OUTCOME OF MENINGOCOCCAL **SEPTIC SHOCK** IN **CHILDHOOD**

ISBN 978-90-9023308-6

Cover & layout Noenus Design, Soest
Cover photo ‘Pièds à Terre’ by Caro Leriche
Print Print Partners Ipskamp, Enschede

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Financial support This study was financially supported by a grant from Hersenstichting Nederland (Dutch Brain Foundation), grant number 14F06.03

OUTCOME OF MENINGOCOCCAL **SEPTIC SHOCK** IN **CHILDHOOD**

UITKOMST VAN MENINGOKOKKEN
SEPTISCHE SHOCK OP DE KINDERLEEFTIJD

(met een samenvatting in het Nederlands)

Proefschrift

Ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag de
rector magnificus

Prof.dr. S.W.J. Lamberts

en volgens het besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
woensdag 17 september 2008 om 13:45 uur

door

Corinne Maria Patricia Buysse
Geboren te Mortsel (Antwerpen)

ERASMUS UNIVERSITEIT ROTTERDAM

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voor mama en papa,
de Ouders van mijn Leven

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GENERAL INTRODUCTION

General Introduction

Yearly approximately 5000 children (0-18 years) are admitted to specialized pediatric intensive care units (PICU) in the Netherlands. Among these children, although relatively low in number, patients with meningococcal sepsis or septic shock form a well identified and special group with high mortality and morbidity.

Meningococcal sepsis in children

Definitions

Invasive meningococcal disease (MD) is classified as:
- meningitis
- sepsis (MS)
- septic shock (MSS)
- or a combination of meningitis with sepsis or septic shock

Meningitis alone is present in about half of the patients; sepsis alone occurs in about 10%, and about 40% have a mixed picture with meningitis and sepsis.[1-3] In the most severe cases rapid progression of the clinical picture can occur and patients deteriorate hemodynamically (table 1).[4]

Table 1. Definitions

Sepsis	Clinical suspicion of severe infection and evidence of systemic response to infection; tachycardia*, tachypnea*, temperature < 36°C or > 38.5°C.
Septic shock	Sepsis-induced hypotension (systolic blood pressure < 75 mm Hg for children between 3-12 months, < 80 mm Hg for 1-5 years, < 85 mm Hg for 6-12 years, <100 mm Hg for children older than 12 years) or the requirement for vasopressors/inotropes to maintain blood pressure despite adequate fluid resuscitation along with the presence of perfusion abnormalities that may include, but are not limited to; a) lactic acidosis (pH < 7.3 or base excess < -5 mmol/l or plasma lactate levels > 2.0 mmol/l) b) oliguria (diuresis < 0.5 ml/kg/h for at least one hour despite acute volume loading or evidence of adequate intravascular volume without pre-existing renal disease) c) acute alteration in mental status

*tachycardia, tachypnea: > 2 standard deviations for age

Epidemiology: a widespread phenomenon

Outbreaks and epidemics of invasive MD occur throughout the world.[5] Since the introduction of a vaccine against *Haemophilus influenzae* type b, more than 90% of the cases of sepsis with purpura in the western world are caused by *Neisseria meningitidis*.

In the Netherlands invasive MD occurs in 4.5 per 100.000 inhabitants (2001), with an estimated annual mortality of 45 children and adults (Statistics Netherlands).
The incidence of meningococcal sepsis is highest among young children (age 0 to 4 years) and adolescents. Unlike adults, sepsis in childhood occurs most frequently in previously healthy children. Furthermore, the sepsis is more overwhelming and the child can die within the first 24-48 hours due to cardiovascular dysfunction. These sepsis-related differences between adults and children are probably caused by developmental aspects in immune response, cardiovascular function and metabolic response.

Pathogenesis: colonisation, invasion and disease

N. meningitidis is a gram negative diplococcus. Because this microorganism is encapsulated, it is protected against complement mediated phagocytosis and killing. There are different serogroups based upon the different composition of the capsular polysaccharide. Thirteen serogroups have been identified, of which serogroups A, B, C, Y and W are responsible for invasive MD. In the industrialized countries serogroup B and C account for the majority of invasive MD.[1]
N. meningitidis is an exclusively human pathogen and asymptomatic nasopharyngeal carriage among the population is approximately 10%.[6] *N. meningitidis* is able to adhere to epithelial cells in the nasopharynx through a number of adhesion factors. Transmission from person to person takes place by airborne spread during prolonged close contact. Despite the high carriage rate invasive MD occurs in only a very small percentage of people. Risk factors are: preceding viral illness, exposure to passive smoking, household crowding, or altered host immune response (absence of antibodies, complement deficiency). Since carriage rates are high and the disease incidence relatively low, susceptibility for invasive MD is thought to be influenced by host genetic polymorphisms in immune response genes or genes associated with the attachment to and invasion of mucosal epithelial cells. The wide range of MD (from mild upper respiratory tract infection to fulminant MSS) suggests that genetic polymorphisms are involved in influencing disease severity as well.
How exactly *N. meningitidis* can pass through the nasopharynx into the bloodstream is poorly understood. Once in the bloodstream the immune system (T-and B-cells) can limit the growth of the meningococci. Specific antibodies are the most important immunoprotective mechanism. However, especially in young children, the immune response can be insufficient, as a result of low levels of bactericidal antibodies and immaturity of the T-cell system. Meningococci then replicate in the bloodstream and release blebs of outer membrane vesicles, which are rich in endotoxin (lipopolysaccharides). Activation of the host immune mechanisms, especially by these endotoxins, is the cause of the damage to the host tissues. The severity of meningococcal sepsis is directly related to levels of circulating

endotoxin.[7] Endotoxin is bound to endotoxin binding protein (lipopolysaccharide binding protein), a circulating plasma protein, which leads to the activation of a wide range of inflammatory cells. This is the start of an intense inflammatory process with the production of proinflammatory cytokines like tumour necrosis factor-α and interleukin-1β. The release of inflammatory proteins, proteases, and other enzymes by activated neutrophils, results in damage of the endothelial surface.

The major pathophysiological event in MSS is related to dysfunction of the microvasculature: increased vascular permeability, pathological vasoconstriction and vasodilatation, loss of thromboresistance and intravascular coagulation, and myocardial dysfunction.[8]

Increased vascular permeability (the capillary leak syndrome) leads to hypovolaemia. Loss of plasma is initially compensated for by vasoconstriction of the vascular beds. However, as the capillary leak progresses, venous return is impaired and the cardiac output decreases.

Although vasoconstriction is an important early protective mechanism to maintain organ perfusion, it may persist, even after fluid resuscitation. Conversely a minority of children have intense vasodilatation, the so-called “warm shock”.

One of the most typical features of MSS is the occurrence of purpura, caused by the extravasation of red blood cells and widespread intravascular thrombosis. The causes of this disseminated intravascular thrombosis are multifactorial: activation of the procoagulant pathways, downregulation of both the anticoagulant pathways (low levels of especially protein C, and to a lesser extent antithrombin and protein S) and of the fibrinolytic systems (release of plasminogen activator inhibitor 1 and thrombin activatable fibrinolysis inhibitor) as well as an extreme consumption of platelets.[9] The combination of widespread intravascular thrombosis and severe vasoconstriction can lead to ischaemia or in worse cases to necrosis of tissue.

It should be noted that also other microorganisms, both viral and bacterial, can cause sepsis with purpura.

Both hypovolaemia and decreased myocardial contractility contribute to the myocardial dysfunction in MSS. Probably several mechanisms are responsible for the impairment of the myocardial contractility: proinflammatory mediators (tumour necrosis factor-α, interleukin 1β and 6), microthrombi, hypoxia, acidosis, hypoglycaemia, and electrolyte imbalance.[10]

Clinical aspects: careful assessment, early recognition

MSS can progress from initial aspecific symptoms to death within hours. So it is crucial that patients are diagnosed as early as possible. Despite prevalence of this disease, studies have reported that a substantial part of children who are admitted to hospital with meningococcal sepsis had been initially misdiagnosed by a doctor before admission. One reason is that doctors may see few cases in their lifetime, especially since the introduction of the meningococcal serogroup C vaccine. Another reason is that the initial symptoms (fever, malaise and vomiting) are non-specific and common to many self-limiting viral illnesses. These symptoms occur in the first 4-6 hours.[1] The classic symptoms of petechial rash, meningism and decreased consciousness develop later. Other important clinical features are leg pain, cold hands and feet, and abnormal skin colour.

The pathophysiological processes in MSS may result in impairment of microvascular blood flow to the tissues:

- cardiovascular: hypovolaemia and myocardial dysfunction may manifest as compensated shock with tachycardia and vasoconstriction (prolonged capillary refill time, cool skin and extremities), but in severe cases as hypotension and impaired organ perfusion leading to metabolic acidosis, reduced urine output and altered mental status.
- kidneys: due to impaired renal perfusion patients become oligo/anuric with a rise in serum urea and creatinine. In most patients this is transient. However, in severe cases acute tubular necrosis develops.
- lungs: pulmonary oedema may result from the capillary leak syndrome. Increased work of breathing occurs, possibly leading to respiratory failure.
- central nervous system: impaired central nervous system function may be seen as a result of both direct invasion of the meninges by the bacteria and as part of the decreased perfusion. Children with meningococcal meningitis may develop cerebral oedema as a result of brain inflammation, which leads to raised intracranial pressure. Children with MSS are at risk of cerebral infarction if perfusion is not improved.
- adrenal glands: deficiency of substrate (cholesterol) and reduced activity of adrenal enzymes, due to endotoxins, cytokines or medication, might lead to lower cortisol levels and to (relative) adrenal insufficiency. Furthermore, shock and disseminated intravascular thrombosis can cause necrosis of the adrenal glands resulting in (relative) adrenal insufficiency.
- muscles: rhabdomyolysis.

Different scoring systems, combining clinical and/or laboratory data, exist to assess the severity and prognosis of invasive MD. Some of these scoring systems are generic and are used for acute illness in childhood.[11] Others are disease-specific.[12-14] According to these disease-specific scoring systems, signs of MSS and poor prognosis are: absence of meningeal inflammation, leucocytopenia, thrombocytopenia, low C-reactive protein, low serum glucose levels.

In this thesis we used the following 3 scoring systems:
- Pediatric risk of mortality score (PRISM); a generic scoring system[11] (appendix 1)
- Vasopressor score (VAS); dopamine dose (mcg/kg/min) x1 + dobutamine (mcg/kg/min) x1 + epinephrine (mcg/kg/min) x100 + norepinephrine (mcg/kg/min) x100 + phenylephrine (mcg/kg/min) x100.[15]
- Disseminated Intravascular Coagulation score (DIC).[16] (appendix 2)

The rationale behind the use of these 3 scoring systems was the following: children with MSS have fulminant disseminated intravascular coagulation and require different and high doses of vasopressors. So in order to examine if physical and psychosocial sequelae were caused by the underlying disease mechanism (shock, disseminated intravascular coagulation), or by the administration of vasopressors, we used a score to examine the severity of the acute illness (PRISM), disseminated intravascular coagulation (DIC) and the use of vasopressors (VAS).
This vasopressor score developed by Wernovsky has not been validated as a severity score for meningococcal sepsis. Seeing that a validated score for vasopressor requirement in children with meningococcal sepsis is lacking we choose to use the vasopressor score as described by Wernovsky as the best alternative. Furthermore this vasopressor score encompasses dobutamine and norepinephrine, which are the inotropic agents/vasopressors we use most often at our PICU.

Treatment: A, B, C, DEFG

Accurate and aggressive early treatment of meningococcal sepsis can reduce morbidity and mortality.[17] Once meningococcal sepsis is suspected, immediate evaluation of airway, breathing and circulation should be done. High flow oxygen should be given, and an intravenous access should be obtained as soon as possible. Parenteral administration of antibiotics (penicillin or a third generation cephalosporin) and restoration of circulating volume are the most important components of resuscitation. Antibiotics effectively kill the bacteria, but the meningococcal LPS release in the bloodstream, which is the major cause of damage, can not be specifically inhibited. Shock is treated with an initial bolus of 20 ml/kg fluid (NaCl 0.9%), given rapidly over a few minutes. If signs of shock persist, further boluses of fluid should be given.[18] In severe cases large volumes of fluid may be required (100-200 ml/kg/first 24 hours), as the capillary leak is ongoing. There exists much controversy around the optimal resuscitation fluid in children with septic shock. No properly conducted studies have been performed in this field. After the initial bolus, human albumin solutions (4.5%) and fresh frozen plasma can be given.[19] In our hospital an important part of resuscitation fluid consists of fresh frozen plasma, because it is a balanced substitute for clotting factors in this situation.

If shock persists after the administration of 40 ml/kg of fluid within 1 hour, administration of an inotrope (like dobutamine) will be required, as well as further fluid administration. After 40-60 ml/kg of fluid resuscitation and persistent shock, endotracheal intubation and mechanical ventilation should be seriously considered.[19,20] Vasoactive agents (like noradrenaline) are advisable in refractory septic shock, and should be started once a central venous access has been established. Hypoglycaemia, electrolyte imbalance and anaemia should be actively sought and treated.[21] Lumbar puncture should only be done if contraindications are absent: shock, raised intracranial pressure, and disseminated intravascular coagulopathy.[22]
Initial resuscitation and stabilisation inevitably take place at the hospital where the child first presents. Following this, some children will require transfer to a PICU. These children are in need of intubation and mechanical ventilation, and/or require inotropic and/or vasoactive agents.
The principles of management in PICU are the same as those during initial resuscitation: maintaining airway, breathing and circulation. If shock is unresponsive to fluid resuscitation and inotropes, corticosteroids can be indicated. The use of hydrocortisone (1-2 mg/kg) is considered if refractory septic shock and/or hypoglycaemia are present.[23,24] Efforts to improve circulation may necessitate the use of adjunctive agents like vasopressin. On the other hand, if capillary vasoconstriction persists, a vasodilatator (nitroglycerine, prostacyclin) could be added. At the PICU further management of the neurological, renal, and metabolic dysfunction will be required. Also anaemia and disseminated intravascular coagulopathy are common, and therefore transfusions of red blood cells and fresh frozen plasma are frequently required. Although the protein C pathway is deranged, the routine use of protein C is not recommended.[25] Several other trials using new therapeutic approaches have been conducted over the last decade. However they did not significantly reduce mortality.[26-29]

Prevention of invasive MD by the development of vaccines against *Neisseria meningitidis* has had high priority. Currently, polysaccharide vaccins against meningococci of serogroup A, C, W135 and Y are available. The polysaccharide of serogroup B, which forms the majority in the Netherlands, is poorly immunogenic. Due to the sudden increase in the incidence of meningococcal disease in 2001 a national vaccination campaign against serogroup C meningococci (2002) was implemented among children aged 1-18 years.

Outcome: life after PICU

Mortality has decreased in recent years due to centralisation of PICU, introduction of serogroup C vaccine, improvement of awareness and clinical guidelines for children with sepsis.

Patients who survive invasive MD may develop neurological sequelae, like deafness, and skin or limb necrosis requiring grafting or amputation. In the second part of this introduction a systematic review of the literature on outcome of invasive MD is presented.

Appendix 1: PRISM II Score

The worst values in the first 24 hours after PICU admission.

Systolic blood pressure (mm Hg)	**Infants**	**Children**	**Score**
	Other values	Other values	0
	130-160	150-200	2
	55-65	65-75	2
	> 160	> 200	6
	40-54	50-64	6
	< 40	< 50	7
Diastolic blood pressure (mmHg)	**All ages**		**Score**
	Other values		0
	> 110		6
Heart rate (beats/minute)	**Infants**	**Children**	**Score**
	Other values	Other values	0
	> 160	> 150	4
	< 90	< 80	4
Respiratory rate (breaths/minute)	**Infants**	**Children**	**Score**
	Other values	Other values	0
	61-90	51-70	1
	> 90	> 70	5
	intubated	intubated	5
PaO_2/FiO_2 (PaO_2 in mmHg)	**All ages**		**Score**
1 kPa = 1/0.13333 mmHg			
	Other values		0
	200-300		2
	< 200		3
$PaCO_2$ ($PaCO_2$ in mmHg)			
1 kPa = 1/ 0.13333 mmHg	**All ages**	**All ages**	**Score**
	(mmHg)	(kPa)	
	Other values	Other values	0
	51-65	6.8-8.7	1
	> 65	> 8.7	5

Glascow Coma Score		**All ages**		**Score**
		Other values		0
		< 8		6
Pupillary reactions		**All ages**		**Score**
		Other values		0
		Unequal/Dilated		4
		Fixed and dilated		10
PT or PTT	**All ages**	**All ages**		**Score**
	Other values	Other values		0
	>= 1.5x control	PT< 60% or PTT> 50 sec		2
Bilirubin	**All ages**	**All ages**		**Score**
mg/dl x 17.1 = µmol/l	(mg/dl)	(µmol/l)		
	Other values	Other values		0
	> 3.5	> 59.9		6
Potassium	**All ages**	**All ages**		**Score**
MEq/l= mmol/l	(MEq/l)	(mmol/l)		
	Other values	Other values		0
	3.0-3.5	3.0-3.5		1
	6.5-7.5	6.5-7.5		1
	< 3.0	< 3.0		5
	> 7.5	> 7.5		5
Calcium	**All ages**	**All ages**	**Ionised calcium**	**Score**
Mg/dl : 4 = mmol/l	(mg/dl)	(mmol/l)	(mmol/l)	
	Other values	Other values	Other values	0
	7.0-8.0	1.75-2.00	0.87-1	2
	12.0-15.0	3.00-3.75		2
	< 7.0	<1.75	< 0.87	6
	> 15.0	> 3.75		6
Glucose	**All ages**	**All ages**		**Score**
Mg/dl : 18.2 = mmol/l	(mg/dl)	(mmol/l)		
	Other values	Other values		0
	40-60	2.2-3.3		4
	250-400	13.5-22.5		4
	< 40	< 2.2		8
	> 400	> 22.5		8
Bicarbonate	**All ages**	**All ages**		**Score**
mEq = mmol/l	(mg/dl)	(mmol/l)		
	Other values	Other values		0
	< 16	< 16		3
	> 32	> 32		3

Appendix 2: DIC score

Platelet count (x10³/l)	
> 100	0
≤ 100	1
≤ 50	2
Fibrine dimers (ml/l)	
< 0.25	0
≥ 0.25 and < 5	2
≥ 5	3
Prothrombin time (sec.)	
< 15	0
≥ 15 and < 19	1
≥ 19	2
Fibrinogen (g/l)	
> 1	0
≤ 1	1

DIC score ≥ 5: presence of disseminated intravascular coagulation.

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Outcome of invasive meningococcal disease in children: a systematic review of the literature

Thirty-two studies were found in which one or more aspects of outcome in survivors of invasive meningococcal disease (MD) and/or their families were described. The patient characteristics, inclusion criteria, methods and main outcomes are described in table 1.

In these 32 studies, with a total of 1847 patients, both children and adults, physical and psychological outcomes were evaluated short-term or long-term after hospital discharge.

Physical sequelae

Orthopaedic sequelae and skin scarring were described in 14 of the 32 studies.[1-14] In these 14 studies, both children and adults were included, severity of illness varied. In some studies there was selection bias; for example, by including only patients referred to the department of Orthopedics.[1,8,11,13,14] Subsequently the incidence and severity of orthopaedic sequelae and skin scarring varied. An interesting study regarding the cause of orthopaedic sequelae is the study of Grogan et al.[14] Based on histological studies they concluded that physeal growth arrest is probably caused by ischemia, not by osteomyelitis.

Renal outcome was investigated in 3 studies.[3,15,16] One of these 3 studies investigated long-term renal function in 12 patients with meningococcal sepsis-associated acute renal failure necessitating renal replacement therapy.[15] In one patient renal failure necessitated kidney transplant.[3]

Pulmonary evaluation was done in 18 MSS patients, who were mechanically ventilated.[17]

Neurological outcome was studied in 10 studies.[3,7,15,18-24] Both meningococcal meningitis as well as meningococcal sepsis resulted in irreversible neurological sequelae. These sequelae varied from mild to severe: focal neurological deficit, hearing loss, speech problems, loss of central vision, epilepsy, spastic quadriplegia with epilepsy and cortical blindness. In most studies the incidence of hearing loss was low.[3,20, 21,23,24]

In 35 patients imaging of the brain was performed; abnormalities were found in 8 patients.[18,22]

Dental complications were described in 4 patients.[25-27] All 4 were young at time of the acute illness (< 2 years). Furthermore in the studies of Faibis and Walton patients had a fulminant course of MS, leading to amputations of limbs.[25,26]

Growth disturbances (< 0.4th centile for height) were described in 3 of the 12 MS patients with acute renal failure necessitating renal replacement therapy.[15]

Psychological sequelae

Psychological evaluation of patients, mainly short-term (≤ 1 year), was done in 4 studies.[28-31] These studies demonstrated that patients were at risk for psychological distress and post-traumatic stress disorder in the year following hospital discharge. Also in parents psychological distress was found in the 2 years following hospital discharge.[28,29,32]

Quality of life

Quality of life was described in 2 studies.[3,4] In one study, 23% of the patients reported a reduction in quality of life due to the meningococcal disease. Reduced energy, increased anxiety, reduction of leisure activities, and reduced ability to work were the most common complaints. Although we need to be careful since no validated quality of life questionnaire was used.[3] In another study quality of life scores were described in 4 patients with physical sequelae, no comparisons were made with normative data or control group.[4]

Conclusions

Some of these reviewed studies have a number of methodological limitations: heterogeneous study population (type/severity of invasive MD, age), small number of patients, no standardized outcome measurements. Consequently, differences in study population, follow-up interval and measurement tools make the comparison and synthesis of the results difficult.

None of these studies give a complete overview of outcome, both physical and psychological, using standardized assessment procedures in a large cohort of survivors of invasive MD.

Table 1. Patient characteristics, inclusion criteria, methods and main outcomes

Reference	Population	Inclusion criteria	Inclusion period	Follow-up interval	Methods	Main results
(1)	children n=21	IMD, admitted to a PICU, requiring debridement, skin grafting or amputation	1987-2000	(4 m-5 y?)	review of medical records interview (n=11)	amputations: 43% late surgical interventions in 43% for the relief of scar contractures, nonhealing lesions, genu valgum or fibula overgrowth causing stump ulceration
(2)	adult n=1	MSS	?	8 m	RX arm	resolution of the multiple radiolucencies (cortical bone destruction) and periosteal reaction
(3)	children and adults n=420	IMD	1990-1994	9 m -6 y	review of medical records telephone interview postal questionnaires	skin scarring scars: 12.5% amputation: 5% sensorineural hearing loss: 3.5% renal failure: 1% (kidney transplant in 1 patient) neurological sequelae: 2% physical impairment score: 47% reduction in QoL: 23%
(4)	young adults n=17?	IMD	1990-1999	?	review of medical records telephone interview (EuroQoL 5D)	amputation: 18% skin scarring: 6% hearing loss: 6%
(5)	child n=1	MS	?	3 y	RX	skeletal deformities
(6)	toddler n=1	MSS with cardiac arrest	?	18 m	RX and MRI ulna	pseudarthrosis midulna (deformity of wrist and forearm) through-knee amputations
(7)	children n=2	MSS	?	6-8 m	clinical examination skeletal radiography	case 1: amputation, hypoxic-ischemic encephalopathy, premature fusion of growth plates of extremities, osteolyses case 2: poor ossification of the femoral capital epiphyses, irregular metaphyses and very short femoral necks
(8)	children n=11	MD and referral to the service of paediatric orthopaedics	?	?	clinical examination skeletal radiography	bone injury (mostly lytic lesions): 91% physeal plate destruction: 82% lower limb lenght inequality: 64% deformity of ankle and /or knee: 55% amputation: 36%
(9)	children n=19	MS	?	4 y	clinical examination skeletal radiography	patellar dystrophy: 21%
(10)	toddler n=1	MSS with quadrilateral limb amputation	?	1.5 y	review of rehabilitation	
(11)	children n=24	MS with late orthopaedic sequelae	?	1-10 y	review of medical records review of radiographs	growth plate arrest: 96% angular deformity (ankle, knee): 92% joint contractures (digits, knee): 25% amputations: 38%
(12)	children n=122	MS	1985-2002	2-9 y	review of radiographs review of medical records	amputation: 5% physeal growth arrest: 13%
(13)	children n=9	MSS, admitted to a PICU, and severe peripheral ischemia	1993-1999	?	?	amputations (below-knee, fingers, forearms): 89%
(14)	children n=9	MS with major orthopaedic problems	?	≥ 3 y	histological studies on specimens of bone and cartilage	growth plates: permanent ischemic damage
(15)	children n=12	MS, admitted to a PICU,with oliguric acute renal failure necessitating renal replacement therapy	1996-2000	2-7 y	blood pressure glomerular filtration rate (GFR) 24-hr urine protein excretion DMSA scan	abnormal GFR, proteinuria and hypertension: 17% renal parenchymal defect: 8% neurologic sequelae: 33% growth disturbances: 25%

Chapter 1 | General Introduction

Reference	Population	Inclusion criteria	Inclusion period	Follow-up interval	Methods	Main results
(16)	children and adults n=10	MS or MSS, admitted to an intensive care unit, with acute renal failure	1989-1995	?	renal biopsy (n=1)	bilateral cortical necrosis (n=1)
(17)	children n=18	MSS, requiring mechanical ventilation	1995-1997	2-5 y	lung function test	desaturation during maximal exercise: 2.5% (range 0-20%)
(18)	children and adults n=93	MD	?	1 y	EEG hearing tests CT brain (n=34) neuropsychological test (n=9)	neurological sequelae: 14% EEG abnormalities: 19% hearing loss: 33% abnormalities on CT brain: 21%
(19)	adolescent n=1	MSS, with cranial nerve palsy	?	6 m	clinical examination	cranial nerve palsy resolved
(20)	children n=115	IMD	1988-1990	8-11 y	neurological examination tone audiometry validated behavior and intelligence tests	sensorineural loss: 4% lower level of cognitive functioning and more Attention Deficit Hyperactivity Disorder in comparison with control group
(21)	children n=391	IMD	1995-2000	2 m-5 y	review of medical records	neurological sequelae: 5% hearing loss: 3%
(22)	adolescent n=1	meningococcal meningitis	?	24 y	neuropsychological examination MRI brain	dyslexia, dysgraphia, dyscalculia and disorders of spatial orientation extensive white matter abnormalities
(23)	children n=68	meningococcal meningitis or bacteremia	1977-1979	?	?	hearing loss: 9%
(24)	children n=118	IMD	1988	?	?	bilateral hearing loss: 3% hemiplegia: 2%
(25)	children n=2	MSS, admitted to a PICU, referred to the department of Dentistry	?	1 y- 7 y	medical history oral examination intra-oral radiographs	tooth hypoplasia or agenesis, ectopic or delayed eruption, hypocalcification, caries both patients had extensive amputations
(26)	child n=1	MS	?	8 y	medical history oral examination intra-oral radiographs	no eruption of the permanent central incisors
(27)	child n=1	MSS	?	7 y	medical history oral examination intra-oral radiographs	discolouration of permanent teeth severely hypoplastic teeth
(28)	children and their mothers n=29	IMD, admitted to a PICU	1996-1997	3-12 m	Behavior Check List Strengths and Difficulties Questionnaires Impact of Event Scales General Health Questionnaire	symptoms of PTSD: children 62%, mothers 48%
(29)	children and their parents n=60	MD	1999-2000	4 m	Strengths and Difficulties Questionnaires General Health Questionnaire Impact of Event Scales	symptoms of PTSD: children 15%, mothers 48% fathers 19%
(30)	children n=66	IMD	?	1 y	Strengths and Difficulties Questionnaires validated questionnaires for psychiatric symptoms	psychiatric disorders (oppositional defiant, phobic): 28% physical sequelae: 6%
(31)	adolescents and young adults n=11	MS	?	1-7 y	interview	high degree of resilience in response to their experiences
(32)	parents of children n=192	MS, admitted to a PICU	1993-2001	3 m-7 y	Goldberg General Health Questionnaire-30	psychological distress in the first 2 y after PICU discharge

MD: meningococcal disease, IMD: invasive meningococcal disease (meningitis, sepsis or both), MS: meningococcal sepsis, MSS: meningococcal septic shock

Chapter 1 | General Introduction

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Aims of the present study

The relatively large, homogeneous cohort of patients with MSS admitted to the PICU of the Erasmus MC-Sophia in the last 2 decades offered the possibility to investigate the neglected area of outcome, both from a medical and psychosocial point of view, with standardized assessment procedures.
The aims were:
- To analyse mortality of children with MSS admitted to our PICU, and the risk factors of mortality.
- To study short-term outcome in survivors of MSS, and their parents.
- To study long-term outcome, both physical and psychosocial, in survivors of MSS, and the effect of that outcome on health-related quality of life (HR-QoL). To study outcome, psychosocial and HR-QoL, in parents of these children.
- To develop recommendations for follow-up research in children admitted to a PICU, not only for children with MSS but critically ill children in general.

The long-term psychosocial outcome in patients and parents is described in the thesis of L. Vermunt.

Structure of this thesis

In chapter 2 epidemiology, mortality and risk factors of non-survival are studied in children with sepsis and purpura admitted to the PICU of the Erasmus MC-Sophia between 1988 and 2006.
The commentary on our findings regarding the epidemiology in children with sepsis and purpura, as well as our response to these comments are presented.
Chapter 3 describes the short-term outcome (up to 2 years after PICU discharge) in survivors of MSS, and their parents. These children were admitted to the PICU of the Erasmus MC-Sophia between 2001 and 2005.
In chapters 4-7 the long-term outcome, physical and HR-QoL, of all consecutive surviving patients with MSS requiring intensive care treatment at the PICU of the Erasmus MC-Sophia between 1988 and 2001 is presented.
Finally, in chapter 8, the main findings and conclusions of this thesis are discussed. Implications and recommendations for follow-up, both patient care and research, are given. These recommendations are developed not only for survivors of MSS, but for PICU patients in general.

2

IMPROVED SURVIVAL OF CHILDREN WITH SEPSIS AND PURPURA: EFFECTS OF AGE, GENDER AND ERA

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Crit Care. 2007;11(5):R112

Abstract

Background In order to gain insight in factors that might affect results of future case-control studies we performed an analysis of children with sepsis and purpura admitted to the Erasmus MC-Sophia Paediatric Intensive Care Unit (PICU).

Methods Between 1988 and 2006, all 287 children consecutively admitted with sepsis and purpura were included in various sepsis studies. Data regarding age, gender, ethnicity, serogroup of *Neisseria meningitidis*, severity, therapy and survival were collected prospectively. These data were pooled into one database and analyzed retrospectively.

Design Prospective cohort study.

Results The case fatality rate (CFR) from sepsis and purpura was 15.7%. During the study period survival improved significantly. Younger age was significantly associated with more severe disease and a higher CFR. Children under the median age of 3.0 years had an increased risk of CF (OR 4.3; 95%CI 2.1-9.2, p< 0.001). Gender was not associated with CFR. However, males did have higher Pediatric Risk of Mortality-scores (PRISM-score), fewer PICU free days and more presence of shock. The course of sepsis and purpura was not related to ethnic origin. A causative organism was isolated in 84.3%. *N. meningitidis* was the major organism (97.5%). Although *N. meningitidis* serogroup B was observed more often in younger children, serogroups were not associated with severity or survival. During the study period the use of inotropic agents and corticosteroids changed substantially (less dopamine, more dobutamine, norepinephrine and corticosteroids).

Conclusions Age and gender are determinants of severity of paediatric sepsis and purpura. Survival rates have improved during the last two decades.

Introduction

Sepsis and purpura in children is a clinically distinct disease entity caused by high concentrations of microbes and their products. Since the introduction of a vaccine against *Haemophilus influenzae* type b more than 90% of the cases of sepsis and purpura in the western world are caused by *Neisseria meningitidis*.[1-3] The resulting disease entity is referred to as meningococcal sepsis.

Meningococcal sepsis in children develops when the initial host response to the infection becomes inappropriately amplified and dysregulated. Clinically, the onset is often insidious. After the development of the first petechiae, the patient rapidly deteriorates and may subsequently develop shock, disseminated intravascular coagulation (DIC) and ultimately organ failure. The severity of these symptoms requires immediate therapy.[4,5] Despite recent advances in therapy, the case fatality rate (CFR) remains high and ranges from 4 to 40%.[1,6-8] The incidence of disease is highest among young children (age 0 to 4 years) and adolescents.[1-3] In the Netherlands meningococcal sepsis occurs in 4.5 per 100,000 inhabitants (2001). Due to the sudden increase in the incidence of meningococcal disease in 2001 a national vaccination campaign against serogroup C meningococci (2002) was implemented among children aged 1-18 years.[9]

In recent years many studies have focused on the elucidation of the pathogenesis of sepsis. However, much is still unknown about the epidemiology of sepsis in children. In this paper we seek to describe the epidemiology of sepsis and purpura in children referred to the Paediatric Intensive Care Unit (PICU) of Erasmus MC-Sophia Children's Hospital in Rotterdam, the Netherlands.

The aim of this study was to analyze the variation in severity and survival of children with respect to age, gender, ethnicity and serogroup of *N. meningitidis*.

Materials and Methods

Participants

All children admitted with sepsis and purpura (and/or petechiae) to the PICU of the Erasmus MC-Sophia Children's Hospital since 1988 were included. A vast majority of the children were previously included in Rotterdam-based sepsis studies.[11-16] Data regarding the remaining children with sepsis and purpura were derived from PICU admission records. Informed consent was obtained from parents or legal guardians of all children that were included in this study. Children were considered to have sepsis when they presented with tachycardia, tachypnea and a body temperature < 36°C or > 38.5°C (rectal).[17] Prospective data on all children were collected at

Chapter 2 | Improved Survival of Children with Sepsis and Purpura: Effects of Age, Gender and Era

various time points in the course of the disease. Both laboratory parameters and disease severity scoring systems, like PRISM-score and predicted death rate (PDR) based on the Rotterdam score, were selected as markers of severity of disease.[18-20] Additionally, presence of DIC and presence of shock were recorded as markers of severity.[17,19,21] The number of PICU free days was determined on day 28 after admission using the date of admission and the date of discharge. A non-survivor had 0 PICU free days.

All laboratory parameters, obtained at baseline from an arterial blood sample, were collected within 4 hours after admission to the PICU.

Ethnicity was determined by checking patient information, and if not specified, first and surname were checked and ethnicity was determined by means of the combined name method.[22] Ethnicity was categorized into Dutch Caucasian, Turkish, Moroccan, Hindustani, African descent and other.

Serogrouping of *N. meningitidis* isolates was performed at the Netherlands Reference Laboratory for Bacterial Meningitis Amsterdam using immunodiffusion with polyclonal antisera.[23]

Statistical analyses

Retrospectively severity and survival of children with sepsis and purpura with respect to age, gender, causative organism and ethnicity was analyzed using SPSS 11.01. Clinical and laboratory parameters were included in the analysis only if they were determined in at least 90% of all children.

Mann-Whitney U test, Student's T test, Chi-squared test and Spearmann correlation (r_s) were used when appropriate. When necessary, variables were log-transformed to obtain an approximately normal distribution. For these variables, geometric mean values and their 95% confidence intervals (CI) are depicted in text and tables. P-values ≤ 0.05 were considered to be statistically significant.

Results

Between August 1988 and June 2006, 287 children with sepsis and purpura were admitted to the PICU of the Erasmus MC-Sophia Children's Hospital. The overall CFR was 15.7% (45 children died). Median age at admission was 3.0 years (range 0.1-17.9 years) (Figure 1). Of the 287 children, 155 (54%) were male and 132 (46%) were female. The male-to-female ratio was 1.2. The majority of the children were Dutch (73.8%).

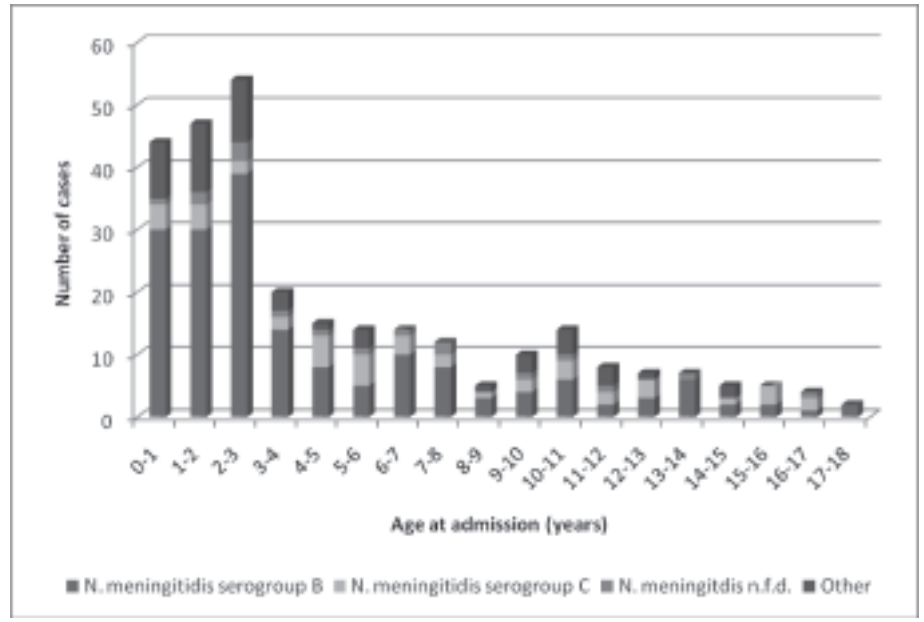

Figure 1. Distribution of age at admission in children with sepsis and purpura
The children are subdivided according to causative organism.

Laboratory parameters present at baseline in more than 90% of the children were base excess, lactate, C-Reactive Protein (CRP), fibrinogen, platelet count, leukocytes and glucose.

Survival

Severity of illness was significantly less in survivors when compared to non-survivors, both in disease severity scoring systems and laboratory parameters (Table 1). Survival was significantly correlated with year of admission (p=< 0.05, r_s0.128), indicating that survival has improved significantly during the study period (Figure 2). Gender did not differ between survivors and non-survivors (p=0.15). The vast majority of fatal cases died of refractory septic shock (75.6%).

Age

Age was significantly correlated with PRISM-score (p< 0.001, r_s-0.317), PDR (p< 0.001, r_s-0.321), presence of DIC (p< 0.001, r_s-0.245), base excess (p< 0.001,

Table 1. Comparison of disease characteristics between non-survivors and survivors

		Survivors	Non-survivors
Total number of children (%)		242	45
		(84.3)	(15.7)
Male-to-female ratio		1.1	1.7
Number of children with DIC (%)		174[ab]	32[b]
		(75)	(97)
N. meningitidis serogroup	B (%)	147 (74.2)	28 (73.7)
	C (%)	37 (18.7)	7 (18.4)
PRISM		14[c]	23[c]
		(1 – 37)	(8 – 44)
PDR (%)[d]		3.1[c]	87.4[c]
		(0 – 100)	(1.1 - 100.0)
Base excess (mmol/L)		-7[c]	-13[c]
		(-23 – 4.4)	(-28 - 0.6)
Lactate (mmol/L) (geometric mean, 95% CI)		3.7[c] (3.4 - 4.3)	6.6[c] (5.8 - 7.4)
CRP (mg/L)		106[c]	53[c]
		(10 – 334)	(6 – 226)
Fibrinogen (g/L)		2.8[c]	0.9[c]
		(0.3 - 6.8)	(0.2 - 5.4)
Platelet count (x10^3/µL)		126[c]	47[c]
		(15 – 475)	(13 – 202)
Leukocytes (x10^3/µL) (geometric mean, 95% CI)		10.6[c] (9.5 – 11.9)	4.7[c] (3.7 - 6.0)
Glucose (mmol/L) (geometric mean, 95% CI)		6.3[c] (5.9 - 6.8)	4.3[c] (3.6 - 5.3)

[a]results represent median (min-max) unless stated otherwise

[b]p< 0.01, [c]p< 0.001, [d]PDR was based on the Rotterdam score

DIC: Disseminated Intravascular Coagulation, PRISM: Pediatric Risk of Mortality Score, PDR: Predicted Death Rate, CRP: C-reactive Protein

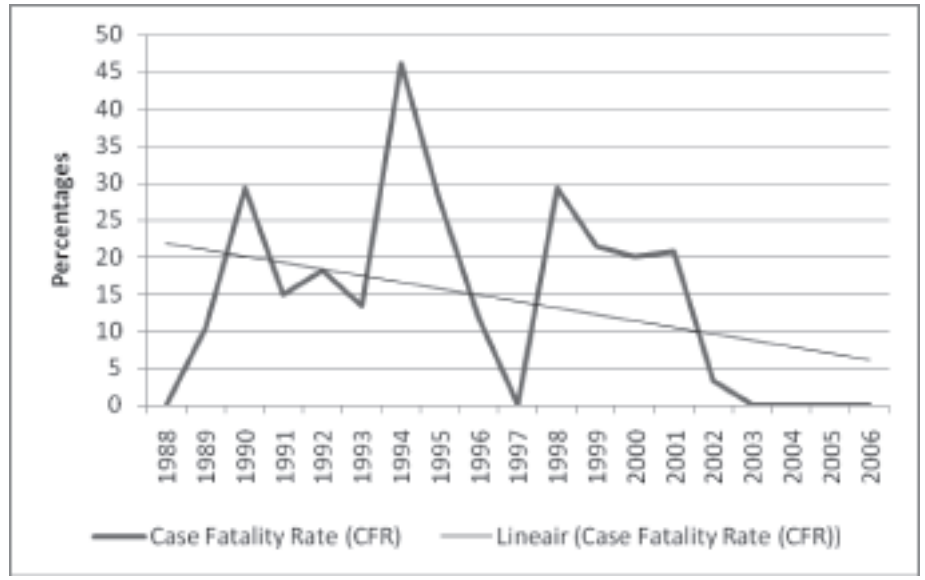

Figure 2. Case fatality rate (CFR) and CFR trend line during the study period

r_s0.313), CRP (p< 0.05, r_s0.161), fibrinogen (p< 0.001, r_s0.301), leukocyte count (p< 0.001, r_s0.284), thrombocyte count (p< 0.01, r_s0.184) and glucose levels (p< 0.001, r_s0.296). This indicates that younger children had higher PRISM scores, higher PDR, more presence of DIC, lower base excess, lower CRP, lower fibrinogen, lower leukocyte count, lower thrombocyte count and lower glucose levels on admission. Median age of children was 3.0 years (range 0.1-17.9 years). Children ≤ 3.0 years had a higher CFR (OR 4.3; 95% CI 2.1-9.2, p< 0.001) (Figure 3).

Gender

The median age did not differ between males (2.8 years) and females (3.5 years) (p=0.16). Male patients had significantly fewer PICU free days (p=0.04) and higher PRISM-scores (p=0.02) than females. Shock was slightly more often present in males than in females (89% versus 80%, p=0.04). Case fatality rate and other markers of severity of disease did not differ between males and females. Since males had higher PRISM-scores, but no increased CFR, we analyzed the different

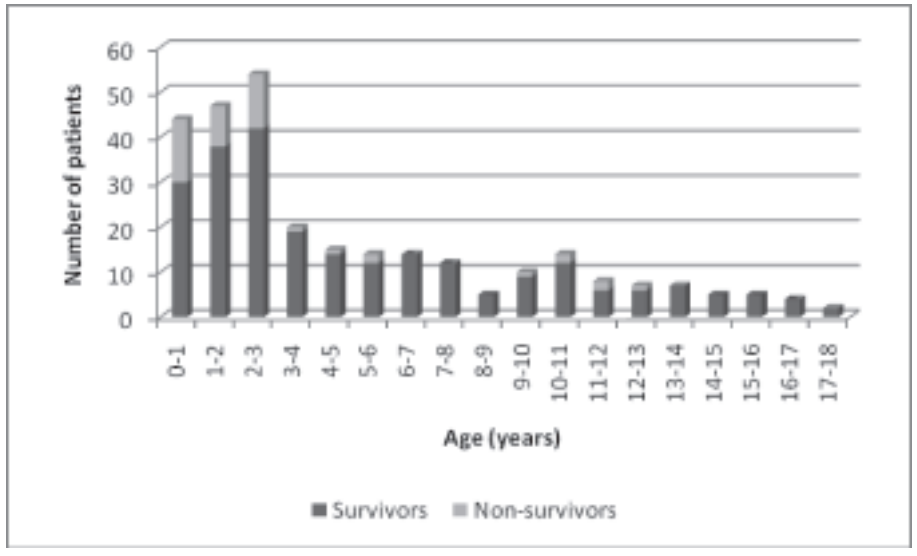

Figure 3. Distribution of age at admission among survivors and non-survivors of sepsis and purpura

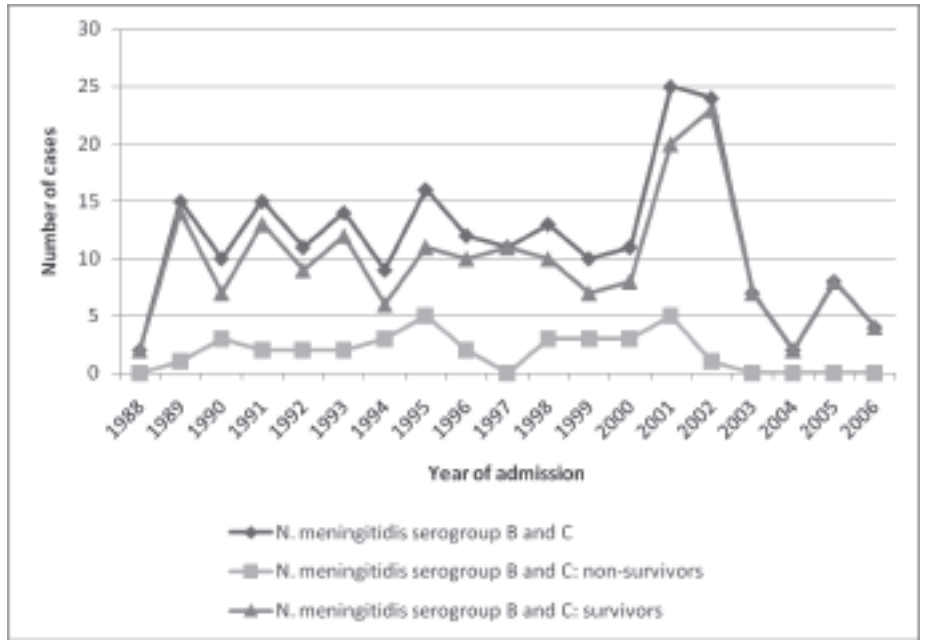

Figure 4. Number of children with sepsis and purpura due to *N. meningitidis* per year (since 1988), admitted to the PICU of Erasmus MC-Sophia Children's Hospital

variables determining the PRISM-score. Of these variables, we only observed a trend for lower glucose levels in males compared to females (p=0.06).

Ethnicity

The majority of the children were Dutch Caucasians (n=211, 73.5%). Of the remaining 76 children, 12 were Turkish (4.2%), 16 were Moroccan (5.6%), 3 were Hindustani (1.1%), 7 were from African descent (2.5%), 7 were designated other

Table 2. Incidence of serogroup, serotype and serosubtype of *N. meningitidis*

Serogroup	Serotype	Serosubtypee	N	%
B	1	P1.4	4	1.8
		P1.16	4	1.8
		NT	3	1.4
		Other	1	0.5
	2A		3	1.4
	4	P1.4	57	26
		P1.6	3	1.4
		P1.7	3	1.4
		P1.9	4	1.8
		P1.10	4	1.8
		P1.15	5	2.3
		NT	28	12.8
		Other	13	5.9
	NT	P1.1	6	2.7
		P1.4	8	3.7
		NT	8	3.7
		Other	4	1.8
	Other		17	7.8
C	2A	P1.2	12	5.5
		P1.5	9	4.1
		P1.7	1	0.5
		NT	7	3.2
	2B	P1.1	1	0.5
		P1.2	7	3.2
	4	P1.4	3	1.4
	NT		2	0.9
	Other		2	0.9

NT: Non-typable

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Table 3. Comparison of disease characteristics based on serogroup of *N. meningitidis*

	N. meningitidis [a]	
	Serogroup B	**Serogroup C**
Total number of children	175	44
Age	2.8[b]	6.0[b]
	(0.1 - 17.9)	(0.1 - 16.5)
PRISM	16	14
	(1 – 37)	(1-35)
PDR (%)[c]	8.9	4.9
	(0 – 100)	(0 – 100)
Number of children with DIC (%)	128	32
	(81)	(74)
Number of PICU free days	24	25
	(0 – 28)	(0 – 27)
Base excess (mmol/L)	-8	-8.0
	(-21 - 4.4)	(-28 – 3)
Lactate (mmol/L) (geometric mean, 95% CI)	4.2 (3.8 - 4.6)	3.5 (2.9 - 4.2)
CRP (mg/L)	82[d]	128[d]
	(6 – 287)	(20 – 326)
Fibrinogen (g/L)	2.4	2.8
	(0.2 - 6.8)	(0.3 - 6.6)
Platelet count (x10^3/µL)	110	113
	(15 – 475)	(13 – 336)
Leukocytes (x10^3/µL) (geometric mean, 95% CI)	8.8[e] (7.6 - 10.1)	12.2[e] (9.9 - 15.0)
Glucose (mmol/L) (geometric mean, 95% CI)	5.9 (5.4 - 6.5)	6.2 (5.5 - 6.9)

[a]results represent median (min-max) unless stated otherwise

[b]p< 0.001, [c]PDR was based on the Rotterdam score, [d]p< 0.01, [e]p< 0.05

PRISM: Pediatric Risk of Mortality score, DIC: Disseminated Intravascular Coagulation, PICU: Pediatric Intensive Care Unit, CRP: C-reactive Protein

(2.5%) and in 31 children ethnicity could not be determined (10.8%). No differences between the different ethnic groups were found with respect to severity of disease or case fatality.

Causative organism

A causative organism could be determined in 242 children (84.3%), with *N. meningitidis* being the major causative organism (n=236 (97.5%), Figure 4). Of these 236, 175 (74.2%) were *N. meningitidis* serogroup B, 44 (18.6%) were serogroup C and in 17 (7.2%) the serogroup was not determined (Table 2). *Streptococcus pneumoniae* was the causative organism in 3 children, *Staphylococcus aureus* in 1 and *H. influenzae* in 2. Of the remaining 45 children, 43 children had clinical features of meningococcal sepsis.[3]

In 2 children, the causative organism could not be determined due to logistic reasons. No differences were observed between *N. meningitidis* serogroup B and C with respect to survival, disease severity scoring systems and presence of shock. However, the median age of children with sepsis and purpura due to serogroup B was lower than that of the serogroup C infected children (2.8 and 6.0 years respectively, p< 0.001, Table 3). The distribution of serogroup, serotype and serosubtype of *N. meningitidis* in the positive cultures is depicted in Table 2.

Meningococcal C vaccination campaign and therapy

In 2001 and 2002 a sudden increase was noted in the incidence of meningococcal infection in the Netherlands. This was mainly caused by serogroup C *N. meningitidis*. The implementation of the meningococcal C vaccination campaign in July of 2002 resulted in a sharp decline of the number of cases caused by serogroup C (Figure 4). Since 2003 there has not been a case of sepsis in our hospital due to *N. meningitidis* serogroup C. Parallel to this, the incidence of serogroup B has declined and is returning to the incidence level before 1989.

Before the national meningococcal C vaccination, 248 children in our study population were admitted with sepsis and purpura, whereas since the vaccination campaign 39 children have been admitted.

Remarkably, since the implementation of meningococcal C vaccination no deaths have occurred in children with sepsis and purpura admitted to our PICU. The median age of the children did not differ significantly before and after vaccination (3.2 and 2.5 years, respectively, p=0.23, Table 4). Glucose levels were significantly lower

Table 4. Comparison of disease characteristics between children with sepsis and purpura before and after the national Meningococcal C vaccination campaign, July 2002

	Before MenC vaccination	After MenC vaccination
Total number of children (%)	248	39
	(86.4)	(13.6)
Case fatality (%)	45[b]	0b
	(18.1)	(0)
Age (yrs)	3.2[a]	2.5
	(0.1 - 17.9)	(0.3 - 13.1)
Number of children with DIC (%)	186[c]	20[c]
	(79.5)	(62.5)
Number of PICU free days	24[c]	25[c]
	(0 – 28)	(0 – 27)
PRISM	15	20
	(1 – 44)	(2 – 37)
PDR (%)[d]	5.6	8.1
	(0 – 100)	(0 – 100)
Base excess (mmol/L)	-7.7	-8
	(-28 - 4.4)	(-18 - -2)
Lactate (mmol/L) (geometric mean, 95% CI)	4.1 (3.8 - 4.4)	4.0 (3.3 - 4.8)
CRP (mg/L)	93	84
	(6 – 326)	(25 – 334)
Fibrinogen (g/L)	2.5	3.2
	(0.2 - 6.8)	(0.3 - 6.4)
Platelet count (x10^3/µL)	110	135
	(13 – 475)	(25 – 227)
Leukocytes (x10^3/µL) (geometric mean, 95% CI)	8.9 (7.9 - 10.0)	12.1 (9.4 - 15.6)
Glucose (mmol/L) (geometric mean, 95% CI)	5.7[c] (5.3 - 6.2)	7.2[c] (6.2 - 8.2)

[a]results represent median (min-max) unless stated otherwise

[b]p< 0.01, [c]p< 0.05, [d]PDR was based on the Rotterdam score

DIC: Disseminated Intravascular Coagulation, PICU: Pediatric Intensive Care Unit, PRISM: Pediatric Risk of Mortality Score, PDR: Predicted Death Rate, CRP: C-reactive Protein

in the patient group before compared to the patient group after the vaccination campaign (p< 0.05). Children admitted before the vaccination campaign had significantly fewer PICU free days and more presence of DIC (both p< 0.05). The PRISM score was not significantly different between patients groups before and after the meningococcal C vaccination campaign. In addition, since 2002 treatment of children with meningococcal sepsis at our PICU has changed due to implementation of international guidelines.[8] After the vaccination campaign more children were treated with corticosteroids (18 (9.3%) before vs. 15 (42.9%) after, p< 0.001) and more children were mechanically ventilated (128 (51.8%) before vs. 28 (71.8%) after, p< 0.05) (Table 3). In addition, year of admission was significantly correlated with the

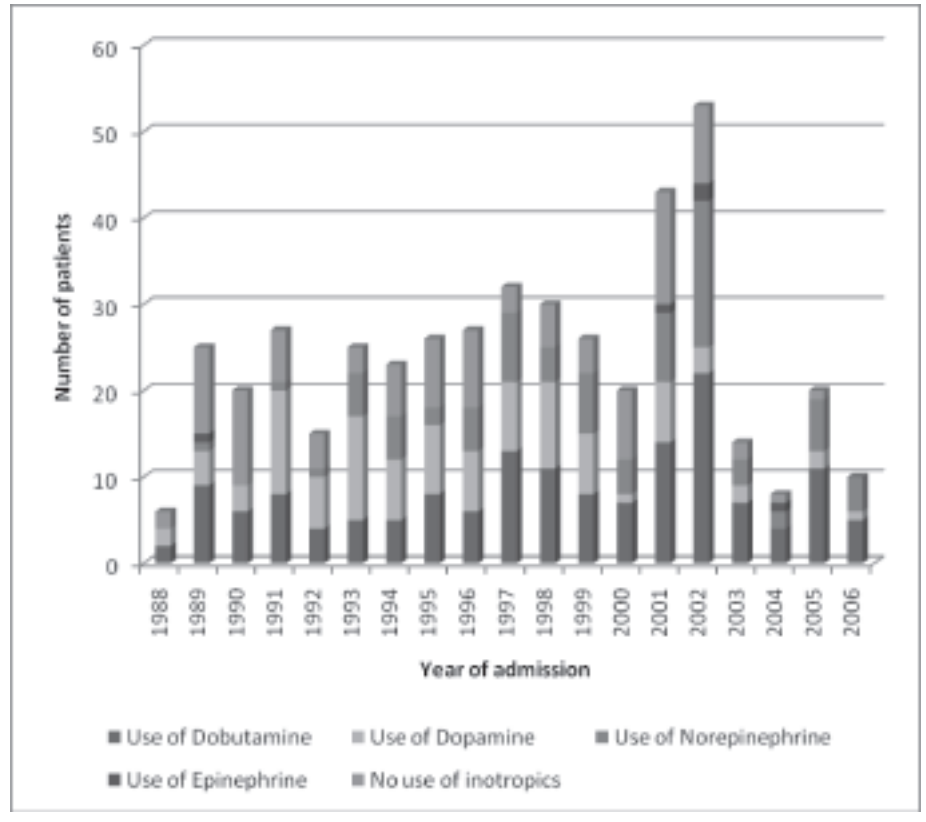

Figure 5. Use of inotropic agents during the study period 1988-2006.

(Note: some patients received more than one inotropic agent, therefore the number of patients in this figure exceeds the number of patients in this study (N=287)).

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use of dobutamine ($p< 0.001$, r_s0.262), dopamine ($p< 0.001$, r_s-0.218), norepinephrine ($p< 0.001$, r_s0.329) and corticosteroids ($p< 0.001$, r_s0.245), but not with the use of epinephrine. This indicates that during the study period the use of dobutamine, norepinephrine and corticosteroids significantly increased in the treatment of sepsis and purpura while the use of dopamine significantly decreased (Figure 5).

Discussion

In this mono-center cohort study of 287 children between 0 and 18 years with sepsis and purpura, we found that younger children had more severe disease and an increased risk of case fatality. The CFR of sepsis and purpura has improved in recent years despite comparable disease severity on admission. Male patients had higher PRISM-scores and fewer PICU free days. However the CFR did not differ between males and females. Ethnicity did not influence disease severity and survival. The serogroups of *N. meningitidis* were not related to severity or survival.

Children with sepsis and purpura admitted to the PICU of the Erasmus MC-Sophia Children's Hospital account for approximately 25% of the total number of paediatric sepsis cases in the Netherlands and may therefore provide a representative sample of cases in the Netherlands. (Source: unpublished data of National PICU registry) In addition, Rotterdam covers an area in the Netherlands (i.e. the South-West of the Netherlands) in which meningococcal disease used to occur frequently.

In this large cohort of paediatric sepsis and purpura, low age was significantly associated with increased severity of disease, higher incidence of DIC and increased CFR. Half of the children in our population were younger than three years of age. A comparison with the literature showed that incidence rates indeed drop after infancy and then increase again slightly during adolescence.[1,9,24] The increased CFR and the more severe disease in younger children may result from the still developing immune, coagulation and stress response systems in young children, and therefore the relative inability to induce an effective immune response to a high load of micro-organisms such as *N. meningitidis*.[13,19]

The case fatality rate due to sepsis and purpura was 15.7% over the past two decades. This is in accordance with other large studies reporting case fatality rates of 10.4 to 20%.[7,24-26] It must be noted that Jensen et al. and Sharip et al. studied meningococcal disease, not specifically paediatric sepsis and purpura.

N. meningitidis was the causative organism of sepsis and purpura in the vast majority of cases. Martin et al. also found that gram-negative bacteria were the predominant causative organisms of sepsis in the US between 1979 and 1987.[27] In our study, the incidence of disease due to serogroup B was much higher than that of serogroup C. Serogroup B was seen more often in younger children compared to serogroup C. No differences were observed between serogroup B and C with respect to severity of illness scores and CFR. Erickson et al. suggested a more severe course of serogroup C infections, indicated by increased mortality due to serogroup C (14%) compared to serogroup B (7%).[28] Spanjaard et al. found a case fatality rate in meningococcal sepsis caused by serogroup B of 8.1% compared to 7.1% in serogroup C.[29] However, Erickson et al. studied both meningitis and sepsis in all culture proven cases of *N. meningitidis*, and Spanjaard et al. studied all culture proven cases including adults in the Netherlands, whereas we studied paediatric cases of sepsis and purpura.[28,29]

After the implementation of the meningococcal C vaccination in July 2002 there has not been a fatal case of sepsis and purpura in our PICU. Since severity of disease before and after the implementation did not differ between the two groups, the increased survival may have resulted from improved treatment strategies.[8] International treatment guidelines were implemented at that time, health care workers received additional training and the public awareness increased, resulting in a decreased patient delay. Furthermore, we observed a change in the choice of inotropic agents used since 2002. It must be noted that the number of children included since 2002 is low. These observations do however warrant further research in a prospective study.

Gender was not associated with CFR from sepsis and purpura, although males did have significantly more severe disease, based on the PRISM-score and fewer PICU free days, compared to females. Bindl et al. found a male to female ratio of 1.7 in sepsis patients aged 1 week to 8 years with severe sepsis and septic shock, whereas we observed a male-to-female ratio of 1.2.[30] However, in those cases caused by *N. meningitidis*, which is the major causative organism in our study, males and females were equally represented among non-survivors. In their articles, Watson et al. and Martin et al. also found a predisposition for male gender in sepsis, but they did not specify the male-to-female ratio in sepsis caused by *N. meningitidis*.[26,27]

Due to the small number of children in the different ethnic groups we may not have been able to detect differences between the different ethnic groups with respect to severity or case fatality of sepsis and purpura as of yet. In addition, during the

18-year study period the dynamics of the Dutch population (especially in Rotterdam) underwent changes, which may not be reflected in this study. Rosenstein et al. proposed a predisposition for sepsis in children of African descent.[1] Sharip et al. found an age-adjusted increased risk of case fatality in individuals of African descent compared to Caucasians and other ethnic groups.[24]

A possible limitation of our study may be that the serotypes of *N. meningitidis* were not determined in all children with meningococcal sepsis. Due to the rapidly progressive nature of this disease, it is possible that we did not include a number of the most severe cases because of case fatality before admission or referral to the Erasmus MC-Sophia. On the other hand, since only children with sepsis and purpura admitted to the PICU were included, this may have resulted in a skewed representation of all children with sepsis and purpura, i.e. children with relatively mild disease admitted to a general ward.

Conclusion

The CFR in this study was 15.7%. Age was the most important predictor of severity and case fatality of sepsis and purpura. Male gender was associated with higher PRISM scores and fewer PICU free days, but no differences were seen in CFR. *N. meningitidis* was the causative organism in the vast majority of cases. No differences were observed between *N. meningitidis* serogroup B and C with respect to disease severity scores and case fatality. Ethnicity was not associated with the course of sepsis and purpura.

In future studies investigating effects on severity and survival of sepsis and purpura, age and gender should be taken into account. The possible effect of different choice of inotropic agents warrants further investigation. Also, other possible differences between male and female sepsis patients should be investigated. With the changing demography in the Netherlands, and especially in the Rotterdam area, differences between ethnic groups require further examination.

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OUTCOME RESEARCH IN MENINGOCOCCAL SEPTIC SHOCK: COMMENTARY ON OUR FINDINGS REGARDING THE EPIDEMIOLOGY IN CHILDREN WITH SEPSIS AND PURPURA, AND RESPONSE TO THESE COMMENTS

Crit Care. 2008;12(1):402. Epub. 2008 Jan 17. Letter

Available online http://ccforum.com/content/11/5/172

Commentary

Improvements in the outcome of children with meningococcal disease

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Published: 29 October 2007
This article is online at http://ccforum.com/content/11/5/172

Critical Care 2007, 11:172 (doi:10.1186/cc6140)

See related research by Maat *et al.*, http://ccforum.com/content/11/5/R112

Abstract

Recent years have seen a marked reduction in the mortality of children with meningococcal disease in paediatric intensive care units (PICU); the reasons for this improvement are multifactorial. The mortality rates for critically ill children overall have improved and reasons for this are probably increased centralisation of PICU services and that fewer critically ill children are now looked after on adult units. Specific treatment pathways for sepsis have improved with the publication of clinical guidelines for children and initiatives such as the Surviving Sepsis Campaign. There is a continuing need to focus on the care delivered to children before reaching PICU and to minimise the morbidity suffered by survivors of this disease.

Meningococcal disease (MCD) continues to be the most common infective cause of death in children. In this issue of the journal, Maat *et al.* describe a paediatric intensive care unit (PICU) based study describing their experience of managing children with MCD (specifically, sepsis and purpura) over an 18 year period [1]. They are in the unusual and valuable position of having collected their data prospectively. The authors found that survival of children presenting to their unit with MCD correlated with *year of* admission indicating a significant ongoing reduction in case fatality. Indeed, the authors have not seen a single death in PICU from sepsis and purpura on their unit since 2003. These findings reflect the significant reduction in mortality seen in MCD in the UK and elsewhere *over recent years* [2,3]. Maat *and* colleagues attribute the improvement in outcome in part to changes in PICU management and resuscitation practices, but the reasons are undoubtedly multifactorial.

Over the last decade there has been a significant improvement in mortality rates in PICU generally [4,5]. These trends have been much more easily examined in the UK since the establishment of the Paediatric Intensive Care Audit Network (PICANet) in 2002; an audit database recording details of the treatment of all critically ill children in NHS PICUs in England, Wales and Scotland (Edinburgh).

There has also been a move towards increased centralisation of PICU services with fewer critically ill children being treated in adult units over recent years. This trend is founded on studies such as that of Pearson who demonstrated an excess mortality and a greater length of stay in a region of the UK with decentralised PICU services compared to the centralised service of Victoria, Australia [6]. Similar findings have been demonstrated in the USA and the Netherlands [7].

There has been an improvement in the awareness, diagnosis and management of patients with sepsis in emergency departments and critical care units since the recent publication of clinical practice guidelines for children with severe sepsis by Carcillo [8] drawing together the evidence of benefit from aggressive early fluid resuscitation and inotrope therapy. We have also seen the launch of the Surviving Sepsis Campaign with the publication of clinical practice guidelines [9] and the evolution of sepsis 'care bundles' which have improved mortality. A specific MCD management algorithm was published in the UK in 1999; a document which has been extensively distributed and utilised throughout emergency departments and paediatric units and which has been recently updated [10].

Maat *et al.* set out to study the epidemiology of sepsis *and* purpura in children 'referred to the PICU' and acknowledge that deaths prior to PICU admission are not addressed. Changes in PICU practice may lead to an increase in these 'hidden' MCD deaths. In a highly centralised PICU system

MCD = meningococcal disease; PICANet = Paediatric Intensive Care Audit Network; PICU = paediatric intensive care unit.

where highly equipped PICU teams travel over great distances, often by air, a significant number of critically ill children may receive early and prolonged care from a PICU team in a referring hospital. If children such as these succumb to their illness before returning to the central PICU, then they may not contribute to published PICU mortality figures. True population based studies of MCD mortality are of crucial importance; a study of this kind carried out in the USA found that MCD mortality rates increased from 1990 to 1997 and decreased from 1998 to 2002 [11].

Policies to reduce mortality in the UK have been designed to raise awareness at every step of the patient journey. Public awareness had been raised with the help of charities such as the Meningitis Research Foundation highlighting the need for parents to seek medical help early for children with a high temperature and a non-blanching rash (identified using the 'tumbler test') and stressing the importance of receiving the meningococcal serogroup C conjugate vaccine. In November 1999, the UK became the first country to incorporate this vaccine into a national immunisation programme. Following this, disease attack rates dropped in the vaccinated, carriage rates dropped and the incidence declined among unvaccinated persons, suggesting the development of herd immunity.

A recent study has demonstrated that up to half of all children presenting to hospital with MCD had previously been discharged home following a primary care assessment [12]. Strategies to increase awareness in primary care have targeted the recognition of presenting clinical features and the administration of penicillin to children prior to transfer to hospital [13].

Ninis *et al.* determined three factors that were independently associated with an increased risk of death in children with MCD after admission to the district hospital. These were failure to be looked after by a paediatrician, failure of sufficient supervision of junior staff, and failure of staff to administer adequate inotropes [14]. The involvement of a skilled multidisciplinary paediatric team in the resuscitation, stabilisation and transfer of any critically ill child with sepsis is paramount and if carried out well will lead to an improvement in outcome [15].

Survivors of invasive disease may sustain permanent sequelae, such as deafness, seizures, limb amputation or tissue loss, chronic renal impairment and developmental delay. Maat *et al.* did not examine morbidity in their large cohort, which would have been clinically highly relevant; there is little published data on changes in the rate of morbidity due to MCD over recent years. As with clinical conditions such as leukaemia, an improvement in overall mortality inevitably leads to greater focus on the quality of life of survivors with survival being at minimum cost rather than at any cost.

Competing interests

The authors have no competing interests.

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Available online http://ccforum.com/content/12/1/402

Letter

Outcome research in meningococcal septic shock

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Published: 17 January 2008
This article is online at http://ccforum.com/content/12/1/402
Critical Care 2008, 12:402 (doi:10.1186/cc6206)

See related commentary by Paize and Playfor, http://ccforum.com/content/11/5/172
and related research by Maat et al., http://ccforum.com/content/11/5/R112

We thank Dr Paize and Dr Playfor for their comments [1] regarding our earlier article in Critical Care [2].

In their commentary Dr Paize and Dr Playfor stated that the reasons for a marked reduction in the mortality of children with meningococcal disease in the paediatric intensive care unit are multifactorial: increased centralization of the paediatric intensive care unit, improvement in awareness, clinical guidelines for children with sepsis, and incorporation of meningococcal serogroup C vaccine.

Dr Paize and Dr Playfor also regretted in their commentary that we did not examine morbidity in our large cohort [1]. We completely agree with Dr Paize and Dr Playfor that both short-term and long-term outcomes in survivors of meningococcal sepsis are clinically highly relevant. Only a few, unsystematic studies have been conducted in this field. These studies used small, heterogeneous patient samples and unstandardized assessment procedures and were focused mainly on short-term outcome. Our relatively large, homogeneous cohort therefore offered the possibility to investigate this neglected area of outcome, both from a medical and psychosocial point of view, with standardized procedures. Parts of our outcome study have been published already or are in press [3-6].

In a prospective cohort study we performed a short-term follow-up of all consecutive children with septic shock and purpura requiring intensive care treatment between 2001 and 2005, and their parents [4]. Up to 2 years after paediatric intensive care unit discharge, chronic complaints were reported in nearly one-half of the children. Significantly lower scores were found on health-related quality-of-life scales concerning mainly physical functioning and health perception in comparison with normative data. Quite a few mothers suffered from anxiety or depression requiring professional help.
The second part of our study concerned a cross-sectional long-term outcome study of all 179 survivors of septic shock and purpura requiring intensive care treatment between 1988 and 2001, and their parents [3,5,6]. Regarding long-term health-related quality of life, we found significantly lower scores in patients – mainly on physical domains (physical functioning, general health perception) – compared with Dutch normative data [3]. Adolescents (aged 12–17 years) who survived meningococcal septic shock in childhood, especially those with skin scarring due to purpura, reported lower self-esteem compared with reference adolescents [5]. Overall, we found favourable long-term behavioural, emotional and post-traumatic stress outcomes in patients [6].

Articles regarding skin scarring, orthopaedic and neurological sequelae, as well as psychosocial adjustment of parents, are under review.

In conclusion, we would like to reassure Dr Paize and Dr Playfor that we did study short-term and long-term morbidity in survivors of septic shock and purpura.

Competing interests

The authors declare that they have no competing interests.

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SURVIVING MENINGOCOCCAL SEPTIC SHOCK: HEALTH CONSEQUENCES AND QUALITY OF LIFE IN CHILDREN AND THEIR PARENTS UP TO 2 YEARS AFTER PICU DISCHARGE

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Crit Care Med. 2008 Feb;36(2):596-602

Abstract

Objective To assess health consequences and health-related quality of life (HR-QoL) in children with meningococcal septic shock up to 2 years after discharge from the paediatric intensive care unit (PICU), as well as their parents. To determine major predictors of that outcome.

Patients and methods A prospective cohort study. Follow-up of all consecutive children with septic shock and purpura requiring intensive care treatment between 2001 and 2005, and their parents. HR-QoL was assessed with the Child Health Questionnaire (children) and SF-36 (parents).

Results Of 53 eligible families, 47 participated (28 boys/19 girls; median age at the time of PICU admission 3.7 years; median PRISM score 21).

Twenty-six children (55%) had scars as result of skin necrosis; 2 (4%) amputation of digit(s). In 21 children (45%) chronic complaints were reported. Children with and without chronic complaints did not differ significantly with regard to severity of illness and age at the time of PICU admission. Significantly lower scores were found on HR-QoL scales concerning mainly physical functioning and health perception in comparison with normative data. There was a significant negative association between severity of illness and the HR-QoL scale concerning physical functioning. Children with chronic complaints had significantly lower scores on the HR-QoL scale concerning pain.

Eight of 47 mothers (17%) currently suffered from anxiety or depression requiring professional help. Mothers with and without these problems differed significantly with regard to age of their child at the time of PICU admission. Parents showed significantly higher scores on HR-QoL scales concerning physical functioning and bodily pain in comparison with normative data. There was a significantly negative association between the presence of emotional problems and HR-QoL scores in mothers.

Conclusions Up to 2 years after discharge from the PICU there is still a considerable impact on health and HR-QoL in children, especially on the physical scales. Severity of illness and chronic complaints negatively affected HR-QoL scales in children. Quite a few mothers suffered from emotional problems.

Introduction

Septic shock with petechial and/or purpuric rash is a life threatening clinical syndrome predominantly caused by *Neisseria meningitidis* (NM). It is characterized by sudden onset and rapid progression in previously healthy children.[1]

Regrettably, better understanding of the pathogenesis of meningococcal septic shock and advances in therapeutic interventions have not reduced its high morbidity.[2] Younger children (< 3 years) are known to have more severe disease and higher risk of case fatality.

Only few studies have reported short-term and long-term incidences of adverse consequences (such as physical and neuropsychological impairments) and HR-QoL.[3-7] These studies are limited, however, in that they do not differentiate as to severity of disease; the study populations included patients with sepsis, septic shock or meningitis.

In addition, major risk factors for developing adverse consequences have not been well identified. Early detection and treatment of children bearing these risks therefore is difficult. We hypothesized that children with more severe meningococcal septic shock, as reflected by higher severity of illness scores and longer PICU stay, are at higher risk for adverse health consequences, both physical and neuropsychological, and for poorer HR-QoL. Furthermore we hypothesized that the underlying disease mechanism (shock and/or disseminated intravascular coagulation) was the cause of skin scarring, and not the administration of vasopressors.

Also little is known about the impact on family life and HR-QoL of parents whose children survived meningococcal septic shock. We hypothesized that more severe disease would have more impact on parents and their HR-QoL.

More insight in these matters could enable anticipatory guidance and support for both the children and their parents after PICU discharge.

The aim of this study was to investigate health consequences and HR-QoL in children with meningococcal septic shock up to 2 years after PICU discharge. Additionally, we assessed the impact of the child's disease episode on HR-QoL in their parents. Finally, we assessed various putative determinants of adverse health and HR-QoL outcomes in children and their parents.

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Materials and Methods

Patient selection

This study concerned a first follow-up study of a longitudinal cohort of all consecutive children with septic shock and purpura requiring intensive care treatment between October 2001 and March 2005, as well as their parents. Children were recruited from the PICU of the Erasmus MC-Sophia Children's Hospital, a tertiary care university hospital. Eligible for this study were children aged 1 month to 18 years with a clinical picture of meningococcal septic shock, defined as septic shock with petechiae/purpura, requiring intensive care treatment, and their parents.[8] The Erasmus MC ethical review board approved the study protocol. Informed consent was sought from the parents during the child's PICU admission. Families who were not Dutch speaking were excluded. Participating families were invited for an interview within 2 years after the child's discharge from the PICU. They were sent HR-QoL questionnaires and invited to complete these at home. Choice of respondent (mother or father) was left to the parents themselves.

Data analysis at the time of PICU admission

During the study period children consecutively admitted with septic shock and petechiae/purpura were included in a descriptive sepsis study.[9]
Severity of illness was determined by the Pediatric Risk of Mortality Score (PRISM), Vasopressor score (VAS) and Disseminated Intravascular Coagulation score (DIC).[10-12]

Assessment methods

Health consequences in children and parents

Children and parents were interviewed by one author (CB) in a semi-structured format using a standard questionnaire on health consequences and medical care in the year after PICU discharge. Symptoms presenting in the weeks after PICU discharge and still present at the time of the interview were defined as chronic. Data on comorbidities prior to PICU admission were extracted from the medical records and from the interview results. Comorbidities were defined as health problems not related to the reason for PICU admission. A general physical examination of the children was performed by one author (CB) with special attention to the skin (scarring) and the extremities (amputation and orthopaedic sequelae).

HR-QoL in children and parents

HR-QoL was assessed by the Child Health Questionnaire (children) and SF-36 (parents).[13-15] The Infant and Toddler Quality of Life Questionnaire (ITQOL) was used for preschool children (0-3 years) (appendix 1).[16,17] Normative data were derived from a general Dutch population sample of 410 children aged 3 months - 3 years.[17] The Child Health Questionnaire- Parent Form 50 (CHQ-PF50) was used for children aged 4-17 years (appendix 2). Normative data are available based on a representative sample of 353 Dutch schoolchildren aged 5 - 13 years.[14] As shown in appendices 1 and 2, 8 of the 12 scales in ITQOL and CHQ-PF50 cover similar content (PF, BP, GB, GH, PE, PT, FC, FA and CH). Subsequently, the results of these scales were added in order to investigate the predictors of HR-QoL outcome. The SF-36 Health Survey was used for parents (appendix 3).[13] Normative data were derived from a nationwide, population-based Dutch health status survey.[18] A sub-selection, i.e. 175 women aged 26-35 years, served as a reference group in our study since it was almost exclusively mothers (96%) who completed the questionnaires, with a median age of 35 years (22-49 years).
HR-QoL scales range from 0 to 100. Lower scores indicate poorer subjective health status, higher scores more favourable subjective health status.

Statistical methods

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

Patient sample

The Mann-Whitney test was used to compare age at the time of PICU admission, length of PICU stay and severity of illness scores between participating children and non-participants, whereas the Chi-Square test was used to establish sex differences between these 2 groups.

HR-QoL in children and parents

The Mann-Whitney test was used to compare children's HR-QoL scores with individual normative data, as provided by Raat et al.[14,17] The paired Wilcoxon test was used to compare HR-QoL scores of parents with published normative data, as individual normative data were not available.[18]

Predictors of health consequences and HR-QoL in children and parents

The Mann-Whitney test was used to compare age at the time of PICU admission, length of PICU stay and severity of illness scores between children with and without health consequences, and between parents with and without current emotional problems.
We also applied multiple logistic regression analysis of the three severity of illness scores regarding the presence of skin scarring.
We tested the association between putative predictor variables (child's characteristics at the time of the PICU admission, health consequences and follow-up interval) and HR-QoL by using Spearman correlation for continuous variables (univariate

analysis) and Mann-Whitney test for dichotomous variables. This was done for both children and parents. Plus versus minus sign indicates respectively the positive versus negative association between the predictor variable and the HR-QoL scale.
In the above mentioned statistical analyses, a P-value of 0.05 (two-sided) was considered the limit of significance.
Multiple linear regression analyses were also applied to predict children's HR-QoL scores. This was done for all scales, irrespective of significant differences between the study population and the reference group. In the first regression analysis, we included child characteristics (age at the time of the PICU admission, sex), disease variables (severity of illness scores, length of stay in PICU) and follow-up interval. In the second regression analysis, we included the child health consequences. P-values of predictors were set to a level of 0.1 in the univariate analysis for entry in the regression analysis. Using backward elimination independent predictors were identified with a P-value < 0.05. Predictors with negative values (regression coefficients) were considered as negatively associated with HR-QoL scales, those with positive values as positively associated.

Results

Patient sample

The target population consisted of 56 children and their parents. We excluded three: 1 child died during PICU admission because of refractory shock, 1 family lived abroad at the time of follow-up, 1 family was not Dutch speaking. Of the remaining 53 eligible families, 47 agreed to participate. Parents of 2 children did not complete the CHQ-PF50 and SF-36 for unknown reason. This resulted in 19 ITQOL, 26 CHQ-PF50 and 45 SF-36 completed questionnaires. The median follow-up interval was 14 months (10-28 months), median age at the time of follow-up 4.8 years (1-17 years). Six families refused participation (reason for refusal unknown). The overall response rate, corrected for deceased children and children lost to follow-up, was 89% (47/53). To check for possible selection bias, we compared characteristics between participating children and non-participants. As shown in table 1 children did differ with respect to PRISM score, which was highest among the participants. In 40 of the full target population of 56 children (73%) *Neisseria meningitidis* had been cultured: serogroup B in 26 (65%), serogroup C in 13 (33%) and not determined in 1 (2%).
Nine children (19%) had 1 or more mild to severe comorbidities prior to PICU admission; cheilopalatoschisis, asthma and/or allergy, autism, prematurity, Opitz syndrome with significant developmental delay and epilepsy, and mild perinatal asphyxia.

Table 1. Characteristics of participating children and non-participants

Data are presented as percentages of cases or as median (range).

characteristics	follow-up	no follow-up	P-value
	n=47	n=6	
Sex	60% boys, 40% girls	83% boys, 17% girls	ns
Age PICU (years)	3.7 (0.1-16.1)	7.1 (1.8-12.2)	ns
Length of stay in PICU (days)	4 (1-18)	3 (2-5)	ns
PRISM	21 (7-48)	10 (5-21)	0.01
DIC*	5 (1-8)	5 (2-6)	ns
Inotropes	81%	83%	ns
VAS	35 (0-281)	6 (0-60)	ns
Mechanical ventilation	70%	33%	ns

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

Health consequences in children

Follow-up clinical examination revealed abnormal extremities in 2 children (4%); i.e. amputation of 3 fingers (distal interphalangeal joint) in 1 child; amputation of 1 finger (distal interphalangeal joint) and lower limb shortening with associated genu varum deformity in 1 toddler, who had suffered from fulminant meningococcal septic shock (PRISM score 35) at age 6 weeks. Twenty-six children (55%) had mild to severe skin scarring as a result of necrosis of the purpuric lesions. In 1 child a wound at the heel of the foot had still not healed.
For 21 children (45%) 1 or more chronic complaints were reported: pain (lower limbs n=7, headache n=3), behavioral/emotional problems (n=6), fatigue (n=2), motor skills problems (n=1), pes equinus (n=1), Raynaud phenomenon at amputated finger (n=1), sleep disturbances (n=1) and stuttering (n=1). The skin scarring did not cause pain (except in 1 patient with the open wound) or physical limitations. Eleven children (23%) still needed follow-up care: 8 (17%) for somatic impairments, 3 (6%) for aggressive behavior. These chronic complaints and the need for follow-up care were not present prior to PICU admission. Despite this, all children had resumed normal school or nursery activity. No school dysfunctioning was reported by their parents and the level of education remained unchanged.

HR-QoL in children

Table 2 shows the mean scores on the ITQOL and CHQ-PF50 of our study population and the Dutch reference groups.

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Table 2. Health-related quality of life (parent report) in children

Data are presented as mean (range) in children and reference groups. Data between brackets represent standard error of the mean.

	children	reference	P-value*	< 5th%**
	n=19			
ITQOL (0-3 years)				
Physical abilities (PF)	91 (10-100) [5.3]	97 [0.5]	< 0.05	11%
Growth and development (GD)	85 (40-100) [3.3]	87 [0.5]	ns	
Bodily pain/discomfort (BP)	88 (33-100) [4.3]	84 [0.8]	ns	
Temperament and moods (TM)	78 (53-96) [3.0]	77 [0.5]	ns	
General behavior perceptions (GB)	67 (16-89) [3.9]	73 [0.7]	ns	
Getting along with others (GA)	68 (48-95) [3.1]	71 [0.5]	ns	
General health perceptions (GH)	57 (20-83) [3.7]	79 [0.7]	< 0.001	37%
Parental impact: Emotional (PE)	85 (32-100) [3.8]	92 [0.5]	< 0.05	16%
Parental impact: Time (PT)	84 (24-100) [4.8]	93 [0.5]	ns	
Family activity (FA)	75 (25-100) [5.7]	86 [0.7]	ns	
Family cohesion (FC)	69 (30-100) [5.1]	75 [0.9]	ns	
Change in health (CH)	97 (50-100) [2.6]	56 [1.0]	< 0.001	
	n=26			
CHQ-PF50 (4-17 years)				
Physical functioning (PF)	98 (83-100) [0.9]	99 [0.2]	< 0.05	8%
Role functioning: Emotional/behavior (REB)	97 (33-100) [2.6]	98 [0.4]	ns	
Role functioning: Physical (RP)	99 (83-100) [0.6]	96 [0.8]	ns	
Bodily pain (BP)	81 (20-100) [4.4]	86 [0.9]	ns	
General behavior (GB)	76 (26-100) [3.0]	79 [0.7]	ns	
Mental health (MH)	80 (45-100) [2.7]	81 [0.6]	ns	
Self-esteem (SE)	80 (58-100) [2.3]	79 [0.6]	ns	
General health perceptions (GH)	62 (9-100) [3.6]	83 [0.7]	< 0.001	35%
Parental impact: Emotional (PE)	81 (25-100) [3.4]	86 [0.8]	ns	
Parental impact: Time (PT)	93 (22-100) [3.2]	94 [0.7]	ns	
Family activities (FA)	90 (25-100) [3.3]	92 [0.6]	ns	
Family cohesion (FC)	68 (30-100) [3.1]	72 [1.0]	ns	
Physical summary (PHS)	52 (39-63) [1.2]	56 [0.3]	< 0.001	8%
Psychosocial summary (PSS)	53 (21-65) [1.7]	53 [0.3]	ns	

*The Mann-Whitney test was used to compare HR-QoL scores of children with individual normative data, as provided by Raat et al.[14,17] **Percentage of children with score < 5th percentile of reference group (this percentage was calculated if P-value < 0.05 in anticipated direction). ***Scores on the CHQ-PF50 scale "change in health" are not presented since individual normative data were not available for this scale.

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Predictors of health consequences and HR-QoL in children

Children with skin scarring had significantly higher severity of illness scores than those without skin scarring (PRISM P=0.02, VAS P=0.002, DIC P=0.001). Simultaneous evaluation of these 3 severity of illness scores using logistic regression showed that DIC was the major variable predicting skin scarring.

Children with and without chronic complaints did not differ significantly with regard to sex, severity of illness and age at PICU admission. Those who needed follow-up care stayed significantly longer in the PICU than those who did not (P=0.01).

Univariate analysis of all HR-QoL scales in relation to predictor variables showed that 4 scales had at least one significant relationship (Table 3). Using multiple linear regression analyses of child's characteristics on HR-QoL, longer PICU stay was significantly associated with a lower score on the HR-QoL scale "physical functioning", with a moderate R square (0.40). This means that 40% of the variance in the scale "physical functioning" could be explained by length of PICU stay. The HR-QoL scale "bodily pain" was predicted both by the presence of chronic complaints (P=0.01) and the need for follow-up care (P=0.02).

Neither in univariate nor in multivariate analysis follow-up interval showed significant associations with HR-QoL scales.

Health consequences in parents

Eight of the 47 mothers (17%) reported current emotional problems (anxiety, depression) requiring professional help and 2 of them (4%) were on long-term sick leave. These phenomena had occurred since their child's acute illness. Marital status had not changed.

HR-QoL in parents

Table 4 shows the mean scores on the SF-36 in parents and the Dutch reference group.

Predictors of health consequences and HR-QoL in parents

Mothers who required professional help because of emotional problems had significantly younger children at the time of PICU admission than those who did not need professional help (P=0.04).

Child severity of illness was not significantly associated with HR-QoL in parents. The need for professional help in mothers was associated with lower scores on the HR-QoL scales "role functioning physical", "social functioning" and "mental health" (P=0.03, P=0.04, P=0.02 resp). Multiple linear regression analysis on HR-QoL in parents was not performed since there was at most 1 predictor with P-value < 0.1 in each HR-QoL scale of the univariate analysis.

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Table 3. Univariate relations between predictor variables and health-related quality of life scales in children

For continuous variables (first 5 items) the Spearman correlation coefficient is shown, for dichotomous variables (last 2 items) the difference (item present minus absent) in mean scale value is shown.

Predictor variables	Physical functioning	Bodily pain	Parental impact emotional	Family cohesion
Age PICU admission	.28***	-.08	-.32*	-.20
PRISM	-.37*	-.11	-.03	.07
DIC	-.45**	.03	-.05	.35*
VAS	-.54**	-.11	-.30*	.21
Length of stay in PICU	-.61**	-.17	-.22	.20
Chronic complaints	-4.3	-17.6**	-9.5	-2.4
Follow-up care	-9.7*	-16.1***	-12.4***	-1.7

P< 0.05 (*), P< 0.01 (**), P< 0.1 (***).

Table 4. Health-related quality of life in parents

Data are presented as mean (range) in parents and reference group. Data between brackets represent standard error of the mean.

	parents	reference	P-value*
	n=45		
SF-36			
Physical functioning (PF)	90 (45-100) [2.2]	92 [0.9]	ns
Role limitations due to physical functioning (RP)	87 (0-100) [4.3]	83 [2.5]	< 0.05
Social functioning (SF)	83 (13-100) [3.5]	86 [1.6]	ns
Bodily pain (BP)	85 (22-100) [2.9]	79 [1.4]	< 0.05
General mental health (MH)	74 (8-100) [3.1]	76 [1.2]	ns
Role limitations due to emotional problems (RE)	78 (0-100) [5.9]	81 [2.6]	ns
Vitality (VI)	67 (20-100) [3.2]	67 [1.3]	ns
General health perceptions (GH)	73 (10-100) [3.4]	78 [1.3]	ns
Physical summary (PHS)	54 (32-66) [1.1]	54 [0.5]	ns
Psychosocial summary (PSS)	49 (14-63) [1.9]	48 [0.8]	ns

*The paired Wilcoxon test was used to compare HR-QoL scores of parents with published normative data.[18]

Discussion

In this follow-up study a relative high proportion of survivors of meningococcal septic shock had scars and chronic complaints since their illness and needed follow-up care up to 2 years after PICU discharge. In children, significantly lower scores were found on HR-QoL scales.
Quite a few mothers reported emotional problems requiring professional help.

Health consequences in children

Children with meningococcal septic shock often have extensive necrotic purpura or even ischaemic digits, which can lead to permanent skin scarring and amputation. In this study more than half of children (55%) had skin scarring and only 2 children (4%) required limited digital amputation.
Furthermore, a significant number of children had chronic complaints (45%) and needed follow-up care (physical or psychosocial) (23%). The most frequent chronic symptom was pain, either in the limbs or headache. Pain in the limbs could have been caused by myositis, rhabdomyolisis, arthritis or osteomyelitis at the time of the acute illness. Treatment with physiotherapy and non-steroidal inflammatory drugs could be beneficial after discharge.
The incidence of emotional/emotional problems in children (13%) is in accordance with that reported by Shears et al.[4] These problems may be attributable to biological effects of meningococcal septic shock on the brain (inflammation, shock), or to the impact of the illness and PICU admission on child and family, or a combination of both. It is not known how long these problems will persist. Standard psychological support after discharge from the PICU is thought to reduce the extent of these behavioral/emotional problems.
Remarkably, despite the important morbidity up to 2 years later, all children had resumed normal school activity. This could be due to the children's coping mechanisms.

HR-QoL in children

Children of both age groups had significantly lower scores mainly on the physical HR-QoL scales and children 4-17 years also on the physical summary score. This could indicate that the child's disease episode and present health status had a negative impact on their present physical HR-QoL.
Notably low is the score on the "general health perception" scale, with as many as 37% and 35% below the 5th percentile of the reference group. This score not only reflects the experience of a serious illness in the past. It also indicates that parents perceived their child's present health as poor and that they worry about their child's

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future health risks. For example, from the interviews it appeared that many parents assumed their child is at great risk for re-occurence of meningococcal septic shock. This brings us to the question of the validity of proxy report by parents. We should be aware that proxy report might differ significantly from the child report, and that several factors might affect HR-QoL assessment by parents. These include parental education, parental health status and parental perception of health problems in their child. Nevertheless it is important to reassure parents that their child is not predisposed for recurrent meningococcal septic shock. Furthermore more studies are needed to investigate long-term morbidity in order to inform parents regarding their child's health in the future.

Predictors of health consequences and HR-QoL in children

We could demonstrate that disseminated intravascular coagulation, expressed by DIC, was the major variable predicting skin scarring, and not the administration of vasopressors.

Surprisingly, children with and without chronic complaints did not differ significantly with regard to severity of illness. This could be due to the heterogeneousity of this variable. The reason to form the composite variable "chronic complaints" was the low number of patients for each separate complaint.

Health consequences in parents

In our study only mothers (17%) reported emotional problems requiring professional help. Uncertainties about a possible death, complications and long-term sequelae if their children survive, can result in increasing stress and anxiety levels. Standard psychological support during PICU admission of their child and continuing afterwards might be beneficial to parents. Furthermore we need to identify parents ad risk in order to make early referrals.

HR-QoL in parents

In parents we did not found significantly lower HR-QoL scores, indicating that the child's disease episode and present health status did not have significantly negative impact on their HR-QoL. These findings are in line with HR-QoL in children, where no significantly lower scores were found on HR-QoL scales concerning the negative impact of the child's health on parents and family (except parental impact emotional in children 0-3 years). The higher scores found on 2 physical SF-36 scales could possibly be explained by parents comparing their physical HR-QoL with that of their child, thus overscoring their own HR-QoL.

Predictors of health consequences and HR-QoL in parents

Only age of the child at the time of PICU admission significantly predicted the presence of emotional problems in parents. Also in HR-QoL in children, age of the child at the time of PICU admission was significantly associated with the scale "parental impact emotional".

Strengths and limitations of the present study

We feel the high response rate (89%) is due to the relatively short follow-up interval, but perhaps the more so to the personal invitations from the PICU research nurse or the paediatric intensivist.

Several limitations of our study should be acknowledged. This is an uncontrolled, observational study in a small number of patients. We were not able to take into account previous health status (severity of comorbidities) and HR-QoL before PICU admission, and did not inform whether parents had encountered the health system prior to PICU admission of their child. As participants differed from non-participants with respect to PRISM scores, our findings may be overestimated.

We only included children with septic shock and purpura requiring PICU treatment. Admitting the milder cases to a general ward may have resulted in selection bias. HR-QoL scores of our children and their parents were compared with normative data derived from general Dutch population samples. A comparison with children matched on age and timing of follow-up interval, and hospitalized because of another disease could be interesting. Normative data used for comparison of CHQ-PF50 scores did not exactly match the age distribution of children in our study.

Conclusions

Awareness of the findings from our study and standard follow-up by a multidisciplinary team (paediatrician, psychologist, physiotherapist) of children who survived meningococcal septic shock, as well as their parents, within weeks after PICU discharge may diminish the extent of physical and psychological health consequences. Further studies are necessary to investigate long-term morbidity (several years) in these patients and their parents.

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Appendix 1: ITQOL scales, items per scale and score interpretation[a]

Scale	Number of items	Description low score	Description high score
Physical functioning (PF)	10	Child is limited a lot in performing physical activities such as eating, sleeping, grasping, and playing due to health problem	Child performs all types of physical activities such as eating, sleeping, grasping, and playing without limitations due to health problem
Growth and development (GD)	10	Parent is very dissatisfied with development (physical growth, motor, language, cognitive), habits (eating, feeding, sleeping) and overall temperament	Parent is very satisfied with development (physical growth, motor, language, cognitive), habits (eating, feeding, sleeping) and overall temperament
Bodily pain (BP)	3	Child has extremely severe, frequent and limiting bodily pain/discomfort	Child has no pain or limitations due to pain/discomfort
Temperament and moods (TM)	18	Child has very often certain moods and temperaments, such as sleeping/eating difficulties, crankiness, fussiness unresponsiveness and lack of playfulness and alertness	Child never has certain moods and temperaments, such as sleeping/eating difficulties, crankiness, fussiness unresponsiveness and lack of playfulness and alertness
General behaviour (GB)	13	Parent believes child's behaviour is poor and likely to get worse	Parent believes child's behaviour is excellent and will continue to be so
Getting along (GA)	15	Child very often exhibits behaviour problems, such as not following directions, hitting, biting others, throwing tantrums, and being easily distracted, while positive behaviours, such as ability to cooperate, appear sorry, and adjustment to new situations are seldom show	Child never exhibits behaviour problems, such as not following directions, hitting, biting others, throwing tantrums, and being easily distracted, while positive behaviours, such as ability to cooperate, appear sorry, and adjustment to new situations are frequently shown
General health perceptions (GH)	12	Parent believes child's health is poor and likely to get worse	Parent believes child's health is excellent and will continue to be so
Parental impact:emotion (PE)	7	Parent experiences a great deal of emotional worry/concern as a result of child's physical and/or psychosocial health and/or growth and development	Parent doesn't experience feelings of emotional worry/concern as a result of child's physical and/or psychosocial health and/or growth and development
Parental impact: time (PT)	7	Parent experiences a lot of limitations in time available for personal needs due to child's physical and/or psychosocial health and/or growth and development	Parent doesn't experience limitations in time available for personal needs due to child's physical and/or psychosocial health and/or growth and development
Family activities (FA)	6	The child's health and/or growth and development very often limits and interrupts family activities or is a source of family tension	The child's health and/or growth and development never limits and interrupts family activities or is a source of family tension
Family cohesion (FC)	1	Family's ability to get along is rated poor	Family's ability to get along is rated excellent
Change in health (CH)	1	Child's health is much worse now than 1 year ago	Child's health is much better now than 1 year ago

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Appendix 2: CHQ-PF50 scales, items per scale and score interpretation[a]

Scale	Number of items	Description low score	Description high score
Physical functioning (PF)	6	Child is limited a lot in performing all physical activities, including self-care due to health	Child performs all types of physical activities, including the most vigorous, without limitations due to health
Role functioning Emotional/behavior (REB)	3	Child is limited a lot in schoolwork or activities with friends as a result of emotional or behavior problems	Child has no limitations in schoolwork or activities with friends as a result of emotional or behavior problems
Role functioning Physical (RP)	2	Child is limited a lot in schoolwork or activities with friends as a result of physical health	Child has no limitations in schoolwork or activities with friends as a result of physical health
Bodily pain (BP)	2	Child has extremely severe, frequent and limiting bodily pain	Child has no pain or limitations due to pain
General behaviour (GB)	6	Child very often exhibits aggressive, immature, delinquent behavior	Child never exhibits aggressive, immature, delinquent behavior
Mental health (MH)	5	Child has feelings of anxiety and depression all of the time	Child feels peaceful, happy and calm all of the time
Self esteem (SE)	6	Child is very dissatisfied with abilities, looks, family/peer relationships and life overall	Child is very satisfied with abilities, looks, family/peer relationships and life overall
General health perceptions (GH)	6	Parent believes child's health is poor and likely to get worse	Parent believes child's health is excellent and will continue to be so
Parental impact:emotion (PE)	3	Parent experiences a great deal of emotional worry/concern as a result of child's physical and/or psychosocial health	Parent doesn't experience feelings of emotional worry/concern as a result of child's physical and/or psychosocial health
Parental impact: time (PT)	3	Parent experiences a lot of limitations in time available for personal needs due to child's physical and/or psychosocial health	Parent doesn't experience limitations in time available for personal needs due to child's physical and/or psychosocial health
Family activities (FA)	6	The child's health very often limits and interrupts family activities or is a source of family tension	The child's health never limits and interrupts family activities nor is a source of family tension
Family cohesion (FC)		Family's ability to get along is rated "poor"	Family's ability to get along is rated "excellent"
Change in health (CH)	1	Child's health is much worse now than 1 year ago	Child's health is much better now than 1 year ago

[a] Reproduced with permission from the principal author J.M. Landgraf[19]
Note: Physical Summary and Psychosocial Summary scores were calculated based on a factor-analytic model, a summary score of 50 (SD 10) representing the mean in the original United States of America population sample.

Appendix 3: SF-36 scales, items per scale and score interpretation

Scale	Number of items	Description low score	Description high score
Physical functioning (PF)	10	very limited in performing all physical activities, including bathing or dressing due to health	performs all types of physical activities, including the most vigorous, without limitations due to health
Role limitations due to physical functioning (RP)	4	problems with work or other daily activities as a result of physical health	no problems with work or other daily activities as a result of physical health
Social functioning (SF)	2	extreme and frequent interference with normal social activities due to physical or emotional problems	performs normal social activities without interference with normal social activities due to physical or emotional problems
Bodily pain (BP)	2	very severe and extremely limiting bodily pain	no pain or limitations due to pain
Mental health (MH)	5	feelings of nervousness and depression all of the time	feels peaceful, happy, and calm all of the time
Role functioning: Emotional (RE)	3	problems with work or other daily activities as a result of emotional problems	no problems with work or other daily activities as a result of emotional problems
Vitality (VI)	4	feels tired and worn out all of the time	feels full of pep and energy all of the time
General health (GH)	5	evaluates personal health as poor and believes it is likely to get worse	evaluates personal health as excellent

Note: Physical Summary and Psychosocial Summary scores were calculated based on a factor-analytic model, a summary score of 50 (SD 10) representing the mean in the original United States of America population sample.

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LONG-TERM SKIN SCARRING AND ORTHOPAEDIC SEQUELAE IN SURVIVORS OF MENINGOCOCCAL SEPTIC SHOCK

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Arch Dis Child. 2008. in press

Abstract

Objective To assess the incidence of skin scarring and orthopaedic sequelae (amputation, limb-length discrepancy) in patients who survived meningococcal septic shock (MSS) in childhood and to determine the severity and predictors of these sequelae.

Design and Patients All 179 consecutive patients (170 were eligible) with septic shock and purpura requiring intensive care treatment between 1988 and 2001 in Rotterdam, the Netherlands. Patients were invited 4-16 years after PICU discharge for a visit to the follow-up clinic.

Results Of the 120 follow-up patients (follow-up interval 10 years; age at follow-up 14.5 years (all medians)), 58 patients (48%) had skin scarring due to purpura. This varied from barely visible scars to extremely disfiguring scars. Ten patients (8%) had to undergo amputation(s) of extremities, ranging from 1 toe to both legs and 1 arm. Seven patients (6%) had lower limb-length discrepancy, in most cases together with angular deformity, requiring 1 or more late surgical intervention(s). Patients with scars or orthopaedic sequelae had significantly higher severity of illness scores, determined by Pediatric Risk of Mortality Score, Vasopressor score and Disseminated Intravascular Coagulation score. Gender or *Neisseria meningitidis* serogroup had no significant influence on the presence of scars or orthopaedic sequelae. Patients with lower limb-length discrepancy were significantly younger at the time of PICU admission.

Conclusions The incidence of long-term skin scarring and orthopaedic sequelae was high (resp. 48% and 14%) in patients who survived MSS in childhood. Severity of these sequelae varied from mild to severe. Patients with scars or orthopaedic sequelae had significantly higher severity of illness scores.

Introduction

Septic shock with petechial and/or purpuric rash is a life threatening clinical syndrome predominantly caused by *Neisseria meningitidis* (NM) and characterized by a sudden onset and rapid progression in previously healthy, young children and adolescents.[1]

Unfortunately, despite advances in understanding the pathogenesis of meningococcal septic shock (MSS) and the increase in therapeutic interventions, there is still a high morbidity.[2] Hemorrhagic skin necrosis, caused by disseminated intravascular coagulation, can lead to permanent cutaneous lesions. In severe cases, widespread vascular thrombosis leads to irreversible ischemia of digits and even limbs.

There are few data in the literature on the incidence and severity of long-term cutaneous and orthopaedic sequelae of MSS.[3-7] In addition, the risk factors for developing these sequelae are not well identified.

More insight in the long-term cutaneous and orthopaedic sequelae of MSS and their risk factors could lead to a different management during PICU admission and to anticipatory follow-up care for these patients after discharge from the PICU.

The aim of this study was to investigate the incidence and severity of long-term skin scarring and orthopaedic sequelae in patients who survived MSS in childhood. Additionally, we determined the predictors of these sequelae.

Materials and Methods

Patient selection

This study concerned a medical and psychological follow-up of a cross-sectional cohort of all consecutive surviving patients with septic shock and purpura requiring intensive care treatment at least 4 years ago (between August 1988 and October 2001). Patients were recruited from the PICU of the Erasmus MC-Sophia Children's Hospital, a tertiary care university hospital. Patients aged 1 month to 18 years with a clinical picture of MSS, defined as septic shock with petechiae/purpura, requiring intensive care treatment were eligible.[8] The more mild cases admitted to a general ward were excluded. The Medical Ethics Committee of the Erasmus Medical Center approved the study protocol. Informed consent was obtained from patients and parents by sending a standard letter requesting their participation in our study. Patients and parents who were not Dutch speaking were excluded. Patients and parents who agreed to participate were sent an invitation to the follow-up clinic. The follow-up took place in 2005-2006.

Data analysis at the time of PICU admission

During the study period patients consecutively admitted with septic shock and purpura were included in several sepsis studies.[9-14] Severity of illness was determined by using the Pediatric Risk of Mortality Score (PRISM), Vasopressor score (VAS) and Disseminated Intravascular Coagulation score (DIC).[15-17]

Assessment methods

Patients and parents were invited to the follow-up clinic 4-16 years after PICU discharge. Patients and parents were interviewed by one author (CB) using a standard questionnaire with regard to the presence of skin scarring and orthopaedic sequelae, and medical care regarding these sequelae in the period after PICU discharge. A general physical examination of patients (by one author, CB) was performed with special attention concerning skin scarring and orthopaedic sequelae (amputation, angular deformity and limb-length discrepancy). The POSAS-scoring system, done by a senior dermatologist (AO), was used to evaluate the skin scarring (appendix 1). POSAS, one of the very few validated scoring systems to assess the severity of skin scarring, is a scoring system designed to make an assessment of scar severity, based on the opinion of both doctor and patient.[18] All items must be scored on a scale ranging from 1 (representing normal skin) to 10 (the worst possible scar). We also used the visual analogue scale with a score ranging from 0 (worst possible scar, poorly healed scar) to 10 (normal skin, well healed scar). This score was given by both parents and patients.[19,20]
All skeletal radiographs in patients with angular deformity and limb-length discrepancy were re-evaluated by our orthopaedic surgeon.

Statistical methods

Statistical analysis was performed with a statistical analysis software program (SPSS 12.0 for WINDOWS 95, SPSS, Inc, Chicago, IL).
The Mann-Whitney test was used to compare quantitative variables between those children included in the study and those unable to be followed up, whereas the Chi-Square test for counts. We tested the association between patient-part and observer-part of the POSAS-scoring system by using Spearman correlation. The Mann-Whitney test was used to compare quantitative variables between the group with and the group without skin scarring or orthopaedic sequelae, whereas the Chi-Square test for counts. The most predictive severity of illness score (PRISM, VAS or DIC) of major sequelae was determined with receiver-operating characteristics (ROC) curve analysis. Logistic regression analysis was applied to determine the predictive chance of major sequelae for each severity of illness score. For the purpose of this predictive model major sequelae were defined as the presence of major scars and/or amputation of extremities and/or limb-length discrepancy. Scars were defined as minor versus major based on number, diameter and position by 2 observers. There was full agreement between these 2 observers, independent of each others score, in 92% of cases (110/120). Calculation of kappa as a measure of interobserver variability resulted in 0.77, which can be rated as good agreement. In case of discrepancy (n=10) final consensus was made by the 2 observers.
The Chi-Square test was used to investigate any secular trend in the frequency of skin scarring and/or orthopaedic sequelae over the time period of the study.
A p-value of 0.05 (two-sided) was considered the limit of significance.

Results

Patient sample

The target population consisted of 179 patients. From these 179 patients 9 were lost to follow-up. Of these 9, 1 patient with severe adverse outcome (mental retardation) died several years after the MSS. Seven patients lived abroad at the time of the follow-up, 1 was untraceable. Of the remaining 170 eligible patients, 145 agreed to participate. Of these 145 participants, 120 patients visited the follow-up clinic. The median follow-up interval was 9.8 years (range 3.7-17.4 years), median age of patients at the time of visit to follow-up clinic 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 (too emotional confrontation with the hospital) grounds and preferred to fill in the questionnaires at home. Twenty-five patients and/or parents did not respond to the invitation or refused to participate on practical or emotional grounds. The overall response rate, corrected for 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).

Incidence and severity of skin scarring

Of the 120 patients who visited the follow-up clinic, 58 (48%) had skin scarring due to necrotic purpura at the time of MSS. Most scars were positioned on the extremities (legs 86%, arms 55%). Eleven patients (19%) also had scars on the face, 13 patients (22%) on the trunk. Scars varied from mild to severe regarding number, diameter and position. In some patients scars were barely visible, other patients were extremely disfigured. The patient-part of the POSAS-scoring system was done in 44 (76%) of the 58 patients with a median score of 9 (range 6-29). Fourteen patients and/or parents did not score the scars for different reasons (like scars

Table 1. Data of participating patients and non-participants

Data are presented as number of patients or median (range)

The Mann-Whitney test was used to compare age at the time of PICU admission, length of stay in PICU and severity of illness between the 2 groups, whereas the Chi-Square test was used to compare sex.

characteristics	follow-up clinic	no follow-up clinic	p-value
	n=120	n=59	
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*	6 (3-8)	6 (2-8)	0.72
VAS	15 (0-403)	11 (0-145)	0.71

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

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 2 patients streptococcus was cultured. These 2 patients were included because they presented with septic shock and purpura requiring intensive care treatment.

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 pros theses 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

barely visible or difficulty scoring items according to patients and/or parents). The observer-part was done in 24 patients (41%) with a median score of 22 (range 5-34). In 34 patients the observer-part was not done due to logistic reasons (unavailability of the senior dermatologist). This resulted in 21 complete POSAS-scores (36%) with a median complete POSAS-score of 28 (range 11-53). There was a significant correlation between the score of the patient-part and observer-part in these 21 patients (respectively 9 and 19, correlation coefficient 0.69). Using the visual analogue scale the median score, given by parents of 50 patients (86%), was 7 (range 2-10), and the median score, given by 46 patients (79%), was also 7 (range 0-10).

Of the 58 patients with skin scarring, 19 (33%) underwent debridement and skin grafting in the weeks following PICU admission because of skin necrotic lesions resulting from purpura. One girl had plastic surgery in the face for aesthetic reasons (disfiguring scars) several years later. Three patients (5%) still had physical complaints (pain at their scars n=2, non-healing lesions on both heels n=1) at the time of the visit to the follow-up clinic.

Signs of postthrombotic syndrome (chronic swelling of the right lower limb, recurrent venous ulcers at the right heel) were observed in a 21 year-old girl. This occurred after symptomatic deep vein thrombosis following a central venous line in the right femoral vein at the time of the MSS.

Incidence and severity of orthopaedic sequelae

Ten patients (8%) had to undergo amputation of extremities because of irreversible necrosis of tissue (skin, muscle and/or bone) (table 2). Four patients (1, 3, 5 and 8) underwent 1 or more revision amputation(s) in the years following MSS because of stump or bone overgrowth. One patient (3) was still in orthopaedic follow-up (12 years after the MSS) because of bone overgrowth causing chronic ulcerations. Patients who required prostheses, were still seen regularly by a rehabilitation team for prosthetic review.

Seven patients (6%) had limb-length discrepancy (table 3). The majority of patients still had pain in the affected limb at the time of their visit to the follow-up clinic. Pain, which occurred mainly during walking or running, resulted in functional impairment in severe cases (like patient 4). Patient 2 could only walk a few meters with prosthesis.

All but 1 patient was already under treatment by the orthopaedic surgeon of our hospital. The most common presenting symptoms in patients with lower limb-length discrepancy were limping, pain in the limbs, difficulty in walking and angular deformity.

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) madelungdeformity 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

Table 4. Predictors of scars and orthopaedic sequelae

Data are presented as number of patients or median (range)

The Mann-Whitney test was used to compare age at the time of PICU admission and severity of illness between the group with and the group without skin scarring or orthopaedic sequelae, whereas the Chi-Square test was used to compare sex and NM serogroup between these groups.

Variables	No scars	Scars	p-value
	n=62	**n=58**	
Sex	35 boys, 27 girls	28 boys, 30 girls	0.47
NM serogroup	35 B, 7 C	43 B, 6 C	0.57
Age PICU (years)	4.0 (0.1-17.9)	2.3 (0.3-17.0)	< 0.05
DIC	5 (3-8)	6 (5-8)	< 0.001
PRISM	11 (1-33)	21 (4-37)	< 0.001
VAS	5 (0-403)	28 (0-310)	< 0.001

Variables	No amputations	Amputations	p-value
	n=110	**n=10**	
Sex	58 boys, 52 girls	5 boys, 5 girls	0.87
NM serogroup	71 B, 10 C	7 B, 3 C	0.15
Age PICU (years)	2.9 (0.1-17.9)	6.7 (0.72-17.0)	0.22
DIC	6 (3-8)	7 (5-7)	< 0.01
PRISM	15 (1-36)	22 (13-37)	< 0.05
VAS	10 (0-403)	53 (10-155)	< 0.01

Variables	No limb-length discrepancy	Limb-length discrepancy	p-value
	n=113	**n=7**	
Sex	60 boys, 53 girls	4 boys, 3 girls	0.84
NM serogroup	71 B, 13 C	6 B	0.76
Age PICU (years)	3.3 (0.1-17.9)	0.7 (0.3-3.5)	< 0.01
DIC	6 (3-8)	7 (5-8)	< 0.05
PRISM	15 (1-36)	31 (27-37)	< 0.001
VAS	10 (0-403)	55 (18-183)	< 0.01

Figure 1. ROC curves for the presence of major sequelae according to severity of illness scores

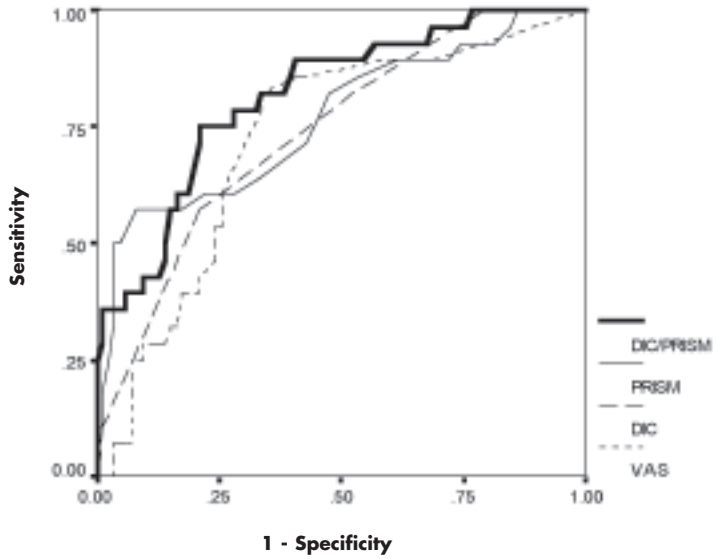
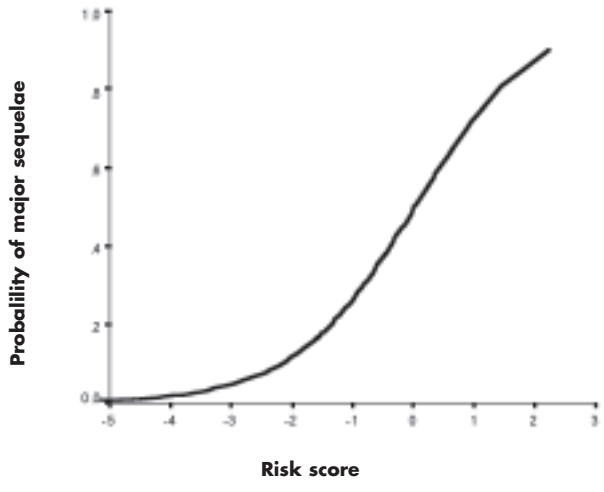


Figure 2. The predictive probability (P) of major sequelae according to risk score.

Equation of the curve: log (odds) = risk score, with odds representing the odds (P/1-P) of the predicted probability P. The risk score, combining PRISM and DIC, was calculated as - 7.53 + 0.1xPRISM + 0.77xDIC



In 1 patient (table 3, patient 7) the lower limb-length discrepancy and varus deformity of the right ankle were diagnosed at the time of her visit to the follow-up clinic. Subsequently she was referred to the orthopaedic surgeon.
All patients, except patient 2, underwent 1 or more (max. 4) surgical intervention(s) (osteotomy, epiphysiodesis) for their lower limb-length discrepancy and/or angular deformity in the months and years following the diagnosis of these sequelae. All patients remained in orthopaedic follow-up.

Predictors of skin scarring and orthopaedic sequelae

Patients with scars or orthopaedic sequelae (amputation, limb-length discrepancy) had significantly higher severity of illness scores (table 4).
Using logistic regression analysis, both PRISM and DIC, but not VAS, were significantly associated with the presence of major sequelae. In figure 1, the ROC curves for each severity of illness score separately are displayed, together with the ROC curve for PRISM and DIC combined. The area under the curve was 0.73 for VAS, 0.74 for DIC, 0.77 for PRISM and 0.82 for the calculated risk score combining PRISM and DIC. The predictive chance of major sequelae according to the combined risk score was calculated as follows: - 7.53 + 0.1xPRISM + 0.77xDIC (figure 2).
There was no significant trend in the frequency of severe skin scarring and orthopaedic sequelae over the time period of the study: from 1988-1990 3 of 16 patients (19%) had severe skin scarring and/or orthopaedic sequelae, from 1991-1995 10/42 (24%), from 1996-2001 16/62 (26%).
None of the patients in our study population had compartment pressures measured nor fasciotomies performed during PICU admission.
A subgroup of our patient sample (n=20) was included in a study where protein C concentrate was supplied.[10] Patients who received protein C concentrate did not differ significantly with regard to the presence of scars or orthopaedic sequelae in comparison with patients who received placebo.

Discussion

In our long-term outcome study in survivors of MSS, we found that nearly half of the patients (48%) had skin scarring, ranging from barely visible scars to extremely disfiguring scars. Also a high number of patients (14%) had orthopaedic sequelae (amputation, limb-length discrepancy) with important long-term morbidity (surgical intervention(s), pain or functional impairment). Patients with scars or orthopaedic sequelae had significantly higher severity of illness scores.

Incidence and severity of skin scarring

A high number of patients (48%) had skin scarring, mostly positioned on the legs. Our findings are in contrast with a study of Erickson, which is probably due to their heterogeneous study population.[5]

In some patients scars were barely visible, other patients were extremely disfigured. A possible explanation could be the variability in extensiveness and appearance of purpura in patients at the time of PICU admission, mainly due to the variability in severity of illness.

This is the first study using the POSAS-scoring system in patients who survived MSS. Patients and/or parents scored scars comparable with the observer. This is in line with a study in burn injury patients.[18] However we need to be careful in comparing patient-part and observer-part since they do not cover the same items and have a different total score.

Also parents and patients seemed to evaluate the scars the same way, reflected by the same visual analogue scale score in parents and patients. In the interviews done during their visit to the follow-up clinic, parents and/or patients often seemed not to be disturbed by the presence nor appearance of scars. Most patients reported they adapted to their scars over time.

Unfortunately no validated, standardised scoring system is available to assess the extensiveness (number, diameter and position) of scars.

Incidence and severity of orthopaedic sequelae

A relative high number of patients (14%) had orthopaedic sequelae due to MSS. Irreversible necrosis of tissue (skin, muscle and/or bone) can necessitate amputation of extremities in severe cases of MSS. Limb-length discrepancy after MSS is probably caused by necrosis of the growth plate due to disseminated intravascular coagulation leading to premature closure or destruction of the growth plate.

In the study of Bache 13% had epiphyseal growth arrest mainly in the lower limbs, which is comparable with our results.[4]

Important is that most of the patients with more extensive amputation (feet, leg or arm) or lower limb-length discrepancy have long-term morbidity because of significant functional impairment and the need of surgical reintervention(s) in the years following MSS. Furthermore the majority of patients with lower-limb length discrepancy still suffered from pain in the affected limb.

Predictors of skin scarring and orthopaedic sequelae

This is the first study to determine predictors of skin scarring and orthopaedic sequelae by using severity of illness scores. Patients with scars or orthopaedic sequelae had significantly higher PRISM, VAS and DIC scores. By using ROC curve analysis, we could demonstrate that the underlying disease, expressed by PRISM and DIC, is predictive for the presence of major sequelae, but not the therapy with vasopressors. Also younger children at the time of PICU admission seemed more at risk for limb-length discrepancy several years after MSS. This is probably due to age-dependent differences in vulnerability of bone vasculature as well as the stage of bone maturity and development.[21]

Although survival of children with MSS improved in the last 2 decades, the frequency of severe skin scarring and orthopaedic sequelae remained the same in our study period.[22] This could be due to better and earlier interventions: international treatment guidelines were implemented, health care workers received additional training, and public awareness increased, resulting in a decreased patient delay.

Limitations of the present study

Several limitations of our study should be acknowledged. This is an observational study (no controls) in one centre. The response rate was relative low (71%). However we think that this may not have influenced the results since participating patients and non-participants did not differ with respect to age at the time of PICU admission and severity of illness. Further, baseline assessments of the purpura (extensiveness and appearance) at the time of PICU admission were not available. Also we did not take into account the local treatment of purpura during the acute phase nor plastic surgery. Unfortunately, we could not obtain reliable data since skin grafting or amputation most often was performed after PICU discharge, and not during the acute phase. Furthermore after PICU discharge part of our patients were transferred to regional hospitals.

The POSAS-scoring system was not done in all patients, especially the observer-part. In future studies more than 1 dermatologist or clinical investigator (2 or 3) should be available not only for doing the POSAS-scoring system, but also to check interobserver variability.

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Implications

Since a significant number of patients who survived MSS in childhood have skin scarring and orthopaedic sequelae with important long-term morbidity, special attention should be given to study the impact of these sequelae on long-term health related quality of life and psychological outcome.
Being aware of these long-term consequences and the possible risk factors, could lead to a standard multidisciplinary follow-up clinic for these patients.

Appendix 1: POSAS- scoring system

a) Observer-part

	Normal skin	1 2 3 4 5 6 7 8 9 10	Worst scar possible
Vascularisation		- - - - - - - - - -	
Pigmentation		- - - - - - - - - -	Hypo 0 Hyper 0 Mixed 0
Thickness		- - - - - - - - - -	
Relief		- - - - - - - - - -	
Pliability		- - - - - - - - - -	

b) Patient-part

if the patient is >12 years: the patient-part is scored by the patient him/herself
if the patient is 4-12 years: the patient-part is scored by the patient and parents
if the patient is 0-4 years: the patient-part is scored by the parents

	No complaints	1 2 3 4 5 6 7 8 9 10	Yes, a lot of complaints
Is the scar painful?		- - - - - - - - - -	
Does the scar itch?		- - - - - - - - - -	

	Normal skin	1 2 3 4 5 6 7 8 9 10	Worst scar possible
Color difference		- - - - - - - - - -	
Stiffness		- - - - - - - - - -	
Thickness		- - - - - - - - - -	
Irregularity		- - - - - - - - - -	

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5

LONG-TERM HEALTH STATUS IN SURVIVORS OF MENINGOCOCCAL SEPTIC SHOCK IN CHILDHOOD

5.1

LONG-TERM HEALTH STATUS IN SURVIVORS OF MENINGOCOCCAL SEPTIC SHOCK IN CHILDHOOD

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Arch Ped Adol Med. 2008. in press

Abstract

Objective To assess long-term health status in patients who survived meningococcal septic shock (MSS) in childhood.

Design A medical and psychological follow-up of a cross-sectional cohort.

Setting PICU of the Erasmus MC-Sophia Children's Hospital, a tertiary care university hospital, the Netherlands.

Patients All consecutive patients with septic shock and purpura requiring intensive care treatment between 1988 and 2001.

Intervention Parents and patients were invited to the follow-up clinic 4-16 years after PICU discharge.

Main outcome measures Health status was assessed with a standard medical interview, physical examination, renal function and Health Utilities Index mark 2 and 3 (HUI2 and HUI3).

Results 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)).

35% had one or more of the following neurological impairment(s): severe mental retardation with epilepsy (3%), hearing loss (2%), chronic headache (28%) or focal neurological signs like paresis of one arm (6%).

One of the 16 patients with septic shock-associated acute renal failure at PICU admission showed signs of mild chronic renal failure (GFR 62 ml/min/1.73m^2, proteinuria and hypertension).

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

Conclusions In patients who survived MSS in childhood, one third showed long-term neurological impairments, ranging from mild to severe and irreversible. Patients reported poorer general health status as measured by HUI2 and HUI3.

Introduction

Septic shock with petechial and/or purpuric rash is a life threatening clinical syndrome predominantly caused by *Neisseria meningitidis* (NM). It is characterized by sudden onset and rapid progression in previously healthy children. Younger children (< 3 years) are known to have more severe disease and higher risk of case fatality.[1]

In spite of better understanding of the pathogenesis of meningococcal septic shock (MSS) and advances in therapeutic interventions, we observed a high morbidity and mortality in the Netherlands until the implementation of a national vaccination campaign against serogroup C meningococci (2002).[2]

Only few studies have reported long-term incidences of adverse physical health consequences in patients who survived MSS.[3-5] These studies have limitations, however, in that they do not differentiate as to severity of disease; the study populations included patients with sepsis, septic shock or meningitis.

In addition, major risk factors for developing adverse consequences have not been well identified.

We hypothesized that patients who survived MSS in childhood are at higher risk for adverse physical health consequences due to permanent organ damage caused by shock and thrombosis (disseminated intravascular coagulation).

More insight in these matters could enable anticipatory guidance and support for patients after PICU discharge.

The aim of this study was to investigate long-term physical health consequences in patients who survived MSS in childhood. Additionally, we assessed various putative determinants of adverse health outcomes in patients.

Materials and Methods

Patient selection

This study concerned a medical and psychological follow-up of a cross-sectional cohort of all consecutive surviving patients with septic shock and purpura requiring intensive care treatment at least 4 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. Eligible for this study were all consecutive surviving patients aged 1 month to 18 years with a clinical picture of MSS, as well as their parents. Meningococcal septic shock was defined as septic shock with petechiae and/or purpura (table 1).[6] The Erasmus MC Medical Ethical Review Board approved the study protocol. Written informed consent was obtained

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from parents and patients by sending a standard letter requesting their participation in our 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 at PICU admission

During the study period patients consecutively admitted with MSS were included in several sepsis studies.[7-11] In these studies medical data were collected prospectively at various time-points in the course of the disease. These data, together with demographic and clinical data were pooled into one database and analyzed.
Severity of illness was determined by using the Pediatric Risk of Mortality Score (PRISM), Vasopressor score (VAS) (table 2) and Disseminated Intravascular Coagulation score (DIC) (table 3).[12-14]

Assessment methods at follow-up

Medical interview and physical examination
Parents and patients were invited to the follow-up clinic 4-16 years after PICU discharge. They were interviewed by one paediatrician (CB) in a semi-structured format using a standard questionnaire with regard to health consequences and medical care since MSS. Complaints 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 one paediatrician (CB). Skin scarring and orthopaedic sequelae due to MSS are described elsewhere. [15]
Briefly, 48% of the patients had skin scarring due to purpura (ranging from barely visible scars to extremely mutilating scars); 8% amputation(s) of extremities (ranging from 1 toe to both legs and 1 arm); 6% lower limb-length discrepancy.
Measurements of body weight, length, head circumference (HC), and mid upper arm circumference (MUAC) were performed.[16] All measurements were performed by one observer in whom intra-observer variability for MUAC was tested prior to the study.

Assessment of renal function
Patients who had developed septic shock-associated acute renal failure (ARF) during PICU admission, defined as serum creatinine 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 (crea P), from which glomerular filtration rate per 1.73m^2 body surface area (GFR) was estimated using the modified Schwartz or Cockroft formula (according to age), the average of 3 measurements of blood pressure (RR) by automated sphygmomanometry (Dynamap), protein and creatinine excretion averaged from 3 first morning urine samples.[17]
Significant proteinuria was defined as a protein/creatinine ratio in urine of above 20 mg/mmol (0.2 mg/mg).[18] Blood pressure standard deviation scores were used from Jackson et al.[19]

Health status questionnaires
Generic health status was assessed with the Health Utilities Index mark 2 and 3 (HUI2 and HUI3), based on the 15-item HUI questionnaire.[20,21] The HUI2 and HUI3 are validated health status classification systems consisting of respectively 6 and 8 attributes. Each HUI-attribute is assigned on the basis of respondents' answers to 1 or more items of the 15-item HUI questionnaire: scores range from 1 (no functional limitations) to 4, 5 or 6 (severe functional limitations). Single-attribute utility scores were calculated and ranged from 0 (worst health status) to 1 (best health status).[21]
A HUI2 and HUI3 multi-attribute utility score, indicating overall health, was calculated based on single-attribute utility scores.[22,23] Norm scores for HUI2 and HUI3 are available based on a representative sample of 1435 Dutch schoolchildren aged 5-13 years.[20,21] The parent-completed 15-item HUI questionnaire was used for patients aged 4-17 years, whereas the patient-completed 15-item HUI questionnaire for patients 18 years and older. We also applied a visual analogue scale to rate overall health with a score ranging from 0 (worst desirable health state) to 100 (best desirable health state).[24] This score was given by parents in patients 4-17 years and by patients themselves if they were 18 years or older.
The 15-item HUI questionnaires were sent by mail with the request to complete these at home. Parents themselves could decide who (mother or father) would complete the HUI questionnaire.

Statistical methods

Statistical analysis was performed with a statistical analysis software program (SPSS 12.0 for WINDOWS, SPSS, Inc, Chicago, IL).
Comparisons between participating patients and non-participants were made with the Mann-Whitney test for age at time of PICU admission, length of PICU stay and severity of illness, with the Chi-Square test for sex.
Comparisons between patients with and patients without adverse neurological outcome were made with the Mann-Whitney test for age at time of PICU admission, severity of illness scores and serum glucose level (lowest and highest), with the Chi-Square test for the presence of meningitis (NM cultured in liquor or pleiocytosis) and convulsions during PICU admission.

Table 1. Definition of septic shock

Clinical suspicion of infection and evidence of systemic response to infection; tachycardia (> 2 standard deviations for age), tachypnea (> 2 standard deviations for age), temperature < 36°C or > 38.5°C.

Sepsis-induced hypotension:

- systolic blood pressure < 75 mm Hg for children between 3-12 months, < 80 mm Hg for 1-5 years, < 85 mm Hg for 6-12 years, < 100 mm Hg for children older than 12 years
- or the requirement for vasopressors/inotropes to maintain blood pressure despite adequate fluid resuscitation along with the presence of perfusion abnormalities that may include, but are not limited to:
  a) lactic acidosis: pH < 7.3 or base excess < -5 mmol/l or plasma lactate levels > 2.0 mmol/l
  b) oliguria: diuresis < 0.5 ml/kg/h for at least one hour despite acute volume loading or evidence of adequate intravascular volume without pre-existing renal disease
  c) acute alteration in mental status

Table 2. Vasopressor score

dopamine dose (mcg/kg/min) x1,
+ dobutamine (mcg/kg/min) x1,
+ epinephrine (mcg/kg/min) x100,
+ norepinephrine (mcg/kg/min) x100,
+ phenylephrine (mcg/kg/min) x100

Table 3. Disseminated Intravascular Coagulation score

Platelet count (x10³/l)	
> 100	0
≤ 100	1
≤ 50	2
Fibrine dimers (ml/l)	
< 0.25	0
≥ 0.25 and < 5	2
≥ 5	3
prothrombin time (sec.)	
< 15	0
≥ 15 and < 19	1
≥ 19	2
Fibrinogen (g/l)	
> 1	0
≤ 1	1

DIC score ≥ 5; presence of disseminated intravascular coagulation.

All obtained anthropometric data 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 program (GROWTH ANALYSER 3, 2001-2006 Nederlandse Groeistichting, Rotterdam -The Netherlands).[25]
We tested the association between putative predictor variables (age at time of PICU admission, severity of illness scores and follow-up interval) and anthropometric SD-scores by using Spearman correlation. The Mann-Whitney test was used to compare anthropometric SD-scores between patients with and without orthopaedic sequelae.
The Mann-Whitney test was used to compare HUI2 and HUI3 scores of our patients with individual normative data from a general population survey.[20]
A P-value of 0.05 (two-sided) was considered the limit of significance.

Results

Patient sample

The target population consisted of 179 patients. From these 179 patients 9 were lost to follow-up: 1 patient with severe adverse outcome (mental retardation with epilepsy) died several years after the MSS; 7 patients lived abroad at time of the follow-up; 1 was untraceable. Of the remaining 170 eligible patients, 145 agreed to participate. Of these 145 participants, 120 patients visited the follow-up clinic. The median follow-up interval was 9.8 years (3.7-17.4 years), the median age of patients at time of visit to follow-up clinic 14.5 years (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 (too emotional confrontation with the hospital) 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 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 4). Patients did not differ with respect to age at time of PICU admission and severity of illness.
At PICU admission a causative organism was isolated in 100 of the 120 patients (83%) who visited the follow-up clinic. In 99 patients (82.5%) *Neisseria meningitidis* was cultured in blood. Of these 99, 78 (79%) had NM serogroup B, 13 (13%) serogroup C and in 8 (8%) the serogroup was not determined. In addition, a lumbar puncture was performed in 67 patients (56%): NM cultured in liquor in 45 patients (67%), pleiocytosis in case of negative culture in 11 patients (16%).

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Health consequences

Of the 120 patients, 3 (3%) developed severe mental retardation (total intelligence score < 70) with epilepsy (2 with spastic quadriplegia) for which they needed multidisciplinary medical care on a regular base. One of these 3 patients died a few months after his visit to the follow-up clinic (cause of death related to severe retardation with epilepsy and spastic quadriplegia). Before the MSS, all 3 had a normal motor, cognitive and emotional development. As to the risk factors during PICU admission, all 4 patients with severe mental retardation (including the patient who died before our follow-up study) differed significantly with respect to age at time of PICU admission (0.7 year, p< 0.01), severity of septic shock (PRISM 32, p< 0.01)(VAS 140, p< 0.05), lowest serum glucose level (1.8 mmol/l, p< 0.01 (all medians)) and the presence of convulsions (p< 0.01), compared with patients without severe retardation. Neuroimaging done in the weeks after PICU discharge showed diffuse atrophy due to ischemia and necrosis (n=2) and bilateral occipital hypodensities due to venous brain infarcts (n=1).

Of the remaining 117 patients, 39 (33%) had 1 or more of the following neurological impairment(s): hearing loss (n=2), chronic headache (n=34) or focal neurological signs (n=7). In the 2 patients (2%) with sensorineural hearing loss this was documented after MSS: 80 db hearing loss bilateral requiring a hearing device in one patient, 30 db perception loss at 250 Hz (55 db at 2000 Hz) in another patient. These 2 patients were already in audiological follow-up. Thirty-four patients (28%) reported chronic headache, ranging from mild to severe. Seven patients (6%) had the following chronic focal neurological signs (one or more): sensory loss in 1 arm, paresis of 1 arm, paresthesia of foot/hand, resting and intention tremor of both hands. Some of these patients already had these focal neurological signs at the time of PICU discharge. In only 1 patient with focal neurological signs (sensory loss and paresis of 1 arm) neuroimaging and electroencephalography was performed in the months following PICU discharge, which showed left cerebral hemisphere atrophy with slow EEG pattern.

Statistical 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.

Table 4. Data of participating patients and non-participants

Data are presented as number of patients or median (range).

The Mann-Whitney test was used to compare age at time of PICU admission, length of PICU stay and severity of illness between the 2 groups, whereas the Chi-Square test was used to compare sex.

characteristics	follow-up clinic	no follow-up clinic	p-value
	n=120	n=59	
Sex	63 boys, 57 girls	27 boys, 32 girls	ns
Age at time of PICU (years)	3.1 (0.1-17.9)	5.4 (0.2-14.3)	ns
Length of PICU stay (days)	3 (1-51)	3 (1-36)	ns
Mechanical ventilation	46	23	ns
PRISM	15 (1-37)	15 (0-41)	ns
Presence of disseminated intravascular coagulation	99	41	ns
DIC*	6 (3-8)	6 (2-8)	ns
Administration of inotropics	86	47	ns
VAS	15 (0-403)	11 (0-145)	ns

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

Growth

Growth data of 113 (95%) patients were collected at follow up. In 7 patients (including 5 of the 16 patients with orthopaedic sequelae) anthropometric measurements were not performed for different reasons (spastic quadriplegia with contractures, extensive amputations, severe lower-limb discrepancy).

Anthropometric SD-scores were similar to those found in the general population. One (0.9%) of the 113 patients had a weight-for-age standard deviation score < -2SD, whereas 3 patients (2.7%) had a length-for-age standard deviation scores < -2SD.

Univariate analysis of anthropometric SD-scores in relation to age at time of PICU admission, severity of illness scores and follow-up interval resulted in one significant relationship: age at time of PICU admission was significantly associated with LFA-SDS (p< 0.01, r_s-0.26), indicating lower LFA-SDS with older age at time of PICU admission. Patients with and without orthopaedic sequelae did not differ with respect to anthropometric SD-scores.

Renal function

Of the 120 patients, 19 (16%) temporarily had developed septic shock-associated acute renal failure during PICU admission. Four (3%) received RRT (continuous venovenous hemofiltration n=1, continuous venovenous hemodiafiltration n=3). In all 4 cases RRT was commenced because of the development of severe acute oliguric renal failure. In these 4 patients renal function improved and RRT was discontinued. At the time of follow-up we referred the 19 patients (including 4 who received RRT) who had septic shock-associated ARF to the outpatient nephrology clinic of our hospital. Twelve of them actually visited this clinic, while another 4 went to their general practitioner (on practical grounds) for investigation of their present renal

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Table 5. Long-term renal function assessment

Nr	age PICU (years)	max. crea* (µmol/l)	RRT**	sex	age follow-up (years)	crea P (µmol/l)	GFR	protein U/crea U (mg/mmol)	syst RR	diast RR
1	13	684	yes	F	25.5	61	105	-	-	-
2	0.8	118	yes	M	17	60	117	6.51	< 95	< 90
3	9	880	yes	M	15	112	62	22.67	> 95	> 95
4	0.7	189	yes	M	10.5	28	-	17.18	< 90	< 90
5	4	124	no	M	10	52	111	11.32	< 90	< 90
6	8.5	137	no	M	17	72	105	-	< 90	< 90
7	10.5	155	no	F	24	71	96	-	> 95	> 95
8	0.7	157	no	F	13	60	115	8.06	< 90	< 90
9	2	159	no	F	15.5	60	108	6.21	< 90	< 95
10	0.7	159	no	M	10	33	143	-	-	-
11	12.5	174	no	F	24.5	92	100	-	-	-
12	1	177	no	M	9	39	139	13.64	< 90	< 95
13	6	189	no	F	21.5	69	124	54.02	< 90	> 95
14	4.5	202	no	F	8.5	45	124	22.22	< 90	< 90
15	13.5	243	no	M	26	79	158	5.52	< 90	< 90
16	3.5	267	no	M	8	40	130	13.27	< 90	< 90

*max. crea: highest creatinine in plasma (µmol/l) during PICU admission **RRT: renal replacement therapy during PICU admission

Note: - in patient nr 4 GFR could not be calculated because measurement of lenght was inpossible due to severe spastic quadriplegia with contractures of lower limbs.

- in patients nr 1, 6 and 11 renal function assessments were performed by their general practioner. Urine protein/creatinine and/or blood pressure were not measured (reason unknown).

function (table 5). The remaining 3 did not show up at the outpatient nephrology clinic (reason unknown) or refused further investigations.

One patient (nr 3 in table 5) was already under treatment by the paediatric nephrologist since PICU discharge because of mild chronic renal failure (GFR 60-90 ml/min/1.73m^2 and proteinuria). This was the only patient with current impaired renal function (GFR 62 ml/min/1.73m^2) in combination with hypertension and proteinuria for which he was treated with an ACE inhibitor. His renal failure was slowly progressive since PICU discharge. This patient had suffered from fulminant MSS (PRISM 30, VAS 155, DIC 7, severe ARF requiring RRT). Two patients (nr 13 and 14 in table 5) had isolated proteinuria with intact GFR. One patient (nr 7) had isolated

Table 6. HUI2, HUI3 and visual analogue scale scores of patients compared with the reference group

Data are presented as mean (standard deviation).

	Patients n=120	Reference n=1435	p-value
HUI3 single-attribute utility score			
vision	0.98 (0.10)	0.99 (0.04)	0.01
hearing	1.00 (0.0)	1.00 (0.04)	0.55
speech	0.93 (0.16)	0.97 (0.08)	0.01
ambulation	0.97 (0.15)	0.99 (0.04)	< 0.01
dexterity	0.98 (0.13)	1.00 (0.02)	< 0.01
emotion	0.96 (0.07)	0.98 (0.07)	< 0.01
cognition	0.90 (0.21)	0.97 (0.09)	< 0.01
pain	0.94 (0.13)	0.98 (0.08)	< 0.01
HUI3 multi-attribute utility score	0.82 (0.25)	0.93 (0.12)	< 0.01
HUI2 single-attribute utility score			
sensation	0.90 (0.18)	0.95 (0.12)	< 0.01
mobility	0.97 (0.15)	1.00 (0.03)	< 0.01
emotion	0.95 (0.10)	0.97 (0.08)	< 0.05
cognitive	0.93 (0.16)	0.98 (0.06)	< 0.01
self care	0.97 (0.16)	0.99 (0.06)	0.41
pain	0.96 (0.09)	0.99 (0.05)	< 0.01
HUI2 multi-attribute utility score	0.88 (0.16)	0.94 (0.09)	< 0.01
visual analogue scale overall health	85.4 (15.3)	92.7 (9.2)	< 0.01

hypertension with intact GFR. This patient suffered from overweight (body mass index 32 kg/m^2).
Statistical analysis to compare severity of illness between patients with and without impaired renal function, was not performed as there was only 1 patient with impaired renal function.

General health status

Table 6 showes HUI2, HUI3 and visual analogue scale scores in patients compared with the reference group. Parents or patients reported significantly lower scores on nearly all HUI2 and HUI3 attributes.

Discussion

In patients who survived MSS in childhood, one third showed long-term neurological impairments, ranging from mild to severe and irreversible. Patients reported poorer general health status as measured by HUI2, HUI3 and visual analogue scale.

Health consequences

One third of the patients had long-term adverse neurological outcome after MSS. Four patients (of whom 2 died several years after MSS) developed severe and irreversible neurological damage. This was probably due to the severity of shock (as expressed by their young age, high severity of illness scores and hypoglycaemia) leading to brain ischemia or infarcts. Another cause could have been prolonged convulsions, probably caused by brain ischemia and/or hypoglycaemia.
The incidence of hearing loss was low (2%) and this is comparable with the study of Koomen et al. who found that the incidence of hearing loss after meningococcal meningitis was 4%.[26] Although our study concerned patients with MSS, the majority (83%) of our patients also had meningitis (NM cultured in liquor and/or pleiocytosis) in case a lumbar puncture was performed. It should however be noticed that in nearly half of the patients, especially patients admitted in the more recent years, a lumbar puncture was not performed because of the possible side effects (further compromise of the haemodynamics, bleeding or cerebral oedema with herniation). Although both patients with hearing loss had meningitis, statistical significant differences regarding presence of meningitis were not found between patients with and patients without hearing loss.

A notable result was that nearly one third of the patients reported chronic headache. Causes of chronic headache in patients after MSS could be: tension-type headache (for example in patients with cognitive dysfunctioning) or chronic hydrocephalus due to meningitis. The focal neurological signs in the extremities, reported by a minority of patients (6%), could be due to venous cortical brain infarcts or brain atrophy.
Headache and focal neurological deficits have previously been described in survivors of bacterial meningitis.[27,28] However in our study significant differences regarding presence of meningitis were not found between patients with and patients without chronic headache or focal neurological signs.

Growth

In MSS survivors growth seemed not impaired since the percentages of SD-scores < -2SD were in line with the normal population (2.5%). Although older age at time of PICU admission was significantly associated with lower LFA-SDS, we don't think that this finding is of clinical significance.
Interestingly we did not found growth abnormalities in patients with orthopaedic sequelae. It should be noted, however, that in the most disabled patients we were not able to perform anthropometric measurements.

Renal function

One (6%) of the 16 examined patients with septic shock-associated ARF (1 of 4 patients (25%) necessitating RRT) showed signs of persistent kidney damage, manifested as mild chronic renal failure, proteinuria and hypertension. His renal failure may progressive further with age, possibly necessitating chronic dialysis or renal transplantation in the future. The incidence of long-term impaired renal function as measured by estimated GFR found in our patients is in line with the study of Slack et al.[3] They reported mild to moderate reduction of estimated GFR in 25% of patients 4 years after meningococcal sepsis-associated ARF necessitating RRT.
Proteinuria after MSS may reflect the loss of a considerable amount of glomeruli due to septic shock-associated acute tubular necrosis. Though the GFR may, by hyperfiltration of the remaining glomeruli, be normal at the time of measurement, it could decline over time with the proteinuria untreated. Therefore, patients with proteinuria and intact GFR, should have periodically check-up of GFR, proteinuria and blood pressure.

General health status

Lower health status was reported in all HUI2 and HUI3 attributes (except HUI3 "hearing" and HUI2 "self care") and visual analogue scale, indicating the patient's present generic health status was perceived as relatively poor. Also in our previous study significantly poorer health-related quality of life scores, mainly on physical (like general health perception) domains, were found in MSS survivors compared with normative data.[29] This could indicate that the patient's disease episode and present health status had a negative impact on their present physical health-related quality of life. Furthermore, the lower scores in HUI2 and HUI3 attributes "cognition" and in HUI3 attribute "speech" were in line with earlier findings, where poorer outcomes on intellectual functioning were found in children who survived invasive meningococcal disease.[30]
Surprisingly lower scores were reported on HUI3 attribute "vision" (indicating that patients were less able to see well enough to read ordinary print or recognize people from a distance), although patients did not report this problem during the medical interview.

Strengths and limitations of the present study

A unique feature of this study is the homogeneous patient sample that has been investigated on the long-term. Standardised assessment procedures were used.
Several limitations of our study should be acknowledged. This is an observational study (no controls) in one centre. The response rate was satisfactory, though not high (71%). However we think that this may not have influenced the results since participating patients and non-participants did not differ with respect to age at time of PICU admission and severity of illness. On the other hand, we only included MSS patients requiring PICU treatment. This could have resulted in a selection bias by excluding the milder cases admitted to a general ward. We did not use a validated headache questionnaire.
Further, baseline assessments of health status, HUI2, HUI3 and visual analogue scale scores (before MSS) were not available.
HUI2, HUI3 and visual analogue scale scores, in patients 4-17 years were elicited by parent-report and in patients ≥ 18 years by self-report; they were compared with normative data derived from parent-reports in a general Dutch population sample (children aged 5-13 years). Dutch normative self-report data are not yet available.
It could be interesting to compare our group with patients, matched on age and timing of follow-up interval, admitted to the hospital or PICU because of another disease.

Implications

If the incidence of chronic headache, assessed with a validated headache questionnaire, remains high, predictors should be identified.
Regarding long-term renal function assessment some careful recommendations can be made. In our opinion MSS survivors with septic shock-associated ARF, especially those necessitating RRT, should undergo periodic measurement of blood pressure, serum creatinine with calculation of estimated GFR, and urine protein/creatinine ratio.
In view of the relatively poor scores found on HUI2 and HUI3 attributes standard assessment of vision, emotional distress, neuropsychological and cognitive functioning is warranted in MSS survivors in order to intervene in an early phase.

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5.2

PULMONARY SEQUELAE IN SURVIVORS OF MENINGOCOCCAL SEPTIC SHOCK IN CHILDHOOD

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Crit Care Med. 2008. in press. Letter

To the editor

We thank Dr. Plötz for his comments regarding our article in Critical Care Medicine (2008).[1]

We completely agree with Dr. Plötz that both short-term and long-term outcomes in survivors of meningococcal septic shock (MSS) are highly relevant. Only a few, unsystematic studies have been conducted in this field. These studies used small, heterogeneous patient samples, unstandardized assessment procedures and were focussed mainly on short-term outcome. Therefore our relatively large, homogeneous cohort offered the possibility to investigate the neglected area of outcome, both from a medical and psychosocial point of view, with standardized procedures. Parts of our outcome study have been published elsewhere or are in press.[1-4]

In his commentary Dr. Plötz asked if we evaluated pulmonary or cardiac function in our cohort of MSS survivors.

In our short-term follow-up study of MSS survivors requiring intensive care treatment between 2001 and 2005, pulmonary and cardiac functions were not tested specifically.[1]

The second part of our study concerned a cross-sectional long-term outcome study of all 179 MSS survivors requiring intensive care treatment between 1988 and 2001.[2-4]

Of the 120 MSS survivors, who visited the follow-up clinic, 46 required mechanical ventilation at the time of PICU admission. In 6 of these 46 patients long-term lung function was performed because they had signs of ARDS at the time of MSS; novel presence of bilateral infiltrates on chest X-ray, $PaO_2/FIO_2 < 200$ (median 53).[5] Duration of mechanical ventilation in these 6 ARDS patients was significantly longer ($P < 0.001$, 12.5 versus 4days) compared with the 40 patients without ARDS.

Other characteristics of the 6 ARDS patients at time of PICU admission; PRISM 27, age at time of PICU admission 2 years, follow-up interval 11.3 years (all medians).

In all 6, except 1, flowvolume curves were normal; forced vital capacity ranged from 100-123% predicted values (median 111) (unpublished data). One patient, who was known with asthma, had a normal forced vital capacity but showed signs of airways obstruction.

Plötz et al. also found normal lung function parameters in MSS survivors. However, they found desaturation (median 2.5%, range 0-20%) during maximal exercise, whereas we did not measure this in our patients. However none of our 120 MSS survivors reported exercise intolerance.

In the study of Plötz the follow-up interval was shorter (3.4 years), patients were older at time of PICU admission (4.7 years) compared with our study.

So several questions remain; does significant desaturation occur during maximal exercise long-term (as in our patients, > 10 years) after MSS? If so, what is the cause? Could this be due to lung fibrosis?

We are planning a long-term cardiac follow-study study in patients who survived fulminant MSS (high severity of illness scores) and who required high doses of inotropes/vasopressors. In this study we will perform electrocardiograms and echocardiographic measurements.

In conclusion, we would like to reassure Dr. Plötz in the fact that we did study long-term morbidity in MSS survivors.

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6

LONG-TERM HEALTH-RELATED QUALITY OF LIFE IN SURVIVORS OF MENINGOCOCCAL SEPTIC SHOCK IN CHILDHOOD AND THEIR PARENTS

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Qual Life Res. 2007 Dec;16(10):1567-76. Epub. 2007. Oct 19

Abstract

Objective To assess long-term health-related quality of life (HR-QoL) in patients who survived meningococcal septic shock in childhood, and their parents.

Patients and methods All consecutive patients with meningococcal septic shock requiring intensive care treatment between 1988 and 2001, and their parents. HR-QoL was assessed by the Child Health Questionnaire and the SF-36. Scores were compared with reference data of Dutch general population samples. Lower scores indicated poorer HR-QoL, higher scores more favourable HR-QoL.

Results 145 patients (response rate 82%) agreed to participate (age PICU admission 3.5 years; follow-up interval 10 years; age follow-up 14.6 years (all medians)).

In patients, regardless of age and of patient- versus parent-report, significantly lower scores were found mainly on physical (physical functioning, general health perception) domains and/or physical summary score.

In patients < 18 years, according to parent-reports, significantly lower scores were also found on psychosocial HR-QoL domains, whereas in patients ≥ 12 years, according to patients themselves, significantly higher scores were found on psychosocial domains.

As to parents themselves, we found significantly higher scores on the majority of HR-QoL scales (both physical and psychosocial).

Conclusions In patients who survived meningococcal septic shock in childhood significantly lower HR-QoL scores were found on the physical domains. This could indicate that the patient's disease episode and present health status had a negative impact on their present physical HR-QoL. Overall long-term HR-QoL in parents was significantly higher.

Introduction

Septic shock with petechial and/or purpuric rash is a life threatening clinical syndrome predominantly caused by *Neisseria meningitidis* (NM). It is characterized by sudden onset and rapid progression in previously healthy, young children and adolescents. Typical clinical signs are shock and haemorrhagic diathesis due to disseminated intravascular coagulation.[1] Treatment consists of fluid resuscitation and the administration of inotropes and/or vasopressors.

In spite of better understanding of the pathogenesis of meningococcal septic shock and advances in therapeutic interventions, we observed a high morbidity and mortality in the Netherlands until the implementation of a national vaccination campaign against serogroup C meningococci (2002).

Data on incidences of adverse consequences of meningococcal septic shock (such as physical and neuropsychological impairments) are rare.[2-4]

As far as we know, only one study has investigated long-term HR-QoL in these patients.[5]

Complementary to clinical measures, HR-QoL has become an essential outcome measure in paediatric studies.[6,7] HR-QoL is defined as the way patients themselves experience and evaluate their physical, social and emotional well-being subjectively, as far as it is influenced by health, disease and disability. This concept is based on the World Health Organization's definition of health as 'a state of complete physical, mental and social well-being, and not merely the absence of disease'.[8]

We surmised that patients who survived meningococcal septic shock in childhood, would show poorer HR-QoL at later age. After all, they had experienced a life threatening illness and might have developed physical and neuropsychological impairments. Likewise, we hypothesized that parents of these children would show poorer HR-QoL due to high stress and anxiety levels. They had experienced a stressfull event, i.e. the life threatening illness of their child, and would be worrying about adverse health consequences.

The aim of this study was to investigate long-term HR-QoL in patients who survived meningococcal septic shock in childhood. Additionally, we assessed long-term HR-QoL in their parents.

Materials and Methods

Patient selection

This study concerned a medical and psychological follow-up of a retrospective cohort of all consecutive surviving patients with septic shock and purpura requiring

Chapter 6 | Long-term health-related quality of life in survivors of meningococcal septic shock in childhood and their parents

intensive care treatment at least 4 years ago (between August 1988 and October 2001), and their parents. Patients were recruited from the PICU of the Erasmus MC-Sophia Children's Hospital, a tertiary care university hospital. Eligible for this study were all consecutive surviving patients aged 1 month to 18 years with a clinical picture of meningococcal septic shock, as well as their parents. Meningococcal septic shock was defined as septic shock with petechiae and/or purpura. Sepsis was defined as body temperature < 36.0 ºC or > 38.5 ºC with tachycardia and tachypnoea. In addition, patients were assigned to have septic shock if they also had persistent hypotension or poor end-organ perfusion as evidenced by at least two of the following: unexplained metabolic acidosis, arterial hypoxia in patients without overt cardiopulmonary disease, acute renal failure or sudden deterioration of the baseline mental status.[9] The Erasmus MC Medical Ethical Review Board approved the study protocol. Informed consent was obtained from parents and patients by sending a standard letter requesting their participation in our 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. They were also sent HR-QoL questionnaires to complete at home. Parents themselves could decide who (mother or father) would complete the HR-QoL questionnaires.
The follow-up visits took place in 2005-2006.

Data analysis at the time of PICU admission

The participating patients had been included in several sepsis studies.[10-15] The medical data collected prospectively at various time-points in the course of the disease were pooled with demographic and clinical data and analyzed retrospectively.
Severity of illness was determined by the Pediatric Risk of Mortality Score (PRISM), the Vasopressor score (VAS), indicating type and dose of vasopressors/inotropes, and the Disseminated Intravascular Coagulation score (DIC), indicating severity of disseminated intravascular coagulation.[16-18]

Assessment methods

a) questionnaires
HR-QoL for patients < 18 years was assessed by the Child Health Questionnaire (CHQ) and for patients ≥ 18 years and parents by the SF-36 (table 1).[19-21] The CHQ is a generic health profile measure covering physical and psychosocial domains that refer to the perceived health status for the collective 4 weeks prior to completing the questionnaire. Designed specifically for children, it includes domains like behavior and self-esteem and the effects of the child's health state on family functioning. Its structure and methodological approach are similar to those of the SF-36, the most used quality of life measure in adults. The parents were asked to complete the CHQ (version CHQ-PF50) for patients aged 4-17 years (appendix 1). Patients aged 12-17 years completed the CHQ themselves (version CHQ-CF87) (appendix 2).[22] In addition, the parents were asked to complete the CHQ-PF50 for these patients.
Both patients ≥ 18 years and their parents completed the SF-36 Health Survey (appendix 3).[19]
HR-QoL scales range from 0 to 100. Lower scores indicate poorer subjective health status, higher scores more favourable subjective health status.

b) population norms for comparison
In absence of a control group, matched on sex and age, we used population norms of HR-QoL scores for comparison with scores in our study samples. For the CHQ-PF50 normative data are based on a representative sample of 353 Dutch schoolchildren aged 5 - 13 years.[20] For CHQ-CF87 normative data are based on a representative sample of 475 Dutch schoolchildren aged 13 - 17 years.[23] For SF-36 normative data were derived from a nation wide, population-based Dutch health status survey in 1742 participants aged 16-94 years.[24] As the median age of patients ≥ 18 years in our study was 22.5 years (range 18-30 years), we used a selection of the normative group, i.e. those aged 16-25 years, as reference group. Likewise, as the median age of parents in our study was 43 years (range 29-59 years) (78% mothers, 22% fathers), we used a selection of the normative sample, i.e. those aged 36-45 years, as reference group.

Statistical methods

Statistical analysis was performed with a statistical analysis software program (SPSS 12.0 for WINDOWS, SPSS, Inc, Chicago, IL).
Comparisons between participating patients and non-participants were made with the Mann-Whitney test for age at time of PICU admission, length of PICU stay and severity of illness, with the Chi-Square test for sex. The Mann-Whitney test was used to compare HR-QoL scores of our patients < 18 years with individual normative data, as provided by Raat et al.[20,23] The paired Wilcoxon test was used to compare HR-QoL scores of patients ≥ 18 years and parents with published normative data, as individual normative data were not available.[24] We used Spearman correlations (r_s) to evaluate associations between patient-report (CHQ-CF87) and parent-report (CHQ-PF50) for patients aged 12-17 years.
A P-value < 0.05 (two-sided) was considered the limit of significance.
Multiple linear regression analyses were applied to predict HR-QoL scores, for both patients and parents. This was done for all scales, irrespective of significance of differences between the study population and the reference groups. We included three potentially influential variables: age at time of PICU admission, sex of parent

Table 1. Health-related quality of life assessment by the Child Health Questionnaire (patients < 18 years) and SF-36 (patients ≥ 18 years and parents)

Patient group according to age	Instrument	Respondent
Patients 4-11 years	CHQ-PF50	parent-report
Patients 12-17 years	CHQ-PF50	parent-report
	CHQ-CF87	self-report
Patients ≥ 18 years	SF-36	self-report

Parents	Instrument	Respondent
Parents	SF-36	self-report

Table 2. Data at the time of PICU admission of the participating patients and the non-participants

Data are presented as percentages of cases or as median (range).

characteristics	follow-up	no follow-up	P-value
	n=145	n=34	
Sex	50% boys, 50% girls	53% boys, 47% girls	ns
Age at the time of PICU admission (years)	3.5 (0.1-17.9)	4.3 (0.2-14.3)	ns
Length of stay in PICU (days)	3 (1-51)	5 (1-36)	< 0.05
PRISM	15 (0-37)	16 (1-41)	ns
DIC*	6 (2-8)	6 (3-8)	ns
Use of inotropes	74%	79%	ns
VAS**	10 (0-402)	11 (0-145)	ns
Mechanical ventilation	36%	50%	ns

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

**VAS: higher score indicates the use of different and higher dose of vasopressors and/or inotropes

Note: a causative organism was isolated in 151 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.

and length of follow-up interval. Independent predictors with a P-value < 0.05 were identified using backward elimination. The resulting regression coefficients (B) related with age and follow-up interval given in the text (results section) both have units year^{-1}.

Results

Study samples

Of 179 eligible patients, 9 had been lost to follow-up. One of these had died several years after the meningococcal septic shock, which had resulted in severe adverse outcome with mental handicap and seizures. The cause of death was related to mental retardation. Seven patients lived abroad at the time of the follow-up, 1 was untraceable. Of the remaining 170 families, 145 agreed to participate. Nevertheless, 5 patients eventually appeared unable (severe mentally handicapped, n=1) or refused (on practical or emotional grounds, n=4) to complete the questionnaire. Thus, questionnaires were completed for a total of 140 patients: 54 patients 4 -11 years (CHQ-PF50), 38 patients 12-17 years (CHQ-CF87, patient-completed, + 38 CHQ-PF50, parent-completed) and 48 patients ≥ 18 years (SF-36). Eleven parents did not complete the SF-36 (on practical or emotional grounds), which resulted in 134 SF-36 in parents. The median follow-up interval was 10 years (3.7-17.4 years), median age of patients at the time of follow-up 14.6 years (5.3-31.1 years).

Twenty-five patients and their parents did not respond to the invitation or refused to participate on practical (for example no time because of a busy job) or emotional (too emotional confrontation with the hospital) grounds. The overall response rate of eligible patients, corrected for patients lost to follow-up, was 82% (140/170), that of eligible parents was 79% (134/170). To check for possible selection bias, we compared characteristics between participating patients and non-participants (table 2). Patients in both groups did not differ with respect to sex, age at time of PICU admission and severity of illness. Length of PICU stay, however, was significantly shorter for the participating patients.

HR-QoL in patients

Tables 3-5 show the mean scores on CHQ-PF50, CHQ-CF87 and SF-36 for our patient samples and the Dutch reference groups.

Parents scored significantly lower for their 4 – 17-year-old children as compared with the reference group on 4 of 12 CHQ-PF50 scales and on the physical summary score (table 3). These particular scales concern the negative impact of the patient's

Table 3. Health-related quality of life (parent-report) in patients 4-17 years

Data are presented as mean (range)

	patients	reference	P-value*	< 5th%**
	n=19			
CHQ-PF50 (4-17 years)				
Physical functioning (PF)	92 (0-100)	99	< 0.001	19%
Role functioning: Emotional/behavior (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 behavior (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	

*The Mann-Whitney test was used to compare HR-QoL scores of our patients < 18 years with individual normative data, as provided by Raat et al.[20,23] **Percentage of patients with score < 5th percentile of reference group (this percentage was calculated if P-value < 0.05). ***Scores on the CHQ-PF50 scale "change in health" are not presented since individual normative data were not available for this scale.

health on both physical (physical functioning and general health perception) and psychosocial (role functioning emotional and self-esteem) domains.

Patients 12-17 years scored significantly lower score on 1 of 11 CHQ-CF87 scales as compared with the reference group (table 4). This scale concerns the negative impact of the patient's health on a physical (general health perception) domain. They scored significantly higher on 2 other CHQ-CF87 scales, concerning the positive impact of the patient's health on psychosocial domains (general behaviour) and on family (family activities).

Patient-report (CHQ-CF87) and parent-report (CHQ-PF50) for patients 12-17 years (n=38) was significantly correlated regarding 6 of 9 HR-QoL scales: "role functioning physical" (r_s=0.48), "bodily pain" (r_s=0.73), "mental health" (r_s=0.37), "self-esteem" (r_s=0.59), "family activities" (r_s=0.44) and "family cohesion" (r_s=0.50). Non-significant correlations were found in 3 of 9 HR-QoL scales.

Table 4. Health-related quality of life (patient-report) in patients 12-17 years

Data are presented as mean (range)

	patients	reference	P-value*	< 5th%**
	n=38			
CHQ-CF87 (12-17 years)				
Physical functioning (PF)	95 (44-100)	96	ns	
Role functioning: Emotional (RE)	93 (56-100)	89	ns	
Role functioning: Behavior (RB)	92 (33-100)	95	ns	
Role functioning: Physical (RP)	94 (33-100)	95	ns	
Bodily pain (BP)	72 (0-100)	74	ns	
General behavior (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	

*The Mann-Whitney test was used to compare HR-QoL scores of our patients < 18 years with individual normative data, as provided by Raat et al.[20,23] **Percentage of patients with score < 5th percentile of reference group (this percentage was calculated if P-value < 0.05). ***Scores on the CHQ-CF87 scale "change in health" are not presented since individual normative data were not available for this scale.

Adult patients scored significantly lower than the reference group on 1 of 8 SF-36 scales (vitality) and on the physical summary score, and significantly higher on 1 other SF-36 scale (role functioning emotional) and on the psychosocial summary score (table 5).

CHQ-PF50 scores on general behavior and family activities were significantly associated with age at time of PICU admission (B=2.2 and B=1.6, resp. with P< 0.001 and < 0.05, resp.); CHQ-PF50 scores on role functioning physical were significantly associated with follow-up interval (B=-1.3, P< 0.05). CHQ-CF87 scores on self-esteem were significantly associated with age at time of PICU admission (B=-3.3, P< 0.01) as well as by follow-up interval (B=-2.2, P< 0.05).

SF-36 physical summary scores were significantly associated with age at time of PICU admission (B=0.7, P< 0.05); follow-up interval significantly associated with SF-36 scores regarding role functioning physical (B=2.8, P< 0.05), general health perception (B=1.3, P< 0.05), vitality (B=1.7, P< 0.01), role functioning emotional (B=1.5, P< 0.05), physical summary (B=1.0, P< 0.05) and psychosocial summary (B=0.7, P< 0.01).

Table 5. Health-related quality of life (patient-report) in adult patients (≥ 18 years)

Data are presented as mean (range)

	adult patients	reference	P-value*	< 5th%**
	n=48			
SF-36				
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 (VI)	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	

*The paired Wilcoxon test was used to compare HR-QoL scores of our adult study population (patients ≥ 18 years and parents) with published normative data.[24] **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 in parents

Data are presented as mean (range)

	parents	reference	P-value*	< 5th%**
	n=134			
SF-36				
Physical functioning (PF)	87 (0-100)	89	< 0.01	12%
Role limitations due to physical functioning (RP)	83 (0-100)	82	< 0.01	
Social functioning (SF)	89 (13-100)	84	< 0.001	
Bodily pain (BP)	80 (0-100)	75	< 0.001	
General mental health (MH)	79 (28-100)	76	< 0.001	
Role limitations due to emotional problems (RE)	87 (0-100)	86	< 0.01	
Vitality (VI)	68 (15-100)	68	ns	
General health perceptions (GH)	75 (0-100)	74	< 0.05	
Physical summary (PHS)	50 (4-68)	52	ns	
Psychosocial summary (PSS)	53 (12-73)	49	< 0.001	

*The paired Wilcoxon test was used to compare HR-QoL scores of our adult study population (patients ≥ 18 years and parents) with published normative data.[24] **Percentage of patients with score < 5th percentile of reference group (this percentage was calculated if P-value < 0.05).

HR-QoL in parents

Table 6 shows the mean SF-36 scores for parents and the Dutch reference group. Parents scored significantly higher on 6 of 8 SF-36 scales and on the psychosocial summary score. These particular scales concerned the positive impact of the parent's health on both physical (role functioning physical, bodily pain and general health perception) and on psychosocial (social functioning, mental health and role functioning emotional) domains. Parents scored significantly lower than the reference group on 1 other SF-36 scale (physical functioning).

SF-36 scores were not significantly affected by the child's age at time of PICU admission, sex of parent and follow-up interval.

Discussion

HR-QoL in patients

In this study significantly poorer HR-QoL scores mainly concerned physical domains in patient groups of all ages. This might indicate that the earlier disease episode and present health status had a negative impact on the patients' present physical HR-QoL. With regard to patients < 18 years, the fact that both parents and their children scored significantly lower on "general health perception", may not only reflect the experience of a serious illness in the past but also that the patient's present health was perceived as poor and that both patients and parents worry about the patient's health in the future.

Our results are comparable with a study by Koomen et al. of 182 children 4-10 years after bacterial meningitis. Significantly poorer scores were also found on the CHQ-PF50 scales "self-esteem" and "general health perception" and on the physical summary score. In contrast with our study they found significantly poorer scores on "parental impact emotional" and on the psychosocial summary score.[25] So, whereas bacterial meningitis differs from meningococcal septic shock long-term HR-QoL seems to be comparable.

Significantly better HR-QoL scores were found on psychosocial domains in patients ≥ 12 years, patient-report. This might indicate that adolescents and young adults who survived a severe illness in childhood may be more inclined to enjoy life.

The discrepancies found between child's HR-QoL scores parent-report versus patient-report may be explained by a proxy effect. Perception of parents seems to differ from the perception of patients themselves. This explanation is supported by the mostly moderate correlations (r_s< 0.7) between parent-reports of the child's HR-QoL (CHQ-PF50) and the child' self-report of HR-QoL (CHQ-CF87) in 6 of 9 HR-QoL scales and non-significant correlations in 3 of 9 HR-QoL scales. Our finding

regarding this aspect is in line with that from a study by Raat and Grootenhuis, who also reported that parents and children themselves had different views on the children's HR-QoL.[6] It has been suggested that parental assessment of their child's HR-QoL on physical domains is better than that on psychosocial domains.[26,27]

HR-QoL in parents

Overall we found better HR-QoL scores in parents, which might indicate that the child's disease episode did not have a negative impact on parental HR-QoL. A possible explanation for our positive findings is the following. Parents are under great stress at the time their child is struck by life-threatening disease. But if their child survives, especially when there are only minor sequelae, they will leave the stress behind. Indeed, during the interviews parents reported that the event made them stronger and made them appreciate life more fully. Parents seemed to worry less about 'futilities' in life. Nevertheless, it is well possible that denial or over-compensation could have influenced the responses.

Strengths and limitations of the present study

An unique feature of this study is the large and homogeneous patient sample, both patients and parents, assessed by standardised procedures. The response rate was high despite the relatively long follow-up interval. It may have helped that parents and patients wanted to know more about possible long-term sequelae. They also wanted to contribute in order to help future patients. As non-participants did not differ from participating patients with respect to age at time of PICU admission and severity of illness, we feel we can exclude a possible selection bias on these grounds.

Several limitations of our study should be acknowledged. For one, this is an observational study (no controls) performed in one centre. Furthermore, baseline assessments of HR-QoL (before PICU admission) were not available. Then, we included only patients requiring PICU treatment. This could have resulted in a selection bias, seeing that milder cases were admitted to a general ward. A possible limitation lies in the fact that HR-QoL scores were compared with normative data derived from population samples. There was no full sex and age match between the study sample and population samples. Differences in HR-QoL scores found between these 2 groups could be due both to PICU admission per se with stress and anxiety involved and to the disease itself with long-term sequelae. Therefore, it could be interesting to compare our group with patients, matched on sex, age and follow-up interval, hospitalised for another disease to a PICU or general ward. A possible advantage of using population norms is that there is no bias. As with any case-control study, control recruitment may introduce bias. Furthermore we used normative data derived from large representative country-specific population samples.

Finally, the different questionnaires and versions (i.e. for the different age groups of patients and their parents) may have affected the results. Although both CHQ versions and the SF-36 used in this study have a common background and a similar structure, each instrument has (partly) different scales and per scale a different number of items, as summarized in appendices 1-3.

Implications

Since overall long-term HR-QoL in patients who survived meningococcal septic shock in childhood is significantly poorer on the physical domains in comparison with the reference groups, it seems very important to identify predictors (like present health status) of poorer HR-QoL. We hypothesize that patients with physical sequelae, such as severe skin scarring or amputations due to septic shock, are at risk for poorer HR-QoL. We are currently investigating the present physical and psychosocial health status in these patients.

Possible risk factors for long-term consequences (both physical and psychosocial) should be routinely screened during standard multidisciplinary follow-up visits, both short-term and long-term. A follow-up clinic team would preferably include a paediatrician, psychologist, plastic surgeon and orthopaedic surgeon. Furthermore, future findings regarding adverse outcomes and their risk factors could eventually lead to modified therapeutic approaches during PICU admission.

Appendix 1: CHQ-PF50 scales, items per scale and score interpretation[a]

Scale	Number of items	Description low score	Description high score
Physical functioning (PF)	6	Child is limited a lot in performing all physical activities, including self-care due to health	Child performs all types of physical activities, including the most vigorous, without limitations due to health
Role functioning Emotional/behavior (REB)	3	Child is limited a lot in schoolwork or activities with friends as a result of emotional or behavior problems	Child has no limitations in schoolwork or activities with friends as a result of emotional or behavior problems
Role functioning Physical (RP)	2	Child is limited a lot in schoolwork or activities with friends as a result of physical health	Child has no limitations in schoolwork or activities with friends as a result of physical health
Bodily pain (BP)	2	Child has extremely severe, frequent and limiting bodily pain	Child has no pain or limitations due to pain
General behaviour (GB)	6	Child very often exhibits aggressive, immature, delinquent behavior	Child never exhibits aggressive, immature, delinquent behavior
Mental health (MH)	5	Child has feelings of anxiety and depression all of the time	Child feels peaceful, happy and calm all of the time
Self esteem (SE)	6	Child is very dissatisfied with abilities, looks, family/peer relationships and life overall	Child is very satisfied with abilities, looks, family/peer relationships and life overall
General health perceptions (GH)	6	Parent believes child's health is poor and likely to get worse	Parent believes child's health is excellent and will continue to be so
Parental impact:emotion (PE)	3	Parent experiences a great deal of emotional worry/concern as a result of child's physical and/or psychosocial health	Parent doesn't experience feelings of emotional worry/concern as a result of child's physical and/or psychosocial health
Parental impact: time (PT)	3	Parent experiences a lot of limitations in time available for personal needs due to child's physical and/or psychosocial health	Parent doesn't experience limitations in time available for personal needs due to child's physical and/or psychosocial health
Family activities (FA)	6	The child's health very often limits and interrupts family activities or is a source of family tension	The child's health never limits and interrupts family activities nor is a source of family tension
Family cohesion (FC)	1	Family's ability to get along is rated "poor"	Family's ability to get along is rated "excellent"
Change in health (CH)	1	Child's health is much worse now than 1 year ago	Child's health is much better now than 1 year ago

[a] Reproduced with permission from the principal author J.M. Landgraf, 1994.[28]
Note: Physical Summary and Psychosocial Summary scores were calculated based on a factor-analytic model, a summary score of 50 (SD 10) representing the mean in the original United States of America population sample.[28]

Appendix 2: CHQ-CF87 scales, items per scale and score interpretation[a]

Scale	Number of items	Description low score	Description high score
Physical functioning (PF)	9	Child is limited a lot in performing all physical activities, including self-care due to health	Child performs all types of physical activities, including the most vigorous, without limitations due to health
Role functioning Emotional (RE)	3	Child is limited a lot in schoolwork or activities with friends as a result of emotional problems	Child has no limitations in schoolwork or activities with friends as a result of emotional problems
Role functioning Behavior (RB)	3	Child is limited a lot in schoolwork or activities with friends as a result of behavior problems	Child has no limitations in schoolwork or activities with friends as a result of behavior problems
Role functioning Physical (RP)	3	Child is limited a lot in schoolwork or activities with friends as a result of physical health	Child has no limitations in schoolwork or activities with friends as a result of physical health
Bodily pain (BP)	2	Child has extremely severe, frequent and limiting bodily pain	Child has no pain or limitations due to pain
General behaviour (GB)	17	Child very often exhibits aggressive, immature, delinquent behavior	Child never exhibits aggressive, immature, delinquent behavior
Mental health (MH)	16	Child has feelings of anxiety and depression all of the time	Child feels peaceful, happy and calm all of the time
Self esteem (SE)	14	Child is very dissatisfied with abilities, looks, family/peer relationships and life overall	Child is very satisfied with abilities, looks, family/peer relationships and life overall
General health perceptions (GH)	12	Child believes it's health is poor and likely to get worse	Child believes it's health is excellent and will continue to be so
Family activities (FA)	6	The child's health very often limits and interrupts family activities or is a source of family tension	The child's health never limits and interrupts family activities nor is a source of family tension
Family cohesion (FC)	1	Family's ability to get along is rated "poor"	Family's ability to get along is rated "excellent"
Change in health (CH)	1	Child's health is much worse now than 1 year ago	Child's health is much better now than 1 year ago

[a] Reproduced with permission from the principal author J.M. Landgraf, 1996.[28]

Appendix 3: SF-36 scales, items per scale and score interpretation

Scale	Number of items	Description low score	Description high score
Physical functioning (PF)	10	Very limited in performing all physical activities, including bathing or dressing due to health	Performs all types of physical activities, including the most vigorous, without limitations due to health
Role limitations due to physical functioning (RP)	4	Problems with work or other daily activities as a result of physical health	No problems with work or other daily activities as a result of physical health
Social functioning (SF)	2	Extreme and frequent interference with normal social activities due to physical or emotional problems	Performs normal social activities without interference with normal social activities due to physical or emotional problems
Bodily pain (BP)	2	Very severe and extremely limiting bodily pain	No pain or limitations due to pain
Mental health (MH)	5	Feelings of nervousness and depression all of the time	Feels peaceful, happy, and calm all of the time
Role functioning Emotional (RE)	3	Problems with work or other daily activities as a result of emotional problems	No problems with work or other daily activities as a result of emotional problems
Vitality (VI)	4	Feels tired and worn out all of the time	Feels full of pep and energy all of the time
General health (GH)	5	Evaluates personal health as poor and believes it is likely to get worse	Evaluates personal health as excellent

Note: Physical Summary and Psychosocial Summary scores were calculated based on a factor-analytic model, a summary score of 50 (SD 10) representing the mean in the original United States of America population sample.

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Chapter 6 | Long-term health-related quality of life in survivors of meningococcal septic shock in childhood and their parents

7

SURVIVING MENINGOCOCCAL SEPTIC SHOCK IN CHILDHOOD: LONG-TERM OVERALL OUTCOME AND THE EFFECT ON HEALTH-RELATED QUALITY OF LIFE

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Abstract

Objective To evaluate associations between long-term outcome variables, both physical and psychological, in patients who survived meningococcal septic shock (MSS) in childhood. To assess the predictors of long-term health-related quality of life (HR-QoL).

Patients and methods All consecutive patients with septic shock and purpura requiring intensive care treatment between 1988 and 2001. Physical health status was assessed with a standard medical interview and physical examination; standard assessment procedures were used to measure behavioural and emotional problems, and cognitive functioning; HR-QoL was assessed with the Child Health Questionnaire and the SF-36.

Results 120 patients (response rate 71%) visited the follow-up clinic (median age PICU admission 3.1 years; median follow-up interval 9.8 years; median age follow-up 14.5 years, range 5-31 years).

Four major outcomes were considered: 1) major physical sequelae (defined as major scars and/or amputation and/or limb-length discrepancy) (29/120), 2) mild neurological impairments (39/120), 3) problem behaviour (defined as a total score above the 90th percentile of the reference groups on questionnaires to screen for psychopathology) (16/114) and 4) total IQ < 85 (18/115).

No differences were found between patients with major physical sequelae and patients without major physical sequelae as to the presence of problem behaviour or total IQ < 85. Also, no differences were found between patients with mild neurological impairments and patients without as to the presence of problem behaviour or total IQ < 85. Finally, no differences were found between patients with major physical sequelae and patients without as to the presence of mild neurological sequelae.

HR-QoL scales, both on the physical and psychosocial domains, were significantly associated with problem behavior: less favourable scores on behavioural and emotional problems were significantly associated with poorer HR-QoL. HR-QoL scales were to a lesser amount predicted by severity of illness at time of PICU admission or by adverse physical outcome.

Conclusions Long-term adverse physical and psychological outcomes in survivors of MSS did not seem to be associated. Poorer HR-QoL was mainly predicted by problem behaviour.

Introduction

The present study is part of a medical and psychological follow-up study of all consecutive surviving patients with meningococcal septic shock (MSS) requiring intensive care treatment between 1988 and 2001 at the Erasmus MC-Sophia Children's Hospital, the Netherlands.

In our previous studies we found that patients who survived MSS in childhood, showed long-term skin scarring, orthopaedic sequelae and neurological impairments, all ranging from mild to severe and irreversible. Furthermore, significantly poorer HR-QoL scores were found, mainly on the physical domains, compared with normative data. Overall, outcomes as to behavioural and emotional problems and cognitive functioning in MSS survivors were favourable.[1-4] (cognitive functioning: unpublished data)

Until now associations between these different outcome variables have not been investigated.

We hypothesized that patients with long-term adverse physical outcome after MSS, such as severe skin scarring or extensive amputation, would also have more problem behaviour and cognitive dysfunctioning.

Furthermore we hypothesized that patients with adverse physical outcome had poorer HR-QoL.

The aim of this study was to evaluate associations between long-term outcome variables, both physical and psychological, in patients who survived MSS in childhood. Additionally, we assessed various putative determinants of adverse overall outcome. Finally, we investigated to what extent long-term HR-QoL in patients can be predicted by: 1) severity of illness at time of PICU admission, 2) long-term physical and psychological outcome variables.

Materials and Methods

Patient selection

This study concerned a medical and psychological follow-up of a cross-sectional cohort of all consecutive surviving patients with septic shock and purpura requiring intensive care treatment at least 4 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. Eligible for this study were all consecutive surviving patients aged 1 month to 18 years with a clinical picture of

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MSS, as well as their parents. Meningococcal septic shock was defined as septic shock with petechiae and/or purpura.[5] 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 our 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 at PICU admission

During the study period patients consecutively admitted with MSS were included in several sepsis studies.[6-10] Severity of illness was determined by using the Pediatric Risk of Mortality Score (PRISM), Vasopressor score (VAS) and Disseminated Intravascular Coagulation score (DIC).[11-13]

Long-term outcome variables

Physical health status

Parents and patients were invited to the follow-up clinic 4-16 years after PICU discharge. They were interviewed by one paediatrician (CB) in a semi-structured format using a standard questionnaire with regard to health consequences since MSS. Complaints 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).

Briefly, of the 120 patients who were interviewed and examined by the paediatrician 58 (48%) had skin scarring due to purpura (ranging from barely visible scars to extremely mutilating scars); 10 (8%) amputation(s) of extremities (ranging from 1 toe to both legs and 1 arm); 7 (6%) lower limb-length discrepancy; 42 (35%) neurological impairment(s) (mental retardation with epilepsy, hearing loss, chronic headache or focal neurological signs); 1 (6%) mild chronic renal failure.[2,3]

Psychological functioning

Patients were interviewed and examined by one psychologist (LV) using standard assessment procedures.

For intellectual functioning two standardized intelligence tests were used for different age ranges: the Wechsler Intelligence Test III (WISC III) for 6-15 year old patients, the Groninger Intelligence Test 2 (GIT2) for 16-31 year old patients.[14-16] Overall, total scores of intellectual functioning in our study group were comparable to those of the reference groups (unpublished data).

Behavioural and emotional problems were assessed by using two different questionnaires: for 6-18 year old patients the Child Behaviour Checklist (CBCL) was used, completed by parents (mothers' reports n=75, fathers' reports n=2) and for 18-31 year old patients the Adult Self-Report was used (ASR, n=37).[17,18] Overall, 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 (adult patients; unpublished data).[4] 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 a) the CBCL or b) the ASR in patients who visited the follow-up clinic. When associating behavioural and emotional problems with patient-reports of HR-QoL, self-reports of patients 11-17 years on the Youth Self-Report (YSR) were also used.[17]

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.[19-23] Significant poorer scores were found mainly on physical domains. In patients < 18 years, according to parents (mothers' reports n=60, fathers' reports n=20), significantly poorer scores were also found on psychosocial HR-QoL domains, whereas in patients ≥ 12 years, according to patients themselves, significantly better scores were found on psychosocial domains.[1]

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.

Overall physical and psychological outcome

In order to associate the different outcome variables and to give an overview of long-term overall outcome, we dichotomised and coded outcome variables (presence or absence of outcome variable), and then composed 4 major outcome variables; 1) major physical sequelae (n=29/120) defined as major scars and/or amputation of extremities and/or limb-length discrepancy, 2) mild neurological impairments (n=39/120) defined as hearing loss and/or chronic headache and/or focal neurological signs, 3) problem behaviour (n=16/114) and 4) total IQ < 85 (n=18/115); these 18 patients included the 3 patients with mental retardation and epilepsy since they had an estimated intelligence score < 70.

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 present study.
The psychological outcome variables were also used as continuous variables. In that case the Mann-Whitney test was used to compare these psychological outcome scores between patients with and without major physical sequelae, with and without neurological impairments.

Predictors of adverse overall outcome
The Mann-Whitney test was used to compare age at the time of PICU admission, length of stay in PICU, severity of illness scores and serum glucose levels (lowest and highest) during PICU admission between patients with and without presence of overall adverse outcome.

Predictors of HR-QoL
We tested the association between putative predictor variables (patient's characteristics at the time of PICU admission, long-term physical and psychological outcome variables) and long-term HR-QoL scores by using Spearman correlation for continuous variables and Mann-Whitney test for dichotomous variables. This was only done for HR-QoL scales, if there were significant differences (poorer or better scores) between the study population and the normative data.
In all above mentioned statistical analyses, a P-value of 0.05 (two-sided) was considered the limit of significance.
Multiple linear regression analyses were also applied to evaluate the predictive value of patient's characteristics at time of PICU admission on long-term HR-QoL scores. This was only done for HR-QoL scales, if there were significant differences between the study population and the normative data.
In the regression analysis, we included patient characteristics (age at the time of PICU admission, sex), disease variables (severity of illness scores, length of stay in PICU) and follow-up interval. P-values of predictors were set to a level of 0.1 in the univariate analysis for entry in the regression analysis. Using backward elimination independent predictors were identified with a P-value < 0.05. Predictors with negative values (regression coefficients) were considered as negatively associated with HR-QoL scales, those with positive values as positively associated.

Results

Patient sample

The target population consisted of 179 patients. From these 179 patients 9 were lost to follow-up: 1 patient with severe adverse outcome (mental retardation with epilepsy) died several years after the MSS; 7 patients lived abroad at time of the follow-up; 1 was untraceable. Of the remaining 170 eligible patients, 145 agreed to participate. Of these 145 participants, 120 patients 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 time of visit to follow-up clinic 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 (too emotional confrontation with the hospital) 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 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.
At PICU admission a causative organism was isolated in 100 of the 120 patients (83%) who visited the follow-up clinic. In 99 patients (83%) *Neisseria meningitidis* was cultured in blood. Of these 99, 78 (79%) had NM serogroup B, 13 (13%) serogroup C and in 8 (8%) the serogroup was not determined.

Overall physical and psychological outcome

Seventy-three of the 120 patients (61%) had adverse outcome on 1 or more of the 4 major outcome variables: major physical sequelae, mild neurological impairments, problem behaviour and total IQ < 85. Of these 73 patients, 47 had adverse outcome on 1 major outcome variable; major physical sequelae n=13, mild neurological impairments n=19, problem behaviour n=7 and total IQ < 85 n=8. Twenty-six patients had adverse outcome on 2 or 3 major outcome variables; major physical sequelae and mild neurological impairments n=8, major physical sequelae and problem behaviour n=2, major physical sequelae and total IQ < 85 n=4; mild neurological impairments and problem behaviour n=4; mild neurological impairments and total IQ < 85 n=5; major physical sequelae, mild neurological impairments and problem behaviour n=2; mild neurological impairments, problem behaviour and total IQ < 85 n=1.

Table 1. Data of participating patients and non-participants

Data are presented as number of patients or median (range).

characteristics	follow-up clinic	no follow-up clinic	p-value
	n=120	n=59	
Sex	63 boys, 57 girls	27 boys, 32 girls	ns
Age at time of PICU (years)	3.1 (0.1-17.9)	5.4 (0.2-14.3)	ns
Length of PICU stay (days)	3 (1-51)	3 (1-36)	ns
PRISM	15 (1-37)	15 (0-41)	ns
DIC*	6 (3-8)	6 (2-8)	ns
VAS	15 (0-403)	11 (0-145)	ns

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

Table 2. Univariate relations between predictor variables at the time of PICU admission and HR-QoL scales

Predictor variables	Physical functioning	General health perception	Self-esteem	Physical summary (< 18 years)	Family activities	Physical summary (≥ 18 years)
Age at time of PICU	-	-	-	-	-	-
Lowest serum glucose	0.23*	-	-	-	-	-
Highest serum glucose	-.23*	-.23*	-	-.34**	-	-
PRISM	-	-	-	-	-	-
DIC	-	-	-	-	0.48**	0.39*
VAS	-	-	0.26*	-	-	-
Length of stay in PICU	-.31**	-	-	-	-	-

P< 0.05 (*), P< 0.01 (**), - = ns

Higher HR-QoL scores indicate more favourable HR-QoL.

The Spearman correlation coefficient is shown. Plus versus minus sign indicates respectively the positive versus negative association between the predictor variable and the HR-QoL scale.

The scales 'Physical functioning', 'General health perception', 'Self-esteem', 'Physical summary (< 18 years)' are part of the CHQ-PF50 (parent-reports, in patients 4-17 years, n=80).

The scale 'Family activities' is part of the CHQ-CF87 (patient-reports, in patients 12-17 years, n=35).

The scale 'Physical summary (≥ 18 years)' is part of the SF-36 (patient-reports, in patients ≥ 18 years, n=38).

Table 3. Univariate relations between physical and psychological outcome variables and HR-QoL scales

A) HR-QoL parent-reports: For dichotomous variables (first 3 items) the difference (item present minus absent) in mean HR-QoL scale value is shown, for continuous variables (last item) the Spearman correlation coefficient is shown. Plus versus minus sign indicates respectively the positive versus negative association between the predictor variable and the HR-QoL scale.

Predictor variables	Physical functioning	General health perception	Self-esteem	Role functioning emotional/behavior	Physical summary
Major physical sequelae	- 6.3*	-	-	-	-
Mild neurological impairments	-	-	-	-	-
IQ < 85	-	-	-	- 28.9**	-
Total CBCL***	-.25*	-.36**	-.34**	-.33**	-.25*

P< 0.05 (*), P< 0.01 (**), - = ns,

(***) CBCL (Child Behavior Checklist) is the parent-report of behavioural and emotional problems in patients < 18 years. Higher CBCL scores indicate unfavourable outcome.

The HR-QoL scales are part of the CHQ-PF50 (parent-reports, in patients 4-17 years, n=80).
HR-QoL scales range from 0 to 100. Higher HR-QoL scores indicate more favourable HR-QoL.

B) HR-QoL patient-reports: For dichotomous variables (first 2 items) the difference (item present minus absent) in mean HR-QoL scale value is shown, for continuous variables (last 2 items) the Spearman correlation coefficient is shown. Plus versus minus sign indicates respectively the positive versus negative association between the predictor variable and the HR-QoL scale.

Predictor variables	Family activities	General health perception	General behaviour	Role limitations emotional	Vitality	Psychosocial summary
Major physical sequelae	6.2*	-	-	-	-	-
Mild neurological impairments	-12.3*	-	-	-10.1*	-11.6*	
Total YSR***	-.52**	-.34*	-.60**	-	-	-
Total ASR****	-	-	-	-.53**	-.44**	-.56**

P< 0.05 (*), P< 0.01 (**), - = ns

(***) YSR (Youth Self-report) and (****) ASR (Adult Self-Report) are self-reports of behavioural and emotional problems in resp. patients 11-17 years and > 18 years. Higher YSR and ASR scores indicate unfavourable outcome.

The scales 'Family activities', 'General health perception', 'General behaviour' are part of the CHQ-CF87 (patient-reports, in patients 12-17 years, n=35).

The scales 'Role limitations due to emotional problems', 'Vitality', 'Psychosocial summary' are part of the SF-36 (patient-reports, in patients ≥ 18 years, n=38).

HR-QoL scales range from 0 to 100. Higher HR-QoL scores indicate more favourable HR-QoL.

The patient with chronic renal failure had amputation of 1 leg (below-knee), major scars and focal neurological signs. One of the 3 patients with mental retardation (estimated IQ < 70) had major scars and amputations; another patient had major scars and lower limb-discrepancy of 13 centimeters.
There were no significant associations between the presence of the major outcome variables. No differences were found between patients with major physical sequelae and patients without major physical sequelae as to the presence of problem behaviour or total IQ < 85. Also, no differences were found between patients with mild neurological impairments and patients without as to the presence of problem behaviour or total IQ < 85. Finally, no differences were found between patients with major physical sequelae and patients without as to the presence of mild neurological sequelae.

Predictors of overall physical and psychological outcome

The 73 patients with adverse outcome had significantly longer length of stay in PICU (P=0.003, 4 versus 2 days), higher severity of illness scores (PRISM P=0.001, 17 versus 12) (VAS P=0.002, 25 versus 6), lower glucose levels (P=0.001, 4.3 versus 4.9 mmol/l) compared with the 47 patients without adverse outcome.

Predictors of HR-QoL

Univariate analysis of HR-QoL scales in relation to predictor variables at time of PICU admission showed that on 6 HR-QoL scales at least one significant relationship was found (table 2). Age at the time of PICU admission and PRISM showed no significant associations with HR-QoL scales.
Using multiple linear regression analyses of patient's characteristics at time of PICU admission on HR-QoL, no significant associations were found.
Concerning the physical and psychological outcome variables, HR-QoL scales were mainly predicted by problem behaviour (table 3). In patients 4-17 years parent-reports, there was a significant negative association between all 5 HR-QoL scales and problem behaviour (assessed with Child Behavior Checklist (total CBCL)) (table 3A). Also in patients ≥ 12 years patient-reports, there was a significant negative association between HR-QoL scales and problem behaviour (assessed with Youth Self-report (total YSR) and Adult Self-Report (total ASR)) (table 3B).

Discussion

No differences were found between patients with major physical sequelae and patients without major physical sequelae as to the presence of problem behaviour or total IQ < 85. Also, no differences were found between patients with mild neurological impairments and patients without mild neurological impairments as to the presence of problem behaviour or total IQ < 85.
HR-QoL scales were mainly predicted by problem behaviour: problem behaviour was significantly associated with poorer HR-QoL.

Overall outcome

To the best of our knowledge, this is the first study in which associations between different long-term outcome variables in MSS survivors were investigated. Erickson et al. described that "some patients had multiple sequelae".[24] Fellick et al. classified the level of impairment, based on physical outcome, total intelligence and motor skills, in different categories (mild, moderate, and severe).[25] However they did not study statistically the correlation between their different outcome variables.
In our homogeneous patient sample of MSS survivors we found no significant associations between the presence of the 4 major outcome variables. Patients with major physical sequelae after MSS had no more neurological impairments, nor cognitive dysfunctioning or problem behaviour, compared with patients without major physical sequelae.
After a life-threatening illness as MSS, patients may be more inclined to appreciate life more. Indeed, during the interviews parents and patients themselves often reported that the event made them stronger and that they tried to make to best of their lives even when they had major physical sequelae. This phenomenon is referred to as 'resilience' in our previous study.[4] This could be in contrast with adult patients with critical illness, as also suggested by Erickson et al.[26] In this study adults, who survived invasive meningococcal disease, often reported "emotional unresolved grief" (anger, anxiety, depression) several years after hospital discharge.
Other possible explanations for the lack of associations between adverse physical and psychological outcomes in survivors of MSS could be that major physical sequelae were directly related to the severity of MSS in our study group.[2] Severity of illness scores however were no significant predictors of long-term mild neurological impairments, levels of behavioural problems nor of cognitive dysfunctioning.[3,4] (cognitive functioning: unpublished data) It could be that these latter outcomes were not specifically related to shock and intravascular thrombosis, but to acute illness in general. Furthermore, we need to emphasize that total scores of intellectual

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functioning and of behavioural and emotional problems in our study group were comparable to those of the reference groups.
So in our study group it seems that adverse long-term physical and psychological outcomes in survivors of MSS were not related. However, some specific cases should be mentioned, but they were insufficient to result in statistical significant differences: for example, 2 of the 3 patients with mental retardation (estimated IQ < 70) had major physical sequelae; the patient with chronic renal failure had major physical sequelae and focal neurological signs.

Predictors of HR-QoL

Long-term poorer HR-QoL was mainly predicted by less favourable scores on behavioural and emotional problems. HR-QoL scales, both on the physical and psychosocial domains, were significantly associated with problem behavior (total CBCL, total YSR, total ASR), regardless of age and parent-report versus patient-report. Our results are comparable with a study by Koomen et al. of children 4-10 years after bacterial meningitis.[27] However, we need to be careful in comparing our results since MSS is a more severe disease compared with bacterial meningitis.
HR-QoL scales were to a lesser amount significantly associated with adverse physical outcome; patients with major physical sequelae had significantly poorer scores on the HR-QoL scale "physical functioning". Indeed, amputation or limb-length discrepancy often resulted in important long-term morbidity (pain, functional impairment) in our study group.[2] Surprisingly the HR-QoL scale "general health perception" was not significantly associated with the presence of major physical sequelae or mild neurological impairments. This could mean that the significantly poorer scores found on this HR-QoL scale mainly reflected the worries about the patient's health in the future, but not the present health status. Another possible explanation is that the number of patients with major physical sequelae or mild neurological impairments was to low to show significant associations.
Studies regarding long-term HR-QoL in survivors of other severe illnesses, e.g. congenital heart diseases, also demonstrated weak associations between present physical health status and HR-QoL.[28,29]
Seeing DIC and VAS, but not PRISM, showed small to moderate correlations ($r_s < 0.7$) on a minority of HR-QoL scales only in univariate analysis, the severity of MSS in childhood, regardless of any adverse outcome, seemed less important for long-term HR-QoL. The significant negative associations found between high serum glucose levels and HR-QoL scales on the physical domains, could indicate that hyperglycemia not only is a major risk factor for increased morbidity and mortality in the intensive care unit, but also for long-term adverse physical outcome.

Limitations of the present study

Several limitations of our study should be acknowledged. This is an observational study (no controls) in one centre. The response rate was satisfactory, though not high (71%). However we think that this may not have influenced the results since participating patients and non-participants did not differ with respect to age at time of PICU admission and severity of illness. On the other hand, we only included MSS patients requiring PICU treatment. This could have resulted in a selection bias by excluding the milder cases admitted to a general ward. Further, baseline assessments of health status, psychological functioning and HR-QoL (before MSS) were not available.
It could be interesting to compare our group with patients, matched on age and timing of follow-up interval, admitted to the hospital or PICU because of another disease.

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8

SUMMARY AND DISCUSSION

"Studies aiming at the psycho-social and medical long term outcome of children after a meningococcal sepsis should be seriously considered." (thesis Jan Hazelzet pag 185, 1998)

Summary and General Discussion

1. Epidemiology of meningococcal sepsis: are we getting better?

In our cohort study of nearly 300 children with sepsis and purpura admitted to the PICU of the Erasmus MC-Sophia (the Netherlands) between 1988 and 2006, we found that younger children had more severe disease and an increased risk of case fatality. Half of the children in our study group were younger than 3 years. This is probably due to the still developing immune, coagulation and stress response systems in young children, and therefore the relative inability to induce an effective response to a high load of micro-organisms such as *N. meningitidis*.

Although our target population was children with meningococcal sepsis, we included all children with sepsis and purpura, not only those with bacteriologic confirmation. In 82% of the children *N. meningitidis* was cultured. Only in 2% other bacterial micro-organisms were the causative organisms, whereas in 16% no causative micro-organism was found. Since in the vast majority *N. meningitidis* was cultured, this thesis addresses primarily children with meningococcal sepsis or septic shock.

The incidence due to serogroup B was much higher than that of serogroup C (74% versus 19%, in 7% the serogroup was not determined). *N. meningitidis* serogroup B was seen more often in younger children compared with serogroup C. This is in accordance with other countries in the Western world, like Canada and Ireland.[1,2]

The case fatality rate (CFR) due to meningococcal sepsis was 16% over the past two decades. This is in accordance with other large studies reporting CFR of 10 to 20%.[1,3-5] It must be noted that some studies included heterogeneous patient samples, not specifically children with meningococcal sepsis admitted to a PICU. No differences were observed between serogroup B and C with respect to severity of illness scores and CFR. Our findings are in accordance with an Irish study of 407 children with invasive MD.[2] Erickson et al. suggested a more severe course of serogroup C infections in Canada, indicated by increased CFR due to serogroup C (14%) compared with serogroup B (7%).[1] However, in this study both children and adults with invasive MD were included.

Although in our study group male patients had more severe disease, CFR did not differ between males and females.

The vast majority of our non-survivors died of refractory septic shock in the first 24-48 hours after PICU admission despite massive fluid resuscitation, inotropes and vasopressors. This is in contrast with adult patients with sepsis, who die in the first weeks after ICU admission due to multiple organ failure.

Starting from 2000 there was an increase in incidence of invasive meningococcal disease (MD) in the Netherlands due to the emergence of a virulent strain of serogroup C. Therefore in July 2002 the vaccination against meningococcal serogroup C was implemented in the Netherlands in children ≥ 1 year. This resulted in a marked decrease not only of serogroup C, but surprisingly also of serogroup B. Indeed, from July 2002 until March 2008 only 45 patients with sepsis and purpura were admitted to our PICU (unpublished data). In the United Kingdom, the introduction of the meningococcal C vaccination in 1999 resulted in a virtual elimination of serogroup C invasive disease. However serogroup B did not decrease significantly in contrast with our observations.[6]

The CFR of meningococcal sepsis has improved in recent years despite comparable disease severity. In the last 7 years, from January 2002 until March 2008 there was only 1 fatal case of the 68 patients (CFR 1.5%) with sepsis and purpura admitted to our PICU. Already in the nineties a significant improvement in CFR of children with invasive MD requiring intensive care treatment was observed in London by the group of St Mary's Hospital.[5] They attributed this to improvements in initial management in the regional hospitals, specialist transport service and centralisation of care in specialized units.

In my opinion, there are several reasons for improved CFR in our PICU, which are similar to the observations by the group of St Mary's Hospital:

1) During the episode of high incidence around 2000, the public awareness increased through various media (e.g. Nederlandse Meningitis Stichting). Parents and general practitioners recognized sick children with fever and petechial/purpuric rash ("koorts en vlekjes") in an earlier phase, resulting in a decreased patient and doctor delay.
2) Healthcare workers, both in our hospital and in regional hospitals, received additional standard paediatric life support training, organized by our department and the Dutch Foundation for the Emergency Medical Care of Children (SSHK®). Since 1998 the SSHK® organises training courses in the Netherlands for doctors and nurses.

3) International treatment guidelines were implemented around 2000.[7] One of the senior doctors in our PICU (JH) is a member of the taskforce which drafted these guidelines. Efficient implementation of this practice could have contributed to improved outcome in Rotterdam. Furthermore, in the last 15 years our department focused on research and treatment of children with meningococcal sepsis.[8-15] Fundamentals of the treatment guidelines were prompt parenteral antibiotic administration, adequate fluid resuscitation and inotropic therapy (combination of dobutamine and noradrenaline in our PICU) in patients with compromised circulation, and early transfer to a PICU.

The clinical presentation of infections caused by *N. meningitidis* is highly diverse. Some patients develop meningitis, and others present with sepsis or even septic shock. Genetic polymorphisms among components of the complement system, inflammatory response and coagulation and fibrinolysis pathways have been shown to be involved in the susceptibility, severity and outcome of invasive MD. It is unlikely that during our study period changes in population in the South-West of the Netherlands, resulting in changes of host genetic polymorphism, have led to a decrease in susceptibility and severity of invasive MD.

As a result of the reasons mentioned above, cases who might previously have died, now survived. In the next chapters we will discuss outcome in survivors of meningococcal septic shock (MSS).

Some limitations and considerations have to be taken into account:

- We did not study the influence of *N. meningitidis* serotypes on severity and outcome.
- We did not include the case fatalities before admission or referral to the Erasmus MC-Sophia. Few illnesses are as rapidly progressive as meningococcal sepsis. Therefore patients may deteriorate so rapidly that death occurs before transfer to a PICU.
- Only children with sepsis and purpura admitted to the PICU were included. This may have resulted in a skewed representation of all children with sepsis and purpura, i.e. exclusion of children with relatively mild course admitted to a general ward.

Implications of our findings:

- Since the incidence decreases, meningococcal sepsis will become more and more a rarity for most healthcare workers. In the coming years both parents and healthcare workers might not easily recognize children with meningococcal sepsis resulting in delay of treatment. Efforts must continue to provide further education on the recognition and treatment of these patients.
- In future studies investigating effects on severity and CFR of children with meningococcal sepsis, age and gender should be taken into account for case-control studies.
- Additional training of healthcare workers (how to recognize and treat acutely sick children) and the international treatment guidelines for patients with sepsis should be implemented universally.
- The implementation of the meningococcal C vaccination in young children should be (re)considered in other parts of the world. For example, in the United States a vaccine with immunogenicity against A, C, Y and W135 meningococci is recommended for children > 11 years.
- The morbidity of meningococcal sepsis together with the improved CFR over time necessitates critical evaluation of outcome, both short-term and long-term, in survivors.

2. Short-term outcome in survivors of MSS and their parents: no cost to improved survival!

This study (chapter 3) concerned a follow-up up to 2 years after PICU discharge of a longitudinal cohort of 47 children with MSS admitted to the PICU of the Erasmus MC-Sophia between 2001 and 2005.

a) Health consequences and HR-QoL in children

More than half of the children (55%) had skin scarring due to necrotic purpura. The severity of disseminated intravascular coagulation, expressed by DIC score, was the major variable predicting skin scarring.

Only 2 children (4%) had orthopaedic sequelae; 1 had to undergo amputation of 3 fingers because of irreversible tissue necrosis. Another child, who suffered from fulminant MSS at the age of 6 weeks, had amputation of 1 finger, but more important, lower limb-length discrepancy at the age of 2 years. He is at risk for significant long-term morbidity (surgical interventions, pain or functional impairment) and will remain in orthopaedic follow-up.[16]

In 45% of the children chronic complaints (most frequently pain in the lower limbs, behavioural and emotional problems) were reported. We even believe that the incidence of (neuro)psychological dysfunctioning in our patients was underscored since we did not use validated instruments. Indeed, our short-term outcome study was a pilot study. At that time a psychologist was not available.
High risk for post-traumatic stress problems, emotional and hyperactivity symptoms and psychiatric disorders such as depressive, oppositional defiant and anxiety disorders were found by others in children with invasive MD 3-12 months after hospital discharge.[17-19] Children even reported near-death experiences (e.g. out-of-body experiences, meeting a deceased relative) during the acute illness.[20] In the study of Elison et al. children had significantly poorer scores on neuropsychological tests (decreased memory and attention functions) 5 months after PICU discharge compared with healthy controls.[21] Pattern recognition memory was specifically affected in children with sepsis. These findings of Elison et al. possibly reflect anomalies in frontal and temporal lobe structures. Problems described in the previous studies may be attributable to the direct biological effects on the brain (inflammation, shock, infection, hormonal disturbances), or to the psychological impact of the acute illness and PICU admission on child and family, or a combination of both. Premorbid developmental problems, behavioural and emotional problems were also found to be of predictive value for short-term psychiatric disorders.[17]

In our study group unfavourable scores were found on HR-QoL scales concerning physical functioning and general health perception. This could indicate that the child's disease episode and present health status had a negative impact on their present physical HR-QoL. Notably low were the scores on the "general health perception" scales, with as many as 37% and 35% below the 5th percentile of the reference group. This score not only reflects the experience of a serious illness in the past. It also indicates that parents perceived their child's present health as poor and that they worry about their child's future health risks. For example, from the interviews it appeared that many parents assumed their child was at great risk for re-occurrence of MSS.

A crucial question needs to be answered: **since CFR improved in recent years, do children, who might previously have died, survive with more sequelae?** Therefore we compared the incidence of the different outcome variables studied in our 2 study groups; patients admitted between 1988 and 2001 versus patients admitted between 2001 and 2005. With regard to skin scarring and orthopaedic

sequelae improved CFR does not seem to have a cost to this survival. The incidences were comparable; skin scarring 48% (1988-2001) versus 55% (2001-2005), orthopaedic sequelae 14% (1988-2001) versus 4% (2001-2005).
In the 14 MSS patients admitted to our PICU between 2005 and March 2008, 2 (14%) required amputation (unpublished data). One of these 2 was a 1-year-old boy with refractory septic shock who required massive fluid resuscitation (305 ml/kg in the first 24hours after PICU admission), and different inotropic agents and vasopressors (including vasopressin) in high doses. He developed widespread tissue necrosis and required quadriple limb amputation. His medical recovery and rehabilitation went very fortunate. He adapted quickly to his altered body; he walks on his residual limbs, he eats and drinks himself. He is now 3.5 years.
If we take into account MSS patients admitted at our PICU from 1988 until present, the incidence of amputation seems even to decrease, i.e. 14% (1988-2001) versus 7% (2001-March 2008)
So despite the extreme case of the patient with quadriple limb amputation, patients survive without more adverse physical outcome. The group of St Mary's Hospital also found little changes in percentages of patients who required skin grafting, amputations or had neurological abnormalities.[5]

b) Health consequences and HR-QoL in parents

In our short-term follow-up study 17% of the mothers reported emotional problems requiring professional help. Again, as in children, this was probably underscored since we did not use validated instruments. Acute, life-threatening illness in children requiring PICU admission and subsequent uncertainties about possible death or adverse outcome can result in increasing stress and anxiety levels in parents.[22,23] High risk for posttraumatic stress disorder (PTSD) was consistently found in several studies, investigating short-term psychological outcome in parents of children who survived invasive MD.[18,19,24] In our study parents often indicated that they would have appreciated psychosocial support shortly after PICU discharge. Also in the long-term follow-up study parents expressed that they perceived the acute phase and the first few years after hospital discharge as difficult. They regretted that psychosocial support was not organized by the PICU team.

Despite the likelihood of psychological distress in parents short-term after PICU admission of their child, we did not found unfavourable HR-QoL scores in parents of MSS survivors.

We recognize a number of limitations of the short-term follow-up study such as:

- An uncontrolled, observational study in a small number of patients.
- No validated instruments for psychological functioning in patients and their parents were used.

Implications of our findings:

- We need to remain vigilant that survival by more aggressive treatment does not result in more adverse outcome.
- Standard psychological support should be started in the PICU and continued after hospital discharge in order to reduce the extent of psychological problems, both in children and their parents. Furthermore we need to identify patients and parents at risk for psychological dysfunctioning, especially behavioural problems and PTSD. As to the timing of a standard psychological screening, we advice to do this for example at 6 weeks and 3 months after PICU discharge. If indicated, adequate interventions or treatment to reduce PTSD symptoms should be offered.
- It is important to reassure parents that their child is not predisposed for recurrent MSS.
- Studies are needed to investigate long-term outcome, both physical and psychological, in MSS survivors using standardised assessment instruments.

3. Long-term outcome in survivors of MSS: how is life after MSS?

This study concerned a long-term follow-up, at least 4 years after PICU discharge, of 145 children with MSS admitted to the PICU of the Erasmus MC-Sophia between 1988 and 2001. Different outcome variables were investigated in a large, homogeneous patient sample using standardised assessment procedures. In this thesis physical outcome and HR-QoL are described (chapters 4-7). The psychosocial outcome is outlined in the thesis of L. Vermunt.

First of all, a long-term outcome study encompasses long-term mortality: i.e. what was survival beyond the PICU? We know for sure that 2 patients, with severe mental retardation after MSS, died several years after PICU. Their cause of death was directly related to this adverse outcome (aspiration pneumonia, withdrawal of therapy).

In 23 patients we were not able to gain information regarding long-term outcome: 7 lived abroad at the time of the follow-up, 1 was untraceable and 15 did not respond to our invitation.
In a study by Taylor et al. in a heterogeneous group of children admitted to a PICU, mortality after 1 year following PICU discharge was 2.5%.[25]

Notable was the high response rate (145/170, 85%) despite the long follow-up interval (median 10 years). Of the 170 eligible patients, 120 patients visited the follow-up clinic and 25 preferred to fill in the questionnaires at home. There are several reasons for this high response rate:
1) Personal invitations by the PICU research nurse or the pediatric intensivist
2) Parents and patients wanted to know more about possible long-term sequelae
3) Parents and patients wanted to contribute in order to help future patients

3.1. Skin scarring and orthopaedic sequelae

Nearly half of the patients (48%) had skin scarring, ranging from 1 barely visible scar on the buttocks to extremely disfiguring scars covering an important part of the body surface (including the face). This was the first study using the POSAS-scoring system in MSS survivors. One part of this scoring system needs to be completed by the patient, while the other part covers the scoring of the scars by the dermatologist. In our study scores of patients and dermatologist were comparable. However we need to be careful in comparing both scores since they do not cover the same items and have a different total score. Furthermore in some patients we were impressed by the extensiveness of the scars, while patients themselves seemed not to be disturbed by their scars and reported they adapted to this over time. However, adolescents in our study group, especially those with skin scarring, reported lower self-esteem than reference adolescents.[26] This might be because they perceived their scars as constant reminders of having experienced a life-threatening illness, which might result in feelings of vulnerability. The worse adolescents scored their scars, the worse their outcomes on close friendship, but the better their outcomes on social acceptance and behavioural conduct. The discounting hypothesis might explain this: adolescents with worse scarring might devaluate physical appearance as less important (the domain of self-esteem in which they fail), and might perceive social acceptance and behaviour as more important. Fear of rejection might interfere with self-esteem in the particular ‘intimacy’ domain (close friendship).[27]
Fourteen percent of the patients had orthopaedic sequelae (amputation, limb-length discrepancy). One of the 7 patients with limb-length discrepancy was only

diagnosed until her visit to our follow-up clinic. In the remaining 6 patients the diagnosis was made fairly late (4.5 years after MSS).

Another important finding was that most of the patients with more extensive amputation (feet, leg or arm) or 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 could demonstrate that the underlying disease, expressed by PRISM and DIC scores, was predictive for the presence of severe skin scarring and orthopaedic sequelae, but not therapy with vasopressors. Also younger children at the time of PICU admission 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. In contrast with other studies, meningococcal serogroup B or C did not predict skin scarring and orthopaedic sequelae.[1]

Determination for each outcome variable separate (severe skin scarring, amputation and limb-length discrepancy) was not possible due to the low number of each of the 3 outcome variables.

Malley et al. retrospectively studied predictive models for adverse outcome defined as death or limb amputation in 153 children with meningococcal disease.[28] It is difficult to draw conclusions from his findings since only a minority had signs of shock or disseminated intravascular coagulation.

Beside “the basics” of MSS treatment some additional and novel therapies have been introduced in our PICU like the administration of prostacyclin and recombinant tissue plasminogen activator in patients with severe ischemic limbs. What was the beneficial effect of these therapies on long-term skin scarring and orthopaedic sequelae?

- 14 of the 120 patients received prostacyclin: 12 of these 14 had long-term skin scarring or orthopaedic sequelae. This most likely reflects the fact that prostacyclin was only administered in those patients with severe purpura and ischemic limbs. In our opinion prostacyclin administration (in a dose of 5-15 ng/kg/min) “saved” limbs in some patients.
- Only 3 of the 120 patients received recombinant tissue plasminogen activator: 2 had long-term skin scarring or orthopaedic sequelae. One patient, who received recombinant tissue plasminogen activator because of an arterial catheter-related thrombosis, had no long-term skin scarring or orthopaedic sequelae.

For the use of prostacyclin and recombinant tissue plasminogen activator the literature contains only single case reports or small uncontrolled series.[29-32] Safety and efficacy of these therapeutic interventions need further evaluation.

Between 1988 and 2001 a subgroup of our patient sample (20/120) was included in a study where protein C concentrate was supplied.[9] The primary endpoints of this study were mortality, safety and dose-response. Patients who received protein C concentrate did not differ significantly with regard to long-term scars or orthopaedic sequelae in comparison with patients who received placebo. In a multicentre phase III randomised control trial no differences were found between the placebo group and the group who received a recombinant form of human activated protein C as to the rate of skin grafts and amputations.[33]

No trend was found over the time period of our study (1988-2001); the frequency of severe skin scarring and orthopaedic sequelae remained the same.

3.2. Neurological sequelae

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

- 3 patients (4, including the patient who died years after the MSS and therefore was lost to follow-up) developed severe mental retardation with epilepsy, probably due to severe shock and prolonged convulsions leading to brain ischemia and infarcts.
- 2 patients (2%), who had MSS and meningitis, developed hearing loss. This low incidence was not surprising; Koomen and Fellick found an incidence of 4% after respectively meningococcal meningitis and invasive MD.[34,35]
- 34 patients (28%) reported chronic headache. However we did not use a validated, standardized questionnaire regarding headache characteristics.
- 7 patients (6%) had focal neurological signs in the extremities: sensory loss in 1 arm, paresis of 1 arm, paresthesia of foot/hand, resting and intention tremor of both hands. Some of these patients already had these focal neurological signs at the time of PICU discharge. In only 1 of these 7 patients (sensory loss and paresis of 1 arm) neuro-imaging and electroencephalography was performed in the months following PICU discharge, which showed left cerebral hemisphere atrophy with slow EEG pattern. It could be that in the remaining 6 patients similar abnormalities due to brain infarcts exist. Another possible cause of these focal neurological signs is neuropathy.

3.3. Growth

In MSS survivors long-term growth was not impaired: weight-for-age and length-for-age standard deviation scores were similar to those found in the general population. Interestingly we did not find growth abnormalities in patients with orthopaedic sequelae. It should be noted, however, that in 5 of the 17 patients with orthopaedic sequelae anthropometric measurements were not performed for different reasons (spastic quadriplegia with contractures, extensive amputations, severe lower-limb discrepancy).

3.4. Renal function

One (6%) of the 16 examined patients with septic shock-associated acute renal failure showed signs of persistent kidney damage, manifested as mild chronic renal failure, proteinuria and hypertension. This 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.[36]

Proteinuria after MSS may reflect the loss of a considerable amount 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 with the proteinuria untreated.

3.5. Pulmonary sequelae

In 6 of the 46 patients, who required mechanical ventilation at the time of MSS, long-term lung function was performed because they had signs of acute respiratory distress syndrome (ARDS).[37] Duration of mechanical ventilation in these 6 ARDS patients was significantly longer (12.5 versus 4 days) compared with the 40 patients without ARDS. In all 6, except 1, flowvolume curves were normal. One patient, who was known with asthma, had a normal forced vital capacity but showed signs of airways obstruction.

Plötz et al. also found normal lung function parameters in MSS survivors.[38] However, they found desaturation (median 2.5%, range 0-20%) during maximal exercise, whereas we did not measure this in our patients. However none of our 120 MSS survivors reported exercise intolerance.

So several questions remain: does significant desaturation occur during maximal exercise long-term after MSS (as in our patients, > 4 years)? If so, what is the cause? Could this be due to lung fibrosis and microvascular obliteration, which are pathologic sequelae after ARDS?

Only few, small studies have investigated pulmonary function in children who survived acute lung injury (ALI) or ARDS. Three months after discharge most children showed restrictive and/or obstructive abnormalities and the recovery during the following months reached a plateau at 12 months with no further improvement.[37,39]

In adult patients outcome of ARDS has been investigated more extensively. In a study by Cheung, adult ARDS survivors continued to have exercise limitation 2 years after ICU discharge.[40] Neff et al. found mild abnormalities in adult ARDS patients beyond 1 year following hospital discharge; in 25% (4 of 16 patients) lung function was obstructive, whereas in another 4 patients lung function was restrictive. Gas exchange during exercise was impaired in nearly half of the patients.[41]

3.6. Association between physical and psychological outcome variables

No differences were found between patients with severe skin scarring and orthopaedic sequelae and patients without severe skin scarring and orthopaedic sequelae as to the presence of problem behaviour (e.g. anxiety, depression, aggressive behaviour) or total IQ < 85. Also, no differences were found between patients with mild neurological impairments and patients without mild neurological impairments as to the presence of problem behaviour or total IQ < 85 (figure 1).

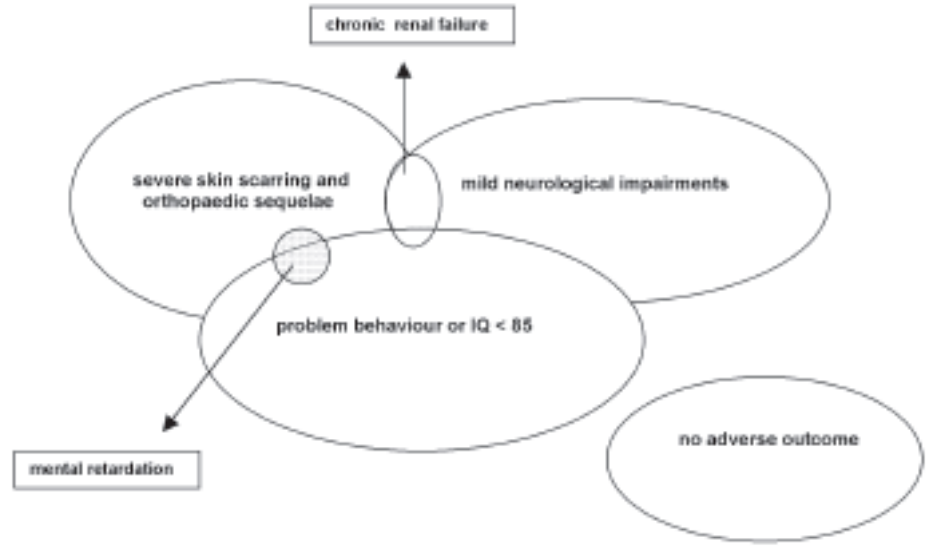

Figure 1. Association between physical and psychological outcome variables

We were surprised by this lack of associations between adverse physical and psychological outcomes. The only outcome variables, directly related to the severity of MSS in our study group, were severe skin scarring and orthopaedic sequelae. Could it be that the adverse outcome variables such as chronic headache or cognitive dysfunctioning (impairments on social and practical reasoning, visual-motor integration, attention and executive functioning in children < 18 years) are not specifically related to MSS, but to sepsis in general? A study that induced cytokine activation in healthy volunteers using intravenous injection of *Salmonella* endotoxin, found impaired verbal and nonverbal memory, which were correlated with endotoxin-induced cytokine release.[42] Or is an acute illness with invasive procedures, sedative and analgesic drugs, 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.[43]

Some specific cases should be mentioned, but they were insufficient to result in statistical significant differences: for example, 2 of the 3 patients with mental retardation (estimated IQ < 70) had severe skin scarring and orthopaedic sequelae; the patient with chronic renal failure had severe skin scarring, amputation of 1 leg and focal neurological signs.

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.

We think that this resilience makes children who survive a severe illness, unique. Also of central importance for long-term outcome is the premorbid health status; the vast majority of children with MSS admitted to the PICU, were previously healthy. Again this is in contrast with adult patients admitted to an ICU.

3.7. Health-related quality of life

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, like functional status

(disability) and HR-QoL (well-being). For example, amputation of a limb may be associated with the inability to walk long distance (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, functional status and HR-QoL have not been thoroughly investigated in MSS survivors.[1,3] Therefore we studied these outcome measures using validated questionnaires. We found poorer HR-QoL scores in our patients mainly on the physical domains. We hypothesized that the earlier disease episode and present physical health status had a negative impact on the patients' present physical HR-QoL. Surprisingly we found that long-term poorer HR-QoL, both on the physical and psychosocial domains, was mainly predicted by problem behavior. HR-QoL scores were to a lesser amount predicted by adverse physical outcome. As mentioned earlier extensive amputation or limb-length discrepancy often resulted in important long-term morbidity.

We also studied the functional status (or generic health status) by using the Health Utility Index (HUI) and the visual analogue scale: poorer health status was reported in nearly all HUI attributes and the visual analogue scale.

General limitations and considerations of our follow-up studies (short-term and long-term):

- These were uncontrolled studies in one centre. It could be interesting to compare our groups with patients admitted to the hospital or PICU because of 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 in patients and their parents.
- HR-QoL in children as reported by parents might differ from the self-report. Several factors might affect HR-QoL reports by parents; parental socio-economic status, education and health status.

General implications of our findings for clinical practice:

- A standard follow-up clinic by a multidisciplinary team including a pediatric intensivist, physiotherapist and psychologist should be organized for MSS survivors. If indicated, other specialist should

be consulted: e.g. an orthopaedic surgeon, especially for early diagnosis and subsequent treatment of lower-limb discre-pancy in patients at risk (high severity of illness scores, young age at time of MSS). A nephrologist should be demanded for patients with septic shock-associated acute renal failure, especially those necessitating renal replacement therapy. These patients should undergo periodic measurement (1x/year) of blood pressure, serum creatinine with calculation of estimated glomerular filtration rate 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 3 months, 1 and 4 years after PICU discharge.

- Structured information (by means of a brochure or internet site) should be given as to possible outcome, not only for parents and patients, but also for healthcare workers.
- An important ethical consideration has to be made: based on our findings regarding overall outcome the requirement of extensive amputations seems to be no reason for withdrawal of treatment.

4. Outcome research in survivors of MSS: future perspectives

1) At the PICU

- We need to study premorbid health status (before MSS, “nulmeting”), both physical and psychosocial, and HR-QoL. In view of recall bias that might be influenced by parental perception of the child’s health, the timing to collect data on premorbid health status prior to PICU admission is important. At PICU or hospital discharge could be a possibility since parents are probably less stressed compared with PICU admission.
- Age at time of PICU admission and severity of illness scores as predictors of outcome: did we make the right choice? Or should we investigate other putative predictors for adverse outcome, not only related to MSS but also to acute illness in general? See “Future outcome research in PICU patients” (Baseline data collected at PICU admission: predictors of outcome).

2) After the PICU

- If the incidence of chronic headache, assessed with a validated, standardized questionnaire regarding headache characteristics, is significantly higher compared with normative data, predictors should be identified.

- In patients who survive fulminant MSS (high severity of illness scores, high doses of inotropes and vasopressors) electrocardiograms and echocardiographic measurements should be performed in order to study long-term myocardial dysfunction. We know that at the time of the acute illness decreased myocardial contractility (e.g. caused by proinflammatory mediators and microthrombi) plays a major role in the pathogenesis of MSS.[44-46] It is possible that irreversible myocardial dysfunction (e.g. due to infarction) occurs during the acute phase.
- Future research should be done to find the causes of cognitive dysfunctioning, i.e. impairments on verbal intelligence. Neuro-imaging (MRI) should be included to detect and locate areas in the brain where damage may have occurred.

5. Future outcome research in PICU patients: a broader perspective

Why should we do outcome research in PICU patients?

The majority of patients in most PICUs are less than five years old, thus the impact of the acute illness occurs during crucial periods of development. This also implies that outcome research is more challenging because development is dynamic. For example, evaluation of certain cognitive skills is not relevant until children are into their school-age years, i.e. at that time these skills only become apparent.

As clinicians, it is crucial for us to obtain a clear understanding of the course of the acute illnesses. While we want to know the likelihood of their surviving in the PICU, their probable outcome over time is of paramount interest. If we evaluate long-term outcome, we can improve the care we provide, with more benefits and less complications. Furthermore we need to share this information with patients and their families. Also survival and future health status are important outcomes for benchmarking PICU practice. Ultimately, this has the potential to improve overall outcome among PICUs, both national and international.

Lastly, we need to know the long-term economic consequences of surviving pediatric intensive care, as healthcare consumes an important part of community resources.

What is already being done at our PICU?

Since 1999 a structural follow-up programme already exists in our PICU for children with severe anatomical congenital anomalies requiring surgical interventions (like congenital diaphragmatic hernia) and for extracorporeal membrane oxygenation survivors (neonatal and pediatric). This programme includes structural medical and psychological assessments using validated, standardized instruments. This is done by a multidisciplinary team including a pediatric intensivist, physiotherapist and psychologist. The children are scheduled to undergo assessment at ages 6, 12, 18 and 24 months and 5, 8, 12, 16 and 18 years.[47]

What do we propose in the near future?

A structural follow-up programme in the following patient-groups, and their parents:

- respiratory failure: upper airway obstruction, status asthmaticus, bronchiolitis, ARDS, pneumonia
- circulatory failure: cardiomyopathy, congenital heart disease, arrhythmias, shock
- neurological failure: status epilepticus, coma, meningitis, neurotrauma
- post-CPR
- other: near-drowning, polytrauma, battered child, intoxication

This should be done by a multidisciplinary team including a pediatric intensivist, physiotherapist, and psychologist. In certain patient-groups or if indicated other specialists should be consulted like a cardiologist (e.g. patients with cardiomyopathy) or nephrologist (e.g. patients who suffered from acute renal failure during their acute illness).

Schedule of follow-up assessments;

- 1, 3 and 12 months after PICU discharge
- at ages 6, 12 and 24 months and 5, 8, 12, 18 and 30 years

Baseline data collected at PICU admission: predictors of outcome

- "basics": age, diagnosis and treatment, length of stay in PICU and hospital
- severity of illness: e.g. severity of illness scores, type and duration of mechanical ventilation, neuromonitoring (neurological failure)
- premorbid health status: physical, psychosocial and HR-QoL. In view of recall bias that might be influenced by parental perception of the child's health, the timing to collect these data is important. At PICU or hospital discharge could be a possibility since parents are probably less distressed compared with PICU admission.
- laboratory parameters: e.g. glucose and cortisol
- pain and sedation management
- nutritional and metabolic management
- PICU environment: nursing and medical procedures, noise and light pollution
- quality of sleep: quantitative and qualitative

Assessment methods at follow-up in patients: use of multiple tools is required for comprehensive assessment:

- interview: in a semi-structured format using a standardized questionnaire with regard to current health status (physical, psychosocial and development)
- physical examination: including anthropometry and standardized neurological examination. In patient-groups like MSS survivors an orthopaedic physical examination (e.g. for early diagnosis of lower-limb discrepancy) and evaluation of skin scarring using a validated scoring system (e.g. POSAS-scoring system) should be done.
- neuromotor assessment: The Movement Assessment Battery (M-ABC), exercise test
- psychological assessment: behavioural and emotional functioning, self-esteem, intellectual and neuropsychological functioning.
- HR-QoL
- in certain patient-groups or if indicated: audiometry (e.g. meningitis, ototoxic drugs), lung function (e.g. ARDS), electrocardiograms and echocardiographic measurements (e.g. cardiomyopathy), renal function (e.g. acute renal failure), neuro-imaging (e.g. in patients who develop neuropsychological dysfunctioning after the acute illness).

Assessment methods in parents:

- during PICU admission: interviews and questionnaires with regard to parental socio-economic status, education, psychological distress, coping styles and HR-QoL
- at follow-up: interviews and questionnaires with regard to psychological distress, PTSD symptoms, coping styles, HR-QoL and impact on family life

In conclusion

All together, based on our findings that a considerable number of MSS survivors show physical and psychological problems after PICU discharge both short-term and long-term, structured follow-up (evaluation of care) should be organized for children who are admitted to a PICU in order to provide adequate quality of care, both during their stay in the PICU and after PICU discharge. Our recommendations are in line with the guidelines (2001) of the Ministry of Health, Welfare and Sport of the Netherlands.

This follow-up has to be done by a multidisciplinary team including a pediatric intensivist, physiotherapist, and psychologist. Structured collaboration with other specialists is necessary (e.g. orthopaedic surgeon, nephrologist).

Eventually when children outgrow the pediatric age group there needs be a transition process to an adult follow-up clinic. Today this already exists for children after invasive treatment for congenital heart disease.[48,49]

Finally, structured multidisciplinary follow-up has financial implications; it requires structured resources.

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NEDERLANDSE SAMENVATTING

Nederlandse samenvatting

Inleiding

Jaarlijks worden er in Nederland ongeveer 5000 kinderen (0-18 jaar) opgenomen op afdelingen gespecialiseerd in pediatrische intensieve zorgen (PICU). Onder deze kinderen vormen patiënten met een meningokokken septische shock een bijzondere groep met hoge morbiditeit en mortaliteit.

Meningokokken septische shock bij kinderen

Definities

Invasieve meningokokken ziekte kan worden onderverdeeld in:

- meningitis
- sepsis (MS)
- septische shock (MSS)
- of een combinatie van meningitis met sepsis of septische shock

Meningitis alleen komt voor bij ongeveer de helft van de patiënten, sepsis alleen bij 10% en ongeveer 40% vertoont het beeld van meningitis en sepsis. In de meest ernstige gevallen is er een snelle progressie: de patiënt ontwikkelt een septische shock met onvoldoende bloedvoorziening (zuurstof en glucose) naar de organen en kan daardoor overlijden binnen 24-48 uur.

Epidemiologie

Invasieve meningokokken ziekte komt over heel de wereld voor. In Nederland is de incidentie 4,5 op 100000 inwoners (cijfers van 2001). MSS komt het meest voor bij voorheen gezonde jonge kinderen (< 5 jaar) en adolescenten.

Pathogenese: kolonisatie, invasie en ziekte

De meningokok (*Neisseria meningitidis*) is een bacterie. Er bestaan verschillende serogroepen naargelang de samenstelling van hun kapsel: in het Westen komen serogroep B en C het meeste voor. Ongeveer 10% van de bevolking is drager van de meningokok in neus en keel. Bij een minderheid komt de meningokok in de bloedbaan terecht. Risicofactoren hiervoor zijn: voorafgaande virale infectie, blootstelling aan rook en afweerstoornissen. Eens in de bloedbaan triggert de meningokok, met name door de vrijzetting van toxines, een hele cascade aan immunologische mechanismen (inflammatie). Hiervan zijn de belangrijkste pathofysiologische gevolgen: verhoogde doorlaatbaarheid van de bloedvaten (capillair lek), abnormale vasoconstrictie en vasodilatatie, diffuse intravasculaire coagulatie en myocard dysfunctie.

Een van de meest typische kenmerken van MSS zijn de petechiën. Dit zijn huidbloedingen (niet-wegdrukbare rode vlekjes), welke veroorzaakt worden door diffuse intravasculaire coagulatie en extravasatie van rode bloedcellen.

Klinische aspecten: zorgvuldige beoordeling, vroegtijdige herkenning

MSS kan razend snel verlopen, van aspecifieke klachten (koorts, malaise en braken) tot overlijden binnen 24-48 uur. Daarom is het cruciaal dat deze patiënten in een vroegtijdig stadium worden herkend aan de hand van typische symptomen zoals petechiën, meningisme, pijn in de benen en koude extremiteiten.
Door de onderliggende pathofysiologische mechanismen komt de bloedvoorziening, en daarmee de aanvoer van zuurstof en glucose, naar de organen in het gedrang. Verschillende organen kunnen betrokken zijn: hart, nieren, hersenen, longen, bijnieren en spieren.
Er bestaan verschillende scoresystemen aan de hand van klinische en laboratorium parameters om de ernst van MSS te beoordelen. In dit proefschrift is gekozen voor “Pediatric risk of mortality score” (PRISM), een algemeen score systeem, “Vasopressor score” (VAS), een score systeem met type en dosis inotropica, en “Disseminated Intravascular Coagulation score” (DIC), een score systeem voor de ernst van de diffuse intravasculaire coagulatie.

Behandeling: A, B, C, DEFG

Adequate opvang van een patiënt met een klinisch beeld van MSS vermindert de morbiditeit en mortaliteit. Hierbij wordt het ABCDE-schema gevolgd: evaluatie van de luchtweg en herkenning van mogelijk respiratoir en circulatoir falen. Hoekstenen van de behandeling zijn: toediening van zuurstof en zorgen voor een intraveneuze toegang, waarna antibiotica en een vochtbolus (20 ml/kg NaCl 0.9%) worden gegeven. Wanneer een patiënt na een eerste vochtbolus nog steeds in shock is, worden volgende vochtbolussen (albumine oplossingen, plasma, erytrocytenconcentraat) gegeven. In de ernstige gevallen van MSS is tot 100-200 ml/kg vulling nodig in de eerste 24 uur als gevolg van het capillair lek. Naast vochtbolussen (> 40 ml/kg in 1 uur) dient men te starten met een inotropicum (dobutamine). Tevens dient men intubatie en beademing te overwegen. Indien ondanks vochtbolussen en dobutamine de shock persisteert, worden ook vasoconstrictieve middelen (noradrenaline) toegediend via een centraal-veneuze lijn.

Aanvullend laboratorium onderzoek omvat: glucose, zuur-base evenwicht en elektrolyten in bloed. Een lumbale punctie dient alleen verricht te worden als er geen contra-indicaties zijn, te weten shock, tekens van verhoogde intracraniële druk, en diffuse intravasculaire coagulatie.
Na de initiële opvang en stabilisatie moet een patiënt met MSS naar een PICU worden getransporteerd voor verdere behandeling. De principes van behandeling blijven dezelfde: behandeling van respiratoir en circulatoir falen. Verder worden neurologische, renale en metabole ontregelingen opgespoord en indien nodig behandeld.

Als gevolg van een stijgende incidentie van invasieve meningokokken ziekte werd er in 2002 in Nederland een vaccinatiecampagne gestart tegen serogroep C meningokokken (tegen serogroep B geen vaccin) bij kinderen tussen 1-18 jaar.

Outcome: is er leven na MSS?
Patiënten die MSS overleven, kunnen ernstige restlesies hebben zoals littekens en amputatie(s) van extremiteiten. In **deel 2 van de inleiding** wordt een overzicht gegeven van literatuur wat betreft korte en lange termijn gevolgen van invasieve meningokokken ziekte.
De beperkingen van eerdere studies waren: heterogene studiegroepen (ernst van ziekte en leeftijd), beperkt aantal patiënten en geen gestandaardiseerde meetmethoden.
Geen enkele studie geeft een volledig overzicht van de lange termijn gevolgen, zowel fysisch als psychosociaal, bij patiënten die MSS hebben overleefd op de kinderleeftijd.

Doel van het onderzoek

Het relatieve grote, homogene cohort van MSS patiënten opgenomen op de afdeling intensive care van het Erasmus MC- Sophia tijdens de afgelopen 20 jaar, bood de mogelijkheid om de lange termijn gevolgen, zowel fysisch als psychosociaal, bij deze patiënten te onderzoeken gebruik makend van gestandaardiseerde meetinstrumenten.
De psychosociale gevolgen op lange termijn werden beschreven in de thesis van Lindy Vermunt.

Inhoud van dit proefschrift
In **hoofdstuk 2** wordt de epidemiologie beschreven bij kinderen opgenomen met sepsis en petechiën op de afdeling intensive care van het Erasmus MC-Sophia tussen 1988 en 2006. **Hoofdstuk 3** geeft de korte termijn gevolgen (tot 2 jaar na ontslag van de PICU) weer van kinderen die MSS hebben overleefd, en hun ouders. Deze kinderen werden opgenomen op de afdeling intensive care van het Erasmus MC- Sophia tussen 2001 en 2005.
In de **hoofdstukken 4 tot 7** bestuderen we de lange termijn gevolgen van kinderen die wegens MSS werden opgenomen op de afdeling intensive care van het Erasmus MC- Sophia tussen 1988 en 2001.
In **hoofdstuk 8** vatten we de belangrijkste bevindingen samen. Ook stellen we de implicaties van onze bevindingen voor. Tenslotte geven we aanbevelingen voor outcome research bij PICU patiënten in de toekomst.

In **hoofdstuk 2** wordt de epidemiologie beschreven bij bijna 300 kinderen opgenomen met sepsis en purpura (bij 82% werd de meningokok ook gekweekt, bij 16% was de kweek negatief), op de afdeling intensive care van het Erasmus MC-Sophia tussen 1988 en 2006. De belangrijkste bevindingen waren dat jonge kinderen een meer ernstig beloop hebben en een hogere mortaliteit. Dit is waarschijnlijk het gevolg van het immatuur immuunsysteem, stollingscascade en stress respons. De incidentie van serogroep B was veel hoger dan serogroep C (74% versus 19%, bij 7% geen serogroep). De mortaliteit was 16%. De meeste kinderen overleden binnen 24-48 uur als gevolg van een fulminante septische shock ondanks vulling en inotropica. Er was geen verschil wat betreft ernst van ziekte en mortaliteit tussen serogroep B en C. Niettegenstaande dat jongens een ernstiger beloop hadden dan meisjes, was er geen verschil in mortaliteit.
Gezien de toename in incidentie van MSS werd er in 2002 gestart met een vaccinatie campagne bij kinderen ≥ 1 jaar in Nederland. Dit heeft geresulteerd in een afname van niet alleen serogroep C, maar ook serogroep B.
In de afgelopen jaren is ook de mortaliteit enorm gedaald: sinds januari 2002 is er slechts 1 van de 68 kinderen overleden als gevolg van MSS (mortaliteit 0,5%) Hiervoor zijn er verschillende verklaringen:
- herkenning van kinderen met MSS (“koorts en vlekjes”) in een vroegtijdig stadium door ouders en dokters.

- speciale cursussen, o.a. georganiseerd door Stichting Spoedeisende Hulp bij Kinderen® voor dokters en verpleegkundigen, gericht op de herkenning en behandeling van acuut zieke kinderen.
- implementatie van internationale richtlijnen (2000) voor kinderen met sepsis.

Als gevolg van de daling in mortaliteit zullen meer kinderen MSS overleven. In de volgende hoofdstukken bestuderen we de outcome bij kinderen die deze ziekte hebben overleefd.

Hoofdstuk 3 geeft de korte termijn gevolgen (tot 2 jaar na ontslag van de PICU) weer van 47 kinderen die tussen 2001 en 2005 werden opgenomen op de afdeling intensive care van het Erasmus MC- Sophia wegens MSS, en de weerslag hun ouders. Meer dan de helft (55%) van de kinderen had littekens als gevolg van purpura. Slechts 2 kinderen (4%) had orthopedische sequelen; 1 onderging amputatie van 3 vingers. Het ander kind met een fulminante MSS op de leeftijd van 6 weken, verloor niet alleen 1 vinger, maar hij vertoonde ook beenlengteverschil op de leeftijd van 2 jaar. Bij 45% werden chronische klachten gerapporteerd, meest frequent pijn in de benen en gedragstoornissen. We vonden ook slechtere scores op de kwaliteit van leven vragenlijsten, met name op de fysieke schalen. Opmerkelijk waren de lage scores op de “general health perception” schaal: 1/3 scoorde lager dan de 5de percentiel van de referentiegroep. Dit betekent dat ouders de gezondheid van hun kind niet goed vinden en dat ze zich hierover zorgen maken voor de toekomst.

Een cruciale vraag dient beantwoord te worden: gezien de daling in mortaliteit, hebben kinderen die MSS overleven nu meer lange termijn gevolgen? Daar lijkt het niet op: de incidentie van littekens en orthopedische sequele is vergelijkbaar tussen de studieperioden 1988-2001 en 2001-2005 (resp. 48% versus 55%, 14% versus 4%).

Wat betreft de ouders: 17% van de moeders had na PICU ontslag van hun kind professionele hulp nodig omwille van emotionele problemen. Ouders gaven vaak aan dat ze behoefte hadden aan psychologische begeleiding na ontslag van hun kind. Ondanks dit alles scoorden de ouders niet slechter op de kwaliteit van leven vragenlijsten in vergelijking tot de normgroep.
Aanvullende studies zijn nodig om de lange termijn gevolgen te onderzoeken zowel bij kinderen die MSS hebben overleefd, als bij hun ouders.

In de **hoofdstukken 4 tot 7** bestuderen we de lange termijn gevolgen (4-16 jaar na MSS) van kinderen die wegens MSS werden opgenomen op de afdeling intensive care van het Erasmus MC- Sophia tussen 1988 en 2001. De opkomst was groot: 145 van de 170 kinderen namen deel aan deze outcome studie.
Hoofdstuk 4 beschrijft de littekens en orthopedische sequelen bij deze groep, alsook de predictoren hiervan. Bijna de helft (48%) van de patiënten had littekens. Dit varieerde van 1 klein litteken nauwelijks zichtbaar op het bovenbeen tot extreme littekenvorming op een belangrijk deel van het lichaam (ook het aangezicht). Bij 14% waren orthopedische sequelen (amputatie(s), beenlengteverschil) aanwezig.

Ernstige orthopedische sequelen (amputatie van voet of been, beenlengteverschil) resulteerde in aanzienlijke lange termijn morbiditeit (pijn, functionele beperkingen, heelkundige interventies).
De ernst van de ziekte (hoge PRISM en DIC scores), was een significante predictor voor ernstige littekens en orthopedische sequelen. Hoe jonger het kind ten tijde van de MMS, hoe meer kans op beenlengteverschil. De serogroep (B of C) was geen significante predictor voor ernstige littekens en orthopedische sequelen. De frequentie van littekens en orthopedische sequelen is niet veranderd tijdens onze studieperiode (1988-2001).

Hoofdstuk 5 omvat de renale, neurologische en pulmonale sequelen, alsook de groei en de gezondheid in het algemeen:
- bij 1 van de 16 patiënten heeft het acuut nierfalen tijdens de MSS geleid tot chronische nierschade (proteïnurie en hypertensie).
- 1/3 vertoonde neurologische sequelen variërend van mild tot zeer ernstig (ernstige psychomotorische retardatie n=3, doofheid n=2, chronische hoofdpijn n=34, focale neurologische symptomen n=7).
- Bij 6 van de 46 patiënten, die mechanisch werden beademd tijdens de MSS, werd een longfunctie verricht omdat deze 6 kinderen tekenen van ARDS vertoonden tijdens de acute fase.
  De flow-volume curven waren normaal, behalve bij 1 patiënt met astma.
- Wat betreft groei (gewicht voor leeftijd en lengte voor leeftijd) vertoonden de patiënten geen afwijkingen.
- De gezondheid in het algemeen, gemeten door een gevalideerde vragenlijst (Health Utility Index), werd slechter gescoord in vergelijking met Nederlandse norm data.

In **hoofdstuk 6** bestuderen we de kwaliteit van leven, zowel bij de patiënten als hun ouders, aan de hand van gevalideerde vragenlijsten. Bij de patiënten vonden we slechtere scores op de fysieke schalen. Onze hypothese was dat hun huidige gezondheid een negatieve impact had op hun huidige fysieke kwaliteit van leven. Echter het bleek dat de slechtere scores op de kwaliteit van leven vragenlijsten, zowel op de fysieke als op de psychosociale schalen, vooral bepaald werden door probleemgedrag, en minder door fysieke sequelen als gevolg van MSS. De ouders scoorden beter op de meerderheid van de schalen betreft hun eigen kwaliteit van leven.

Het verband tussen de fysieke en psychosociale gevolgen van MSS wordt onderzocht in **hoofdstuk 7**. Tot onze verbazing werd er geen verschil gevonden tussen patiënten met en patiënten zonder ernstige littekens en orthopedische sequelen wat betreft probleemgedrag (vb. angst, depressie of agressief gedrag) of laag IQ (totaal IQ < 85). Ook werd er geen verschil gevonden tussen patiënten met en patiënten zonder milde neurologische sequelen (doofheid, chronische hoofdpijn, focale neurologische symptomen) wat betreft probleemgedrag of laag IQ. Zou het kunnen zijn dat lange termijn gevolgen na MSS zoals chronische hoofdpijn of cognitieve problemen (vb. aandacht) niet specifiek het gevolg zijn van deze ziekte in het bijzonder, maar van sepsis in het algemeen? Of sterker nog, zijn ze het gevolg van acuut ernstig ziek zijn op de kinderleeftijd?
Er waren een paar uitzonderingen: vb. 2 van de 3 patiënten met ernstige psychomotorische retardatie hadden ook ernstige littekens en orthopedische sequelen. De jongen met chronisch nierfalen had ook ernstige littekens, amputatie van het onderbeen en focale neurologische symptomen.
Een zeer belangrijke vaststelling tijdens de interviews op onze follow-up polikliniek was de mentale kracht van de patiënten en hun ouders. Het leek er zelfs op dat het doormaken van een dergelijke ernstige ziekte de gezinnen sterker had gemaakt in de zin van meer relativeringsvermogen en levensvreugde.

Implicaties van onze bevindingen (hoofdstuk 8)

Patiënten, die MSS overleven op de kinderleeftijd, dienen gevolgd te worden op een gestandaardiseerde manier door een multidisciplinair team (o.a. kinderarts-intensivist en psycholoog). Dit zowel op korte termijn als ook op lange termijn. Indien nodig moeten deze patiënten worden doorverwezen naar andere specialisten: vb. orthopedisch chirurg (beenlengteverschil), nefroloog (acuut nierfalen ten tijde van de MSS).

Ook bij andere patiëntengroepen, die opgenomen zijn op een PICU, moet gestructureerde follow-up deel uitmaken van de zorg. Dit om verschillende redenen:
- de meeste kinderen opgenomen op een PICU zijn jonger dan 5 jaar en dus in volle ontwikkeling. Wat is de impact van een levensbedreigende ziekte op hun ontwikkeling?
- als kinder-intensivisten zijn we niet alleen geïnteresseerd in de overleving, maar zeker ook in de korte en lange termijn gevolgen. Deze kennis kan bijdragen tot een betere zorg (minder complicaties, meer voordelen) tijdens de acute fase op de PICU.
- informatievoorziening van kinderen en hun ouders: wat kunnen ze verwachten?
- “benchmarking” met als uiteindelijk doel de kwaliteit van zorg verbeteren, zowel nationaal als internationaal.

Wat stellen we voor?

Follow-up volgens een vastgelegd schema (aan de hand van periode na ontslag PICU en op vaste leeftijden) bij patiëntengroepen zoals:
- respiratoir falen: vb. status astmaticus, bronchiolitis, ARDS
- circulatoir falen: cardiomyopathie, post-harttransplantatie
- neurologisch falen: status epilepticus, coma, meningitis, neurotrauma
- post-reanimatie
- andere: bijna-verdrinking, politrauma, kindermishandeling, intoxicatie

Door een multidisciplinair follow-up team:
- kinderarts-intensivist
- psycholoog
- fysiotherapeut
- andere specialisten zo nodig: vb. kindercardioloog (cardiomyopathie)

Wat gaan we onderzoeken?

- predictors van outcome: reden van opname op de PICU, ernst van ziekte, voor geschiedenis, laboratorium parameters (vb. glucose), behandeling, PICU omgeving (vb. slaap, medische interventies)
- outcome: fysiek, psychosociaal, ontwikkeling en kwaliteit van leven met behulp van anamnese, klinisch onderzoek en gevalideerde meetinstrumenten

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BETEKENIS EN BEKENTENIS

BETEKENIS EN BEKENTENIS

Het belangrijkste hoofdstuk voor mij (en waarschijnlijk ook voor jullie) begint hier. Mijn levenswerk, op professioneel vlak, is klaar. Eigenlijk zou ik willen dat het opnieuw kon beginnen. Ik heb genoten. Vond het GEWELDIG.

Lieve “kinderen”, lieve ouders, ik kan niet anders dan met jullie beginnen. Dank voor jullie belangeloze bereidheid om jaren later opnieuw naar het ziekenhuis te komen. Er zijn onvergetelijke momenten geweest tijdens onze follow-up poli! Jullie kracht en levensvreugde hebben me geraakt!

Diegenen die dit prachtig project mee hebben weten realiseren.
Koen Joosten, mijn copromotor. Jij hebt mij ertoe aangezet om deze follow-up poli te starten omdat je voelde dat dit HET was voor mij (“Buysje, die varkentjes zijn niets voor u”). Onderzoek doen met u als begeleider was een feest. Lieve Koen, dierbare vriend, ook buiten het onderzoek heb je een belangrijke rol gespeeld.
Jan Hazelzet, cher Jean, uw doorzettingsvermogen en optimisme zijn inspirerend. Prachtig dat we samen aan uw onderzoek bij deze kinderen jaren later dit gevolg hebben kunnen geven. Merci!
Dick Tibboel, van het allereerste begin heeft u dit project gesteund. Met boeiende VAKinhoudelijke gesprekken vanuit uw enorme onderzoekservaring. Fantastisch dat outcome research een onderzoekslijn is binnen onze ICK.
Marianne Maliepaard, uw enthousiasme en hulp waren onmisbaar.
De bijdrage van verschillende mensen laten zien hoe multidisciplinair dit outcome onderzoek werd benaderd. En zo moet het ook!
Lindy Vermunt (psychologie), Lisbeth Utens (psychologie), Hein Raat (kwaliteit van leven), Arnold Oranje (huid), Ad Diepstraten (orthopedie), Karlien Cransberg (nieren), Mariëlle Pijnenburg (longen), Jessie Hulst (groei), Martine Maat (epidemiologie) en Wim Hop (statistiek, van “putative” associations tot “toppie”).
Dank voor de fijne samenwerking!

Heren professoren van de leescommisie, ik wil u hartelijk danken voor het kritisch lezen van mijn manuscript.

Collega’s van de ICK, dokters en niet-dokters, oud en nieuw, jong en oud, dank voor de samenwerking en steun.
Matthijs de Hoog, mijn paranimf, bedankt om naast mij te staan, maar vooral om mij het vak te leren zoals je dat hebt gedaan.

Sytske, bedankt om van mijn levenswerk een kunstwerk te maken.

Wij hebben bijzondere vrienden. Vrienden, die veel geduld met ons hebben gehad, die ons tijd en ruimte hebben gegeven. Vrienden, die gelukkig zijn als wij gelukkig zijn. Waarmee we samen genieten (zelfs paardrijden in De Karmeliet). Vrienden, die onze grootste droom mee hebben weten waar te maken. DANK U voor jullie vriendschap.

Lieve Barbara en Jean-Marc, Balthazar zit voor eeuwig en altijd in mijn hart. Mijn respect en liefde voor jullie is immens.

Onze familie. Nina, mijn tantes en nonkels, nichten en kozzes (groot en klein), Magali, Api, moeke en vake, de meters en peters van onze kinderen. Bedankt voor jullie steun en vriendschap. In het heel bijzonder tante Mariëtte, mijn waardige meter, die mij ALTIJD op de voor haar kenmerkende discrete manier heeft gevolgd. Tante Mariëtte, u bent een Mooi Mens. Ik zie u graag.

Isaac, Luiz en Manu. Lieve jongens, we zijn pas begonnen samen. Ik ga jullie altijd blijven volgen. Wil weten wat jullie plannen zijn, wat jullie gelukkig maakt, wat jullie dromen zijn. Miljoen miljard keer.

Timothy, mijn broer, vandaag mijn paranimf. Zonder al te veel woorden zullen we altijd naast elkaar staan. En gaan onze kinderen samen groot worden. Koester het mooie wat je samen hebt met Niii en jullie jongens.

Mijn aller-allerliefste mama, dank u voor uw onvoorwaardelijke liefde en ons nest in Buitenland. Tim en ik hebben alle kansen gekregen. Ik bewonder uw kracht. U bent een grote dame. LY2unlimited.

Onze 3 prachtige kinderen, Elena, Max en Luisa. Voor mama en mij zijn jullie de Promotie van ons leven. Door jullie ben ik Moemie geworden, het ultieme geluk in mijn leven. Onze grootste wens is dat jullie uitgroeien tot gelukkige mensen, dat het beste in jullie naar boven komt.

Elisabeth, Liefde van mijn leven, je hebt me het allermooiste gegeven, “Onsch”!
Als ik samen met u in de spiegel kijk, zie ik de rest van mijn leven. Aljsm.

JE HOORT ME
ZONDER WOORDEN
DAT BEDOEL IK

JE BENT ER. **NAAST MIJ. ALTIJD.**
DAT VOEL IK

JE **KENT** ME, **BEGRIJPT ME,** BEHOEDT ME,
DAT WEET IK

CURRICULUM VITAE

Curriculum vitae

Corinne Buysse werd geboren op 18 augustus 1968 te Mortsel (Antwerpen). In 1986 behaalde ze het diploma van de humaniora (Latijn-Wetenschappen) afgelegd aan het Sint-Jozefinstituut (Antwerpen). In datzelfde jaar startte zij de studie geneeskunde aan de Universiteit Antwerpen. Ze behaalde de titel dokter in de Genees-, Heel- en Verloskunde in 1993 met grote onderscheiding. Aansluitend was zij werkzaam als kinderarts in opleiding in het Algemeen Kinderziekenhuis Antwerpen (opleider Dr. G. Janssens), het Universitair Ziekenhuis Antwerpen (opleider Prof. Dr. K.J. Van Acker). De laatste 6 maanden van de opleiding werkte zij op de afdeling intensieve zorgen voor kinderen van het Academisch Ziekenhuis Vrije Universiteit Brussel (opleider Prof. Dr. Y. Vandenplas). Na haar registratie als kinderarts in 1998 startte ze een fellowship intensieve zorgen voor kinderen in het Sophia Kinderziekenhuis te Rotterdam. Dit resulteerde in 2001 in een aanstelling als kinderarts-intensivist op de afdeling ICP van het Sophia Kinderziekenhuis. In 2003 werd aanvang gemaakt met het follow-up onderzoek dat resulteerde in dit proefschrift.
Corinne Buysse leeft sinds 1993 samen met Elisabeth Elst, kinderarts. Samen hebben ze 3 kinderen, Elena Victoria (2003), Luisa Valentina (2004) en Max Julius (2004).

LIST OF PUBLICATIONS

List of Publications

1. Buysse C, Pijnenburg M, Hazelzet JA, Joosten KF. **Pulmonary sequelae in survivors of meningococcal septic shock in childhood**. *Crit Care Med 2008. in press.*

2. Buysse CMP, Raat H, Hazelzet JA, et al. **Long-term health status in survivors of meningococcal septic shock in childhood.** *Arch Ped Adol Med 2008. in press.*

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LIST OF ABBREVIATIONS

List of Abbreviations

ARF	acute renal failure
ASR	Adult Self-Report
CBCL	Child Behaviour Checklist
CFR	case fatality rate
DIC	disseminated intravascular coagulation score
HR-QoL	health-related quality of life
HUI2	Health Utilities Index mark 2
HUI3	Health Utilities Index mark 3
MD	meningococcal disease
MSS	meningococcal septic shock
MUAC	mid upper arm circumference
NM	*Neisseria meningitidis*
PDR	predicted death rate
PICU	paediatric intensive care unit
POSAS	Patient Observer Scar Assessment Scale
PRISM	Pediatric Risk of Mortality Score
RRT	renal replacement therapy
VAS	vasopressor score
YSR	Youth Self-Report

Notes

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