highly speculative. Two main

hypotheses could be advanced a priori: (1) anthropometrical parameters truly represent nutritional status, and a better nutritional status increases severity or, conversely, a worse nutritional status protects against severe meningococcal infection; and (2) some other factors related to anthropometrical parameters and/or nutritional status, such as poverty or poverty-linked conditions, increased exposure to bacteria and endotoxin, overcrowding or even late referral (referral bias), are responsible for the observed phenomenon.

Referral bias seems unlikely. The hospital is situated near the most populated areas of the province. More than 80% of meningitis patients are from the hospital area and referral from other centres is linked to the suspicion or diagnosis of meningococcal disease, regardless of nutritional status. The death of children with severe infection at home or before arrival is another potential source of bias. Death at home is a very infrequent event in the province of Buenos Aires for cultural, social and legal reasons. However, even if we consider such a possibility unlikely, death at home or before arrival cannot be formally excluded from our data.

Even though seriously ill children are not ideal subjects for determining nutritional status, height and weight for age may be easily obtained and remain among the most common indices for assessing nutritional status. The values for weight and height for age of children with non-severe meningococcal disease were similar to data from a low-income population of La Plata.¹² As seen in fig 1, the data showed a deviation from the mean towards negative values for height, with near-normal weight. Similar findings are usually seen in chronically undernourished populations.¹³ Conversely, children with severe infection showed very good nutritional status, as judged by their high weight and height for age.

It is well established that inflammatory mediators and cytokines are elevated in serum from patients with meningococcal disease, and serum levels correlate with severity of disease.¹⁴ In vitro production of inflammatory mediators such as TNF and interleukin-6¹⁵ is diminished in malnourished individuals. In our patients, BMI and weight for height, two age-independent measurements of the relationship between weight and height, seemed to be higher in severe cases. Fat excess may be a proinflammatory condition, and fat tissue may be an important source of TNF and other proinflammatory mediators.¹⁶ Therefore, our findings may represent an associa-

tion between nutritional status and the ability to mount a subnormal, normal or exaggerated inflammatory response.

It is also known that exposure to lipopolysaccharide (LPS) in humans is followed by a so-called refractory period, defined as a reduced ability to produce TNF or other inflammatory mediators.¹⁷ This is also true in patients with meningococcal infection.¹⁸ A similar phenomenon of LPS tolerance seems to occur in situations of frequent or continuous exposure to LPS. Continuous exposure of farmers' children to high concentrations of LPS in vivo seems to be associated with diminished TNF production by their mononuclear cells in response to LPS in vitro.¹⁹ Increased exposure to bacteria and endotoxin, as a consequence of consumption of contaminated food, is frequently associated with malnutrition and sometimes seems to occur without clinical consequences.^{20, 21} In children with repeated exposure to LPS, a diminished in vivo response to endotoxin may represent an adaptive mechanism (as a "price to pay" for survival), limiting a potent but potentially catastrophic inflammatory response to their dangerous environment.

High rates of meningococcal carriage associated with poverty²² or other poverty-linked conditions may explain the increased frequency of meningococcal infections in some populations.^{23, 24} It would be interesting to know if case-fatality rates are linked to anthropometrical parameters within these communities, particularly if children with good and bad nutritional status live close together. The potential possibility and relevance of referral bias should be explored in future population-based studies controlled for socio-economic status.

We anticipate that answering the outstanding questions on the relationship between the severity of meningococcal infections and anthropometrical parameters, nutritional status or other related conditions will further contribute to our understanding of the mechanism of sepsis-induced morbidity and death.

ACKNOWLEDGEMENTS

We thank Dr Luis Guimarey, Investigator from the Comisión de Investigaciones Científicas de la Provincia de Buenos Aires and one of the authors of Sisces, for his kind gift of the software.

Authors' affiliations

N Perez, L Regairaz, J Bustamante, Immunology Unit, Hospital de Niños "Sor María Ludovica" and Instituto de Desarrollo e Investigaciones Pediátricas, La Plata, Argentina

N Osimani, A Rodrigo, Nutrition Unit, Hospital de Niños "Sor María Ludovica" and Instituto de Desarrollo e Investigaciones Pediátricas, La Plata, Argentina

D Bergna, C Peltzer, Intensive Care Unit, Hospital de Niños "Sor María Ludovica" and Instituto de Desarrollo e Investigaciones Pediátricas, La Plata, Argentina

J Morales, M R Agosti, S Gonzalez-Ayala, Infectious Diseases Unit, Hospital de Niños "Sor María Ludovica" and Instituto de Desarrollo e Investigaciones Pediátricas, La Plata, Argentina

Competing interests: None declared.

N Perez, N Osimani and A Rodrigo are members of the Comisión de Investigaciones Científicas de la Provincia de Buenos Aires, Argentina.

What is already known on this topic

- Malnutrition has been associated with increased frequency and severity of infectious diseases.
- Children with higher weight for age had increased fatality rates from meningococcal disease in one previous study.
- However, weight is potentially modified by fluid resuscitation and is not a "clean" proxy for nutritional status.

What this study adds

- Children who had higher weight for age, height for age and BMI were more likely to have severe meningococcal disease.
- Good nutritional status is associated with death or complications from meningococcal disease in Argentina.

REFERENCES

- 1 Riedo F, Plikaytis B, Broome C. Epidemiology and prevention of meningococcal disease. *Pediatr Infect Dis J* 1995;14:643-57.
- 2 Kirsch E, Barton P, Kitchen L, et al. Pathophysiology, treatment and outcome of meningococemia: a review and recent experience. *Pediatr Infect Dis J* 1996;15:967-79.
- 3 Rosenstein N, Perkins B, Stephens D, et al. Meningococcal disease. *N Engl J Med* 2001;344:1378-88.
- 4 Emonts M, Hazelzet J, de Groot R, et al. Host genetic determinants of *Neisseria meningitidis* infections. *Lancet Infect Dis* 2003;3:565-77.
- 5 Fauzi W, Herrera G, Spiegelman D, et al. A prospective study of malnutrition in relation to child mortality in the Sudan. *Am J Clin Nutr* 1997;65:1002-9.

- 6 **Gonzalez-Ayala S**, Altschuler M, Ramirez Gronda G, et al. Meningococcal disease in children (abstract). *Clin Microbiol Infect* 1997;**3**(Suppl 2):319.
- 7 **Sociedad Argentina de Pediatría**. *Guías para la evaluación del crecimiento*. Buenos Aires: SAP, 2001:63–78.
- 8 **US National Center for Health Statistics**. *NCHS growth curves for children birth-18 years*, Vital and Health Statistics Series 11, No 165, DHEW Publication No PHS 78-1650. Rockville, MD: National Center for Health Statistics, 1977.
- 9 **Malley R**, Huskins WC, Kuppermann N. Multivariable predictive models for adverse outcome of invasive meningococcal disease in children. *J Pediatr* 1996;**129**:702–10.
- 10 **Havens P**, Garland J, Brook M, et al. Trends in mortality in children hospitalized with meningococcal infections, 1957 to 1987. *Pediatr Infect Dis J* 1989;**8**:8–11.
- 11 **Blanco Quiros A**, Casado Flores J, Nieto Moro M, et al. Meningococcal sepsis in pediatrics. Parameters associated with poor outcome. *An Pediatr (Barc)* 2004;**61**:305–13.
- 12 **Rodrigo M**. *Observatorio de calidad de vida. Capítulo Salud*. Municipalidad de La Plata: Universidad Nacional de La Plata, 2001:94–5.
- 13 **United Nations**. *United Nations ACC/SCN 4th report on the world nutrition situation*. Geneva: UN, 2000.
- 14 **Lehmann A**, Haltensen A, Sørnes S, et al. High levels of interleukin 10 in serum are associated with fatality in meningococcal disease. *Infect Immun* 1995;**63**:2109–12.
- 15 **Doherty J**, Golden M, Remick D, et al. Production of interleukin-6 and tumor necrosis factor-alpha in vitro is reduced in whole blood of severely malnourished children. *Clin Sci* 1994;**86**:347–51.
- 16 **Hotamisligil G**, Arner P, Caro J, et al. Increased adipose tissue expression of tumor necrosis factor-alpha in human obesity and insulin resistance. *J Clin Invest* 1995;**95**:2409–15.
- 17 **Granowitz EV**, Porat R, Mier JW, et al. Intravenous endotoxin suppresses the cytokine response of peripheral blood mononuclear cells of healthy humans. *J Immunol* 1993;**151**:1637–45.
- 18 **van Deuren M**, van der Ven-Jongekrijg J, Demacker PN, et al. Differential expression of proinflammatory cytokines and their inhibitors during the course of meningococcal infections. *J Infect Dis* 1994;**169**:157–66.
- 19 **Braun-Fahrlander C**, Riedler J, Herz U et al. Allergy and Endotoxin Study Team. Environmental exposure to endotoxin and its relation to asthma in school-age children. *N Engl J Med* 2002;**347**:869–77.
- 20 **Klein K**, Fuchs G, Kulapongs P, et al. Endotoxemia in protein-energy malnutrition. *J Pediatr Gastroenterol Nutr* 1988;**7**:225–8.
- 21 **Penny M**, Paredes P, Brown K, et al. Lack of a role of the duodenal microflora in pathogenesis of persistent diarrhea and diarrhea-related malabsorption in Peruvian children. *Pediatr Infect Dis J* 1990;**9**:479–87.
- 22 **Emele F**, Ahanotu C, Anyiwo C. Nasopharyngeal carriage of meningococcus and meningococcal meningitis in Sokoto, Nigeria. *Acta Paediatr* 1999;**88**:265–9.
- 23 **Baker M**, McNicholas A, Garrett N, et al. Household crowding a major risk factor for epidemic meningococcal disease in Auckland children. *Pediatr Infect Dis J* 2000;**19**:983–90.
- 24 **Kriz P**, Bobak M, Kriz B. Parental smoking, socioeconomic factors, and risk of invasive meningococcal disease in children: a population based case-control study. *Arch Dis Child* 2000;**83**:117–21.

ARCHIVIST

Children dying in hospital: too many on ICU?

A paper from the Great Ormond Street Hospital for Children in London (Padmanabhan Ramnarayan and colleagues. *Journal of Medical Ethics* 2007;**33**:255–60) has raised the question of whether too many children who are terminally ill with chronic conditions are being admitted to intensive care units (ICUs) in the final acute phase of their illness and die there.

A total of 1127 children died in the hospital during a 7-year period (1997–2004). Of these, 650 were aged <1 year, 407 were aged 1–14 years and 70 were aged 15–18 years. The chief diagnostic categories were congenital malformations (22%), perinatal conditions (18%), cardiovascular diseases (15%) and neoplasms (12%). Death occurred on the ICUs in 86% of cases and there was a significant trend with 80% of deaths on ICUs in 1997–98 and 91% in 2003–04. Among the 161 children who died outside the ICU, 51 (32%) died on the oncology, cardiology or neurology wards, but most had been transferred from an ICU having spent, on average, 12 days there. The proportion of ICU admissions that were from within the hospital increased from 15% in 1998 to 25% in 2004. A larger proportion of children with neoplasms died on the hospital wards (43% compared with 15% of children who died of congenital malformations).

The strong implication is that too many children are dying in ICUs when they and their families would be better served if the children were allowed a more dignified and peaceful death elsewhere. Without individual case analysis it is not possible to judge how many children were admitted to ICUs without hope of useful recovery. Some of the children must have been previously well and admitted with acute illnesses, but the categories of injury, poisoning and infection accounted for only 12% of deaths. There is no information about how many children left hospital to die at home or in a hospice or were not admitted in the terminal stages of their illness. The Great Ormond Street Hospital is not a typical children's hospital and practice may differ elsewhere. The authors of this paper suggest it might be useful to establish a multidisciplinary combined paediatric intensive care/palliative care team to oversee end-of-life provision.