

REVIEW

Surviving meningococcal septic shock in childhood: long-term physical and psychological outcomes

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Abstract - Objective: to evaluate long-term physical and psychological outcomes in patients who survived meningococcal septic shock (MSS) in childhood. **Search strategy:** all patients with septic shock and purpura requiring intensive care treatment between 1988 and 2001. At follow-up physical health status was assessed with a standard medical interview and physical examination; validated assessment procedures were used to measure behavioural and emotional problems, cognitive functioning, general health status and health-related quality of life (HR-QoL). **Summary of findings:** 120 patients (response rate 71%) visited the follow-up clinic (age PICU admission 3.1 years; follow-up interval 9.8 years; age follow-up 14.5 years (all medians). 48% had skin scarring, ranging from barely visible to extremely disfiguring. 14% suffered from orthopaedic sequelae (amputation/s, limb-length discrepancy) resulting in important long-term morbidity. One third showed neurological sequelae: severe mental retardation with epilepsy (3%), hearing loss (2%), chronic headache (28%) or focal neurological signs such as paresis of one arm (6%). Patients reported impaired general health status as measured by Health Utilities Index mark 2 and 3. Significantly impaired HR-QoL was found in the physical domains (physical functioning, general health perception). Intellectual functioning was comparable to the reference groups, whereas neuropsychological functioning in children was poorer. Patients showed similar levels of behavioural and emotional problems compared with reference groups. Adverse physical and psychological outcome variables were not associated with one another. **Conclusions:** patients who survived MSS in childhood mainly had mild to severe adverse physical outcome. There were no associations between adverse physical and psychological outcomes.

Keywords - long-term; meningococcal; outcome; paediatric intensive care; septic shock

ABBREVIATIONS: PICU = paediatric intensive care unit; NM = *Neisseria meningitidis*; PRISM = Pediatric Risk of Mortality Score; VAS = Vasopressor score; DIC = Disseminated Intravascular Coagulation score; MSS = meningococcal septic shock; HR-QoL = health-related quality of life

Introduction

Every year approximately 5000 children (0-18 years) are admitted to specialized paediatric intensive care units (PICU) in the Netherlands. Among these children, although relatively low in number, patients with meningococcal septic shock (MSS) form a well-identified group. MSS is characterized by sudden onset and a fulminant course in previously healthy young children (0 to 4 years) and adolescents. The sepsis is overwhelming.

In our cohort study of 287 children with MSS admitted to the PICU between 1988 and 2006, mortality was 16% [1]. Mortality was due to refractory shock and occurred within the first 24-48 hours after admission to PICU. Younger age (under the median age of 3.0 years) was significantly associated with more severe

disease and a higher mortality. Fortunately, in recent years mortality has decreased due to centralization of PICU, introduction of serogroup C vaccine (2002, the Netherlands), improvement of awareness and clinical guidelines for children with sepsis [1,2].

Children who survive MSS may develop neurological sequelae such as deafness, and skin or limb necrosis requiring grafting or amputation [3-6]. None of the previous MSS outcome studies have given a complete overview of outcome in a homogeneous study population, both physical and psychological, using standardized assessment procedures in a large cohort of MSS survivors.

The relatively large, homogeneous cohort of children with MSS admitted to the PICU of the Erasmus MC-Sophia over the last two decades offered the possibility of investigating this area of outcome, both from a medical and psychosocial point of view, with standardized assessment procedures.

The aims of the present study were to assess long-term outcomes (at least 4 years), both physical and psychosocial, in MSS survivors, and the association between outcome variables. Additionally, we assessed predictors of outcome variables. Finally, we developed recommendations for follow-up in MSS survivors.

The present article is not an original article but is composed of research published earlier and contained in the theses of the two principal authors (C. Buysse and L. Vermunt) [7-13].

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Materials and methods

Patient selection

This study concerned the medical and psychological follow-up of a cross-sectional cohort of all consecutive surviving patients with septic shock and purpura who required intensive care treatment at least four years ago (between 1988 and 2001), and their parents. Patients were recruited from the PICU of the Erasmus MC-Sophia Children's Hospital, a tertiary care university hospital. All consecutive surviving patients aged from 1 month to 18 years with a clinical picture of MSS, and their parents, were eligible for inclusion in this study. Meningococcal septic shock was defined as septic shock with petechiae and/or purpura [14]. The Erasmus MC Medical Ethical Review Board approved the study protocol. Written informed consent was obtained from parents and patients by sending a standard letter requesting their participation in the study. Those with insufficient command of the Dutch language were excluded. Parents and patients who agreed to participate were invited by mail to visit the follow-up clinic. The follow-up visits took place in 2005-2006.

Data analysis on PICU admission

During the study period, patients consecutively admitted with MSS were included in several sepsis studies [15-19]. Severity of illness was determined by using the Pediatric Risk of Mortality Score (PRISM), Vasopressor score (VAS) and Disseminated Intravascular Coagulation score (DIC) [20-22].

Long-term outcome variables

Physical health status

Parents and patients were invited to the follow-up clinic 4-16

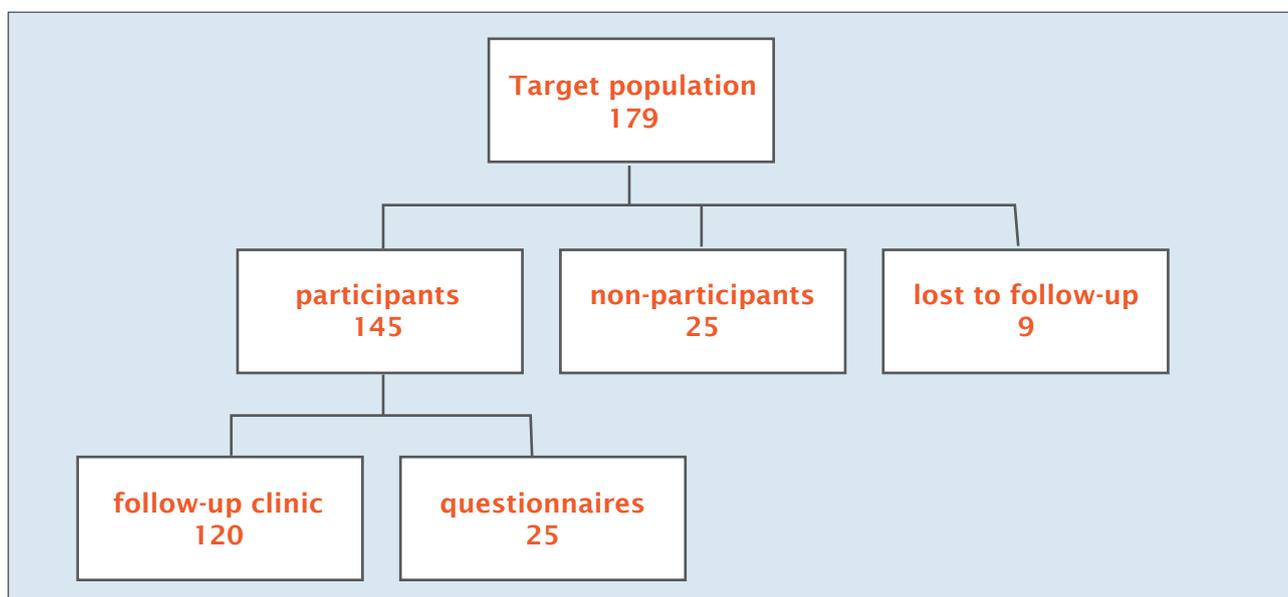
years after discharge from PICU. They were interviewed by one paediatrician (CB) in a semi-structured format using a standard questionnaire concerning consequences to their health of MSS. Symptoms were defined as chronic if they occurred after MSS and if they were still present at time of visit to the follow-up clinic. A general physical examination of the patient was performed by the same paediatrician (CB). Measurements of body weight, height, head circumference (HC), and mid-upper arm circumference (MUAC) were done [23].

Patients who during admission to PICU had developed septic-shock-associated acute renal failure (ARF) - defined as a serum creatinine of more than twice the upper level of normal range for age, (including patients who received renal replacement therapy (RRT)) were identified. In these patients persisting renal damage was assessed at the time of follow-up with the following measurements: serum creatinine, from which glomerular filtration rate per 1.73m^2 body surface area (GFR) was estimated using the modified Schwartz or Cockcroft formulas (according to age), the average of three measurements of blood pressure, protein and creatinine excretion averaged from three early morning urine samples [24].

In patients with signs of acute lung injury (ALI) at the time of MSS, lung function tests were performed [25].

Generic health status was assessed with the Health Utilities Index mark 2 and 3 (HUI2 and HUI3), based on the 15-item HUI questionnaire [26,27]. The parent-completed 15-item HUI questionnaire was used for patients aged 4-17 years, and the patient-completed 15-item HUI questionnaire was used for patients aged 18 years and older.

Figure 1. Patient sample



Psychological functioning

Patients were interviewed and examined by one psychologist (LV) using standard assessment procedures. For intellectual functioning two tests were used: the Wechsler Intelligence Test III for 6-15 year old patients, the Groninger Intelligence Test 2 for 16-31 year-old patients [28-30]. Neuropsychological tests were also used to test cognitive outcome in children [31-35]. Behavioural and emotional problems were assessed by using the Child Behaviour Checklist (CBCL) for 6-18 year-old patients (parent-completed), and the Adult Self-Report (ASR) for 18-31 year-old patients [36,37]. For the purpose of this study, problem behaviour (a dichotomous variable) was defined as a total problem score above the 90th percentile of the cumulative frequency distribution of the reference groups on the CBCL or the ASR. Self-esteem was measured with the Dutch versions of Harter's Self-Perception Profile for Children and Adolescents [38,39].

HR-QoL

HR-QoL for patients < 18 years was assessed with the Child Health Questionnaire (CHQ) and for patients ≥ 18 years with the SF-36. (27, 40-43) The parents were asked to complete the CHQ (version CHQ-PF50) for patients aged 4-17 years. Patients aged 12-17 years completed the CHQ themselves (version CHQ-CF87). In addition, the parents were asked to complete the CHQ-PF50 for these patients. In the absence of a control group matched for sex and age, we used population norms of HR-QoL scores for comparison with scores in our study samples [27,43,44].

Statistical methods

Statistical analysis was performed with SPSS 12.0 for Windows (SPSS, Inc, Chicago, IL).

Patient sample

Comparisons between participating patients and non-participants were made with the Mann-Whitney test for age at time of PICU admission, length of stay in PICU and severity of illness scores, with the Chi-Square test for sex.

Physical health status

The Mann-Whitney test was used to compare quantitative variables between the groups with and without skin scarring or orthopaedic sequelae, and also between the groups with and without adverse neurological outcome, and the Chi-Square test was used for counts [7,8].

All anthropometric data obtained were compared with published standards based on a Dutch population study performed in 1997 and transformed into standard deviation scores (SD-scores) by means of a software programme (GROWTH ANALYSER 3, 2001-2006 Nederlandse Groeistichting, Rotterdam -The Netherlands) [45].

The Mann-Whitney test was used to compare the HUI2 and HUI3 scores of our patients with individual normative data from a general population survey [26].

Psychological functioning

All statistical analyses were performed with two-sided tests. One sample t-tests were used to test differences in group means between the patient sample and normative data.

Binomial testing was used to compare the proportion of children who were receiving or had received special education, with that of the general population. Differences in proportions scoring in the deviant psychopathological range for problem behaviour between patient samples versus normative data of reference groups were analyzed by binomial testing. Differences in mean scores of the patient samples versus reference groups were assessed with analyses of (co)variance (AN(C)OVAs).

Table 1. Data on participating patients and non-participants. Data are presented as number of patients or median (range)

CHARACTERISTICS	FOLLOW-UP CLINIC N=120	NO FOLLOW-UP CLINIC N=59	P-VALUE
Sex	63 boys, 57 girls	27 boys, 32 girls	0.43
Age at the time of PICU (years)	3.1 (0.1-17.9)	5.4 (0.2-14.3)	0.12
Length of stay in PICU (days)	3 (1-51)	3 (1-36)	0.55
PRISM	15 (1-37)	15 (0-41)	0.64
DIC score*	6 (3-8)	6 (2-8)	0.72
VAS score	15 (0-403)	11 (0-145)	0.71

*DIC score: score ≥ 5 indicates presence of disseminated intravascular coagulation

The original table was published in Archives of Diseases in Childhood [7].

Note: a causative organism was isolated in 151 of the 179 patients (84%). In 149 patients (83%) *Neisseria meningitidis* was cultured. Of these 149, 113 (76%) had NM serogroup B, 24 (16%) serogroup C and in 12 (8%) the serogroup was not determined. In two patients streptococcus was cultured. These two patients were included because they presented with septic shock and purpura requiring intensive care treatment.

HR-QoL

The Mann-Whitney test was used to compare the HR-QoL scores of our patients < 18 years with individual normative data, as provided by Raat et al [27,44]. The paired Wilcoxon test was used to compare HR-QoL scores of patients ≥ 18 years with published normative data, as individual normative data were not available [43].

Associations between physical and psychological outcome variables

In order to associate the different outcome variables, we dichotomized and coded outcome variables (presence or absence of outcome variable), and then composed four major outcome variables; 1) major physical sequelae defined as major scars and/or amputation of extremities and/or limb-length discrepancy, 2) mild neurological impairments defined as hearing loss and/or chronic headache and/or focal neurological signs, 3) problem behaviour and 4) total IQ < 85.

Associations between these major outcomes (all as dichotomous variables) were made with the Chi-Square test. Associations between patients with problem behaviour and total IQ < 85 were not made, since this was not the objective of our study.

The psychological outcome variables were also used as continuous variables. In this case the Mann-Whitney test was

used to compare the psychological outcome scores between patients with and without major physical sequelae and with and without neurological impairments.

In all the above-mentioned statistical analyses, a P-value of 0.05 (two-sided) was considered the limit of significance.

Results

Patient sample

The target population consisted of 179 patients (Figure 1). Of these 179 patients nine were lost to follow-up: one patient with severe adverse outcome (mental retardation with epilepsy) died several years after the MSS; seven patients were living abroad at the time of the follow-up; one was untraceable. Of the remaining 170 eligible patients, 145 agreed to participate. Of these 145 participants, 120 visited the follow-up clinic. The median follow-up interval was 9.8 years (range 3.7-17.4 years), the median age of patients at the time of visit to follow-up clinic was 14.5 years (range 5.3-31.1 years). Twenty-five patients and/or parents did not want to visit the follow-up clinic on practical (for example no time because of a busy job) or emotional (confrontation with the hospital too emotional) grounds, and preferred to fill in the questionnaires at home. Another 25 patients and/or parents did not respond to the invitation or refused all participation

Table 2. Amputations

PATIENT	AMPUTATIONS	MOTOR FUNCTIONING
1	Bilateral feet (through-ankle), 1 finger (midphalanx)	Walks with bilateral prostheses
2	1 finger (distal phalanx)	Uses hands normally
3	Bilateral feet (midtarsal)	Unable to walk without prostheses, with prostheses and crutches max. 10 minutes because of severe pain and chronic ulcerations
4	8 toes	Able to walk and run normally without limitation
5	1 arm (below-elbow), 2 legs (1 below-knee and 1 above-knee)	Requires wheelchair to get around independently, can walk with prostheses max. 10 minutes because of severe contracture of hips
6	1 finger (distal phalanx)	Unable to use hands because of severe mental retardation
7	2 fingers (midphalanx)	Uses hands and fingers with some limitations but does not require help
8	1 leg (below-knee)	Walks with prosthesis
9	4 toes	Able to walk and run normally without limitation
10	1 toe	Able to walk and run normally without limitation

The original table was published in Archives of Diseases in Childhood [7].

Figure 2. Limb-length discrepancy of 13 cm in a 5-year-old girl



on practical or emotional grounds. The overall response rate, excluding patients lost to follow-up, was 71% (120/170). To check for possible selection bias, we compared characteristics between participating patients and non-participants (Table 1). Patients did not differ with respect to age at time of PICU admission and severity of illness.

Physical health status

Of the 120 patients who visited the follow-up clinic, 48% had skin scarring due to necrotic purpura at the time of MSS. Scars varied from mild to severe regarding number, diameter and position. In some patients scars were barely visible (one small scar on the buttocks), while other patients were extremely disfigured with scars covering a large part of the body surface (including the face). Patients themselves seemed not to be disturbed by their scars and reported that they had adapted to them over time. However, MSS adolescents with scars reported lower global self-worth than MSS adolescents without scars. The worse MSS children evaluated their scars, the worse their outcomes on social acceptance.

Fourteen percent had orthopaedic sequelae (amputation, limb-length discrepancy) with important long-term morbidity (surgical intervention, pain or functional impairment) (Tables 2 and 3) (Figure 2).

Patients with scars or orthopaedic sequelae had significantly higher PRISM, DIC and VAS scores. Also younger children at the time of admission to PICU were more at risk for limb-length discrepancy several years after MSS.

Thirty-five percent had one or more of the following neurological impairments: severe mental retardation (total intelligence score < 70) with epilepsy (3%) (two with spastic quadriplegia), hearing loss (2%), chronic headache (28%) or focal neurological signs such as paresis of one arm (6%). Patients with severe mental retardation (including the patient who died before our follow-up study) were significantly younger at time of PICU admission and had more severe septic shock compared with patients without severe retardation. Statistically significant differences regarding severity of illness scores or presence of meningitis, were not found between patients with and patients without hearing loss, chronic headache or focal neurological signs.

With regard to growth, anthropometric SD-scores were similar to those found in the general population.

One of the 16 patients with septic-shock-associated ARF on admission to PICU showed signs of mild chronic renal failure (GFR 62 ml/min/1.73m², proteinuria and hypertension). His renal failure had slowly progressed since discharge from PICU. This patient had suffered from fulminant MSS with severe ARF requiring RRT.

Of the 46 patients who required mechanical ventilation in PICU, six had signs of ALI at the time of MSS. In five of the six, flow volume curves were normal; forced vital capacity ranged from 100-123% predicted values (median 111). One patient, who had asthma, had a normal forced vital capacity but showed signs of airways obstruction.

Significantly lower scores were found on nearly all HUI2 and HUI3 attributes compared with normative Dutch data, indicating poorer health status.

Table 3. Limb-length discrepancy

PATIENT	AGE MSS	AGE FOLLOW-UP	INTERVAL*	ORTHOPAEDIC SEQUELAE	RADIOGRAPHIC ASPECTS
1	0.5	11.3	10	Lower limb discrepancy (3.5 cm, R femur) upper limb discrepancy (R radius) madelung deformity R under arm	Premature closure epiphyseal plate R distal radius+femur
2	0.3	5.3	3	Lower limb discrepancy (13 cm, R femur+tibia) genu varum joint contracture R knee	Premature closure epiphyseal plate R+L proximal femur, R distal femur, R proximal+distal tibia
3	0.5	6	2	Lower limb discrepancy (3 cm, L tibia) L foot smaller genu varum L	Premature closure epiphyseal plate L distal femur, L proximal and distal tibia
4	0.8	17.5	3	Lower limb discrepancy (5 cm, R leg) genu varum R genu valgum L	Premature closure epiphyseal plate R+L proximal femur, R distal femur
5	0.7	10.7	3	Lower limb discrepancy (3 cm, R leg) genu varum R	Premature closure epiphyseal plate R+L proximal femur, R proximal tibia
6	3.5	7.8	3	Lower limb discrepancy genu varum R	Destruction epiphysis R proximal tibia Tethering
7	2.3	10.6	8	Lower limb discrepancy (3.5 cm, R tibia) varus deformity R ankle	Premature closure epiphyseal plate R distal tibia

*interval (years) between diagnosis limb-length discrepancy and MSS. R = right; L = left. The original table was published in Archives of Diseases in Childhood [7].

Psychological functioning

Overall, total scores of intellectual functioning in our study group were comparable to those of the reference groups. However, in children < 18 years, impairments relating to social and practical reasoning, visual-motor integration, attention and executive functioning were found.

No significant differences were found between the proportions of patients (6-18 years and 18-31 years separately) scoring in the deviant psychopathological range for problem behaviour and same-aged reference groups. Ten percent of the children (6-17 years of age) were receiving or had received in the past, some sort of special education service which is significantly more than in the general population (4%).

HR-QoL

Significantly poorer scores were found mainly in physical domains (physical functioning, general health perception, physical summary) (Tables 4-6). In patients <18 years, according to their parents, significantly poorer scores were also found on psychosocial HR-QoL domains (self-esteem, role functioning emotional/behaviour) (Table 4), whereas in patients \geq 12 years, according to patients themselves, significantly better scores were found in psychosocial domains (general behaviour, family activities, role limitations due to emotional problems and psychosocial summary) (Tables 5 and 6).

An important observation was that patients seemed more inclined to appreciate life more after their life-threatening illness. Indeed, during the interviews, parents and patients themselves often reported that the event made them stronger. Patients seemed to have the intrinsic capacity to rehabilitate from severe physical disability. For example, adult patients appeared to function well and lead normal lives considering their outcomes on living conditions, having offspring, daily activities, marital status, occupational status and educational attainments.

Associations between physical and psychological outcome variables

There were no significant associations between the major outcome variables (Figure 3). No differences were found between patients with major physical sequelae and patients without major physical sequelae in relation to problem behaviour (e.g. anxiety, depression, aggressive behaviour) or total IQ < 85. Also, no differences were found between patients with and without mild neurological impairments in relation to problem behaviour or a total IQ < 85. Finally, no differences were found between patients with and without major physical sequelae in relation mild neurological sequelae.

The patient with chronic renal failure underwent a below-knee amputation of one leg, and had major scars and focal neurological signs. One of the three patients with mental retardation (estimated IQ < 70) had major scars and had undergone amputations; another patient had major scars and a lower limb discrepancy of 13 centimeters.

Discussion

Patients who survived MSS in childhood mainly had an adverse physical outcome. The severity of this adverse outcome varied from mild to severe. Also poorer general health status and HR-QoL (physical domains) were reported. Overall, levels of cognitive functioning and behavioural and emotional problems were comparable to those of the reference groups. There were no associations between adverse physical and psychological outcomes.

Physical health status

Nearly half of the patients (48%) had skin scarring, ranging from one barely visible scar on the buttocks to extremely disfiguring scars. Adolescents with skin scarring reported lower self-esteem than reference adolescents. This might be because they perceived their scars to be constant reminders of having experienced a life-

Table 4. Health-related quality of life (parent-report) in patients 4-17 years. Data are presented as mean (range).

	PATIENTS	REFERENCE	P-VALUE*	<5 TH %*
	n=92			
CHQ-PF50 (4-17 years)				
Physical functioning (PF)	92 (0-100)	99	<0.001	19%
Role functioning: Emotional/behaviour (REB)	92 (0-100)	98	<0.05	12%
Role functioning: Physical (RP)	94 (0-100)	96	ns	
Bodily pain (BP)	81 (10-100)	86	ns	
General behaviour (GB)	78 (26-100)	79	ns	
Mental health (MH)	80 (40-100)	81	ns	
Self-esteem (SE)	76 (0-100)	79	<0.05	19%
General health perceptions (GH)	64 (9-98)	83	<0.001	37%
Parental impact: Emotional (PE)	82 (17-100)	86	ns	
Parental impact: Time (PT)	92 (0-100)	94	ns	
Family activities (FA)	89 (33-100)	92	ns	
Family cohesion (FC)	69 (0-100)	72	ns	
Physical summary (PHS)	51 (-5-62)	56	<0.001	13%
Psychosocial summary (PSS)	52 (19-65)	53	ns	

*Percentage of patients with score < 5th percentile of reference group (this percentage was calculated if P-value <0.05).

threatening illness, which might result in feelings of vulnerability [12].

Fourteen percent of the patients had orthopaedic sequelae (amputation, limb-length discrepancy). Most of the patients who had undergone more extensive amputations (of foot, leg or arm) or with lower limb-length discrepancy had long-term morbidity because of pain, significant functional impairment and the need of surgical re-intervention/s in the years following MSS.

This was the first study to determine predictors of severe skin scarring and orthopaedic sequelae by using severity of illness scores. We were able to demonstrate that the underlying disease, expressed by PRISM and DIC scores, was predictive for the presence of severe skin scarring and orthopaedic sequelae. Also at the time of PICU admission, younger children seemed more at risk for limb-length discrepancy. This is probably due to age-dependent differences in vulnerability of bone vasculature as well as the stage of bone maturity and development.

One third of the patients had a long-term adverse neurological outcome after MSS, ranging from mild to severe and irreversible.

One (6%) of the 16 examined patients with septic-shock-associated ARF showed signs of persistent kidney damage. His chronic renal failure may progress further with age, possibly

necessitating chronic dialysis or renal transplantation in the future. The incidence of long-term impaired renal function in our patients was in line with the study of Slack et al [46]. Proteinuria after MSS may reflect the loss of a considerable number of glomeruli due to septic-shock-associated acute tubular necrosis. Though the glomerular filtration rate may, by hyperfiltration of the remaining glomeruli, be normal at the time of measurement, it could decline over time if the proteinuria is untreated.

In five of the six patients with ALL, lung function was normal. None of our 120 MSS survivors reported exercise intolerance. Some important questions concerning pulmonary sequelae remain: does significant desaturation occur during maximum exercise in the long-term (as in our patients, > 4 years)? If so, could this be due to lung fibrosis and microvascular obliteration, which are pathological sequelae after ALI?

Psychological functioning

Overall, we found favourable outcomes of long-term psychosocial functioning. This is remarkable since MSS has an immense biological and emotional impact on children.

A possible explanation for our positive findings regarding behavioural and emotional problems might be that MSS

Table 5. Health-related quality of life (patient-report) in patients 12-17 years. Data are presented as mean (range).

	PATIENTS	REFERENCE	P-VALUE*	<5 TH %*
CHQ-CF87 (12-17 years)	n=38			
Physical functioning (PF)	95 (44-100)	96	ns	
Role functioning: Emotional (RE)	93 (56-100)	89	ns	
Role functioning: behaviour (RB)	92 (33-100)	95	ns	
Role functioning: Physical (RP)	94 (33-100)	95	ns	
Bodily pain (BP)	72 (0-100)	74	ns	
General behaviour (GB)	87 (61-99)	81	<0.001	
Mental health (MH)	81 (50-100)	76	ns	
Self-esteem (SE)	77 (48-100)	75	ns	
General health perceptions (GH)	66 (38-97)	74	<0.01	13%
Family activities (FA)	88 (50-100)	80	<0.01	
Family cohesion (FC)	75 (0-100)	71	ns	

*Percentage of patients with score < 5th percentile of reference group (this percentage was calculated if P-value <0.05).

Table 6. Health-related quality of life (patient-report) in adult patients (≥ 18 years). Data are presented as mean (range).

	ADULT PATIENTS	REFERENCE	P-VALUE*	<5 TH %*
SF-36	n=48			
Physical functioning (PF)	90 (20-100)	94	ns	
Role limitations due to physical functioning (RP)	81 (0-100)	88	ns	
Social functioning (SF)	85 (25-100)	88	ns	
Bodily pain (BP)	78 (10-100)	83	ns	
General mental health (MH)	79 (48-100)	78	ns	
Role limitations due to emotional problems (RE)	94 (33-100)	84	<0.01	
Vitality (V)	63 (30-90)	71	<0.01	21%
General health perceptions (GH)	72 (35-100)	78	ns	
Physical summary (PHS)	49 (9-61)	55	<0.001	19%
Psychosocial summary (PSS)	52 (36-61)	49	<0.01	

*Percentage of patients with score < 5th percentile of reference group (this percentage was calculated if P-value <0.05).

survivors show resilience. MSS survivors may, paradoxically, be strengthened by their life-threatening illness. It might also be that MSS survivors are more appreciative of life [11].

The impairments in children seen on some neuropsychological tests could be due to brain damage (infarction) as a result of cerebral hypoperfusion [10].

HR-QoL

The primary aims of intensive care treatment are the reduction of mortality and morbidity, and the maintenance of health status and functional capacity. Traditionally, outcome research has focused on mortality and assessment of health status in terms of objective, physiological measurements. Recently, there has been a move also towards subjective measures of health status, such as functional status (disability) and HR-QoL (well-being). For example, amputation of a limb may be associated with the inability to walk long distances (disability), which may be associated with the inability to play football resulting in less satisfaction (HR-QoL). The subjective nature of these measures is not a shortcoming, but an essential component. If we, clinicians, are concerned with the patient's outcome, we should also measure it directly from the perspective of the patient.

Until now, HR-QoL has not been thoroughly investigated in MSS survivors [5,47]. We found poorer HR-QoL scores in our patients, mainly on the physical domains. This was not surprising since patients mainly had adverse physical outcome.

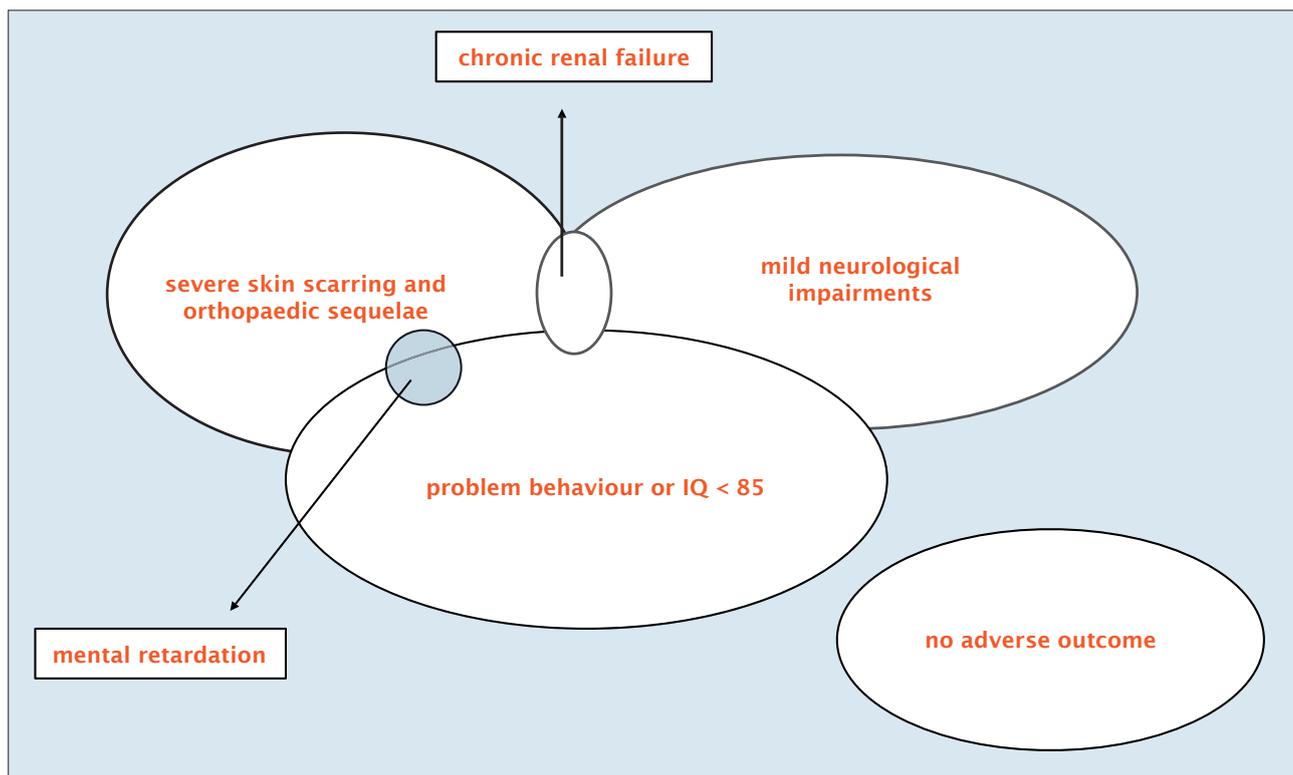
Associations between physical and psychological outcome variables

We were surprised by this lack of associations between adverse physical and psychological outcomes. The outcome variables, in our study group directly related to the severity of MSS, were severe skin scarring, orthopaedic sequelae, chronic renal failure and mental retardation. Could it be that the adverse outcome variables such as chronic headache or cognitive dysfunctioning are not specifically related to MSS, but to sepsis in general? Or is an acute illness with its accompanying invasive procedures, sedative and analgesic drugs, and sleep deprivation, the cause of these problems? Furthermore, we need to emphasize that total scores of intellectual functioning and of behavioural and emotional problems in our study group were comparable to those of the reference groups.

Limitations of the present study

Several limitations of our study should be acknowledged. This is an observational study (no controls) in one centre. It could be interesting to compare our groups with patients admitted to the hospital or PICU with another disease, matched for age, gender and follow-up interval. However finding such a large, homogeneous group of patients admitted to the PICU remains difficult. We did not take into account previous health status (severity of co-morbidities) and HR-QoL before PICU admission.

Figure 3. Associations between physical and psychological outcome variables



Implications of our findings for clinical practice

A standard follow-up clinic comprising a multidisciplinary team including a paediatric intensivist, physiotherapist and psychologist should be organized for MSS survivors. If indicated, other specialists should be consulted, e.g. an orthopaedic surgeon, especially for early diagnosis and subsequent treatment of lower-limb discrepancy in patients at risk (high severity of illness scores, young age at time of MSS). Patients should undergo periodic measurement (1/year) of blood pressure, serum creatinine with calculation of estimated GFR and urine protein/creatinine ratio. As a consequence all MSS survivors admitted to our PICU since 2001 are now scheduled to undergo follow-up assessments at 3 months, 1 and 2 years after PICU discharge and at the ages of 5, 8, 12 and 18 years.

Structured information (by means of a brochure or internet site) about possible outcome should be provided; not only for parents and patients, but also for healthcare workers.

In addition, we have started a structured follow-up clinic by a multidisciplinary team for other PICU patients, especially patients with cardiomyopathy, neurological failure, post-cardiopulmonary resuscitation and post-extracorporeal membrane oxygenation (neonatal and paediatric).

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