An explorative study on quality of life and psychological and cognitive function in pediatric survivors of septic shock

Madelon B. Bronner, MA;[1] Hendrika Knoester, MD, PhD;[1] Jeanine J. Sol, MD; Albert P. Bos, MD, PhD; Hugo S. A. Heymans, MD, PhD; Martha A. Grootenhuis, MSc, PhD

Objective: **To evaluate self-reported health-related quality of life, anxiety, depression, and cognitive function in pediatric septic shock survivors.**

Design: **A retrospective cohort study.**

Setting: **A 14-bed tertiary pediatric intensive care unit.**

Patients: **Children aged ≥8 yrs at the time of the follow-up who were admitted between 1995 and 2004 for septic shock. Inotropic and or vasoconstrictive agents were administered to these patients for ≥24 hrs.**

Intervention: **Health-related quality of life was assessed with the KIDSCREEN-52, anxiety with the State Trait Anxiety Inventory for Children, depression with the Children's Depression Inventory, and cognitive function with the cognitive scale of the TNO-AZL Children's Quality of Life Questionnaire Child Form.**

Measurements and Main Results: **Fifty of 82 eligible pediatric septic shock survivors were evaluated. The median age of the children at pediatric intensive care unit admission was 4.2 yrs (range, 0.0–17.0 yrs); the median age at follow-up was 10.7 yrs (range, 8.0–20.4 yrs). Health-related quality of life and anxiety scores were comparable to the age-related Dutch norm population. Depression scores were significantly better than the norm population, whereas cognitive function was significantly lower than the norm population. We found that 44% of the children had cognitive scores <25% of the norm population. Young age at the time of pediatric intensive care unit admission was predictive of cognitive problems, and cognitive problems were associated with lower emotional function.**

Conclusions: **In this group of septic shock survivors, health-related quality of life, anxiety, and depression are equal to or slightly better than the age-related Dutch norm population. Cognitive function is decreased, especially in children admitted at younger ages. Follow-up studies with adequate neuropsychological testing are warranted to evaluate the association between septic shock, cognitive function, and risk factors for cognitive problems. (Pediatr Crit Care Med 2009; 10:636–642)**

Key Words: outcome assessment (health care); follow-up studies; health status; quality of life; shock septic; anxiety; depression

The incidence and mortality rate of sepsis in children are lower compared with those in adults, but sepsis is one of the leading causes of death in children (1). Adult sepsis survivors suffer from persisting symptoms, such as dyspnea, fatigue, depression, impaired cognitive function and functional status, and reduced health-related quality of life (HRQoL) compared with the general population (2, 3). Recognition of these long-term sequelae has resulted in "patient-centered outcome" research in adult intensive care unit (ICU) survivors (4). Studies on long-term sequelae and HRQoL in pediatric sepsis survivors are scarce.

Quality of life is defined as an individual's perception of his or her position in life in the context of culture and value systems as well as in relationship to his or her goals, expectations, standards, and concerns. HRQoL is defined as quality of life in which a dimension of personal judgment of one's health and disease is added (5). In the case of children, HRQoL is also influenced by factors, such as the ability to participate in peer groups and the ability to keep up with developmental activities. Difficulties in measuring HRQoL in children include a lack of consensus on suitable (cross-cultural) instruments and the need for different instruments in different age groups (6). Recently, the KIDSCREEN-52 was developed in Europe as a generic, cross-national questionnaire that evaluates HRQoL regardless of whether children are in good health or suffer from a chronic medical condition. It is a self-report questionnaire that evaluates HRQoL in children aged 8 to 18 yrs (7). The self-report questionnaire is based on psychosocial aspects of well-being rather than physical function.

In the few follow-up studies evaluating HRQoL in pediatric ICU (PICU) survivors, HRQoL was satisfactory in the majority of children (8–12). In studies evaluating HRQoL in pediatric septic shock survivors, HRQoL was decreased on physical domains (13, 14). Long-term psychological problems like posttraumatic stress disorder have been reported, but other psychological problems, such as anxiety and depression, are hardly studied in pediatric ICU survivors (15–18). Evaluation of cognitive function in pediatric meningitis survivors and adult septic shock survivors does show substantial problems that interfere with daily life (19–23). Possible pathophysiologic mechanisms mediating cognitive dysfunction in septic shock survivors include hypoxemia, sedatives or analgesics, hypotension, delirium, hyperglycemia, and sepsis and in-

[1]Both authors are first author.

From the Psychosocial Department (MBB, MAG), Pediatric Intensive Care Unit (HK, JJS, APB), and the Department of Pediatrics (HSAH), Emma Children's Hospital, Academic Medical Center, Amsterdam, Netherlands.

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For information regarding this article, E-mail: h.knoester@amc.uva.nl

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flammation (20). Based on these observations, we believe that follow-up research on pediatric septic shock survivors and their families is needed to evaluate long-term sequelae and to improve support after discharge.

The aim of our study was (1) to evaluate HRQoL, psychological function (anxiety and depression), cognitive function, and educational level in children who survived septic shock compared with normative data from the Dutch population; (2) to explore possible medical determinants that are related to cognitive problems; and (3) to determine whether cognitive function is related to HRQoL and psychological function.

MATERIALS AND METHODS

Protocol and Procedure

This study was part of a retrospective study in which we evaluated cardiac function, HRQoL, psychological function (anxiety and depression), and cognitive function in pediatric septic shock survivors. The PICU of the Emma Children's Hospital/Academic Medical Center Amsterdam is a tertiary pediatric ICU with 14 beds that admits medical, surgical, and trauma patients from the greater Amsterdam area. Previously, healthy children who survived septic shock in our PICU between 1995 and 2004 were included in this study. The term *previously healthy* was defined as having no need for medical supervision at any time before PICU admission. Inclusion criteria were survival of the clinical diagnosis of septic shock according to the Conference Consensus Criteria (24, 25), the administration of inotropic and/or vasoconstrictive agents for ≥24 hrs, and age ≥8 yrs at the time of the follow-up study. Children were invited to visit our outpatient follow-up clinic where they were evaluated for physical sequelae, HRQoL, anxiety, depression, and cognitive function. Physical sequelae were defined as any physical complaints or abnormalities found at the outpatient follow-up clinic by physical examination (e.g., neurologic abnormalities). Children with language barriers were excluded due to the inability to complete Dutch questionnaires. In addition, children <8 yrs were excluded because they were unable to complete the questionnaires by themselves. Written informed consent was obtained from all participating parents and children. The Medical Ethical Board of the Academic Medical Centre Amsterdam has approved the study protocol.

Questionnaires

HRQoL was evaluated by the KIDSCREEN-52, a generic self-report questionnaire that uses questions derived from focus groups of children and adolescents across Europe. It is applicable for both healthy and chronically ill children and adolescents aged between 8 and 18 yrs. The KIDSCREEN-52 consists of three sociodemographic questions (gender, age, and educational level) and ten domains of HRQoL: Physical well-being, psychological well-being, moods and emotions, self-perception, autonomy, parent relations and home life, financial resources, peers and social support, school environment, and bullying. Items were scored on a 5-point scale. Within each domain, item scores were summed and transformed to Rasch person parameters by an algorithm that gives children in the reference population a mean score of 50 with a standard deviation of 10 (26). This instrument was validated in a Dutch population of 1960 children, with an age distribution of 8 to 11 yrs (n = 641) and 12 to 18 yrs (n = 1270). The normative groups for our analysis were based on these data. The internal consistency (Cronbach's α) was satisfactory and ranged from 0.68 to 0.88 in all scales.

Psychological function measures anxiety and depression. Anxiety was evaluated by the State-Trait Anxiety Inventory for Children (27). The trait scale, a 20-item self-report scale, measures differences between children in their tendency to experience anxiety states. The scale ranges from 20 to 60 points, and children with high scores are more prone to respond with anxiety to situations perceived as threatening than children with low scores. This instrument was validated in a Dutch population of 1229 children, with an age distribution of 8 to 12 yrs (n = 643) and 13 to 17 yrs (n = 586). Boys (n = 596) and girls (n = 633) differed significantly on State Trait Anxiety Inventory for Children in the Dutch population. The normative groups for our analysis were based on these data (28). The internal consistency (Cronbach's α) was satisfactory and ranged from 0.73 to 0.83.

Depression was evaluated by the Children's Depression Inventory (29). This questionnaire contains 27 items, each of which consists of three statements. For each item, the individual was asked to select the statement that best describes his or her feelings for the last 2 weeks. The Children's Depression Inventory is designed to provide information about the presence and severity of depressive symptoms. This instrument was validated in a Dutch population of 886 children, with an age distribution of 8 to 12 yrs (n = 673) and 13 to 17 yrs (n = 213). Boys (n = 419) and girls (n = 467) differed significantly on Children's Depression Inventory in the Dutch population. The normative groups for our analysis were based on these data (30). The internal consistency (Cronbach's α) was satisfactory and ranged from 0.71 to 0.89.

Cognitive function was evaluated by the cognitive scale of the TNO-AZL Children's Quality of Life Questionnaire Child Form that included eight items (31, 32). These items measure limitations concerning cognitive functioning and school performances (child's ability to pay attention, understand schoolwork, understand what others say, perform arithmetic, read, write, learn, and say what he/she means). This self-report questionnaire is a generic Dutch instrument that measures health status problems and is weighted by the impact of health problems on the child's well-being. If a problem occurred in the last few weeks, the child can indicate how he or she felt about this problem on a 4-point Likert scale: (very) good (3); not so well (2); rather bad (1); and bad (0). The score was calculated by adding up item scores, and higher scores indicated a better quality of life. Maximum domain scores for the cognitive scale were 32. The internal consistency (Cronbach's α) was satisfactory (0.79). This instrument was validated in a Dutch population of 2331 children, with an age distribution of 8 to 11 yrs (n = 1078) and 12 to 15 yrs (n = 1253). The normative groups for our analysis were based on these data.

Besides a scale score, the percentage of children with cognitive problems was determined. The definition of children with cognitive problems was based on the value of the 25th percentile in the norm population (33). According to this concept, an individual scoring below the 25th percentile norm is in the quarter of the population most impaired. The 25th percentile for healthy children (8 to 11 yrs of age) is a score of 27, and the score for healthy adolescents (12 to 15 yrs of age) is 26.

Patient characteristics (age at PICU admission; length of PICU stay; [length of] artificial ventilation; risk of mortality; highest creatinine and lactate measurements during PICU stay; causative organisms; and number, dosages, and duration of vasoactive agents) were obtained retrospectively from medical records and the Patient Data Management System. In our unit, it is no standard procedure to perform a lumbar puncture in septic shock patients; therefore, meningitis could not be evaluated as a risk factor for decreased HRQoL, and psychological and cognitive function.

Statistical Analysis

The Statistical Package for Social Sciences (SPSS), Windows version 12.0, was used for all analyses. First, missing values were handled according to the guidelines given in the manuals for the relevant questionnaires. In general, data were imputed if children completed at least 90% of the questionnaire by mean scores of the other items. Two missing items were allowed for the cognitive function scale. Second, Mann-Whitney U tests and χ^2 tests

were used to compare participants and nonparticipants. Third, differences in HRQoL, anxiety, depression and cognitive function between patients and the norm group were analyzed by one-sample Student's t tests. In addition to this, effect sizes were calculated by dividing the difference in mean scores between the patients and the norm group by the standard deviation of the scores from the norm group. According to Cohen, effect sizes of about 0.2 were considered to be small, effect sizes of about 0.5 to 0.8 were considered to be moderate, and effect sizes of ≥0.8 were considered to be large (34). Fourth, cognitive function was also evaluated by analyzing differences in educational levels between patients and healthy control subjects (data from Dutch Health Statistics); for this analysis, we used a one-sample Student's t test. Fifth, cognitive function scores were dichotomized to determine cognitive problems. A score <25th percentile value for the appropriate age and gender population stratum indicated perceived impaired cognitive function. To analyze whether children with and without cognitive problems differed with regard to medical characteristics, Mann-Whitney U tests and χ^2 tests were used. Multivariate linear regression analysis with stepwise backward variable elimination was performed to explore risk factors (gender, length of stay in PICU, length of artificial ventilation, risk of mortality, the age of child at the time of follow-up study, and the age of child at PICU admission) for cognitive function. Finally, the relationship among cognitive function, HRQoL, anxiety, and depression was analyzed by calculating Spearman rank correlations.

Bonferroni correction was carried out to compensate for multiple testing. A significance level of $p < .005$ was used in all tests, except for comparisons of patient characteristics. In these tests (participants vs. nonparticipants), $p < .05$ was used as the significance level.

RESULTS

Participants

From 1995 through 2004, 124 patients survived admission to our PICU with septic shock and inotropic and/or vasoconstrictive support for ≥24 hrs. Of these 124 patients, 82 children were aged ≥8 yrs at follow-up and eligible for this study. Seventeen of these patients were lost to follow-up. Sixty-five children were invited to participate in the study. Eight patients refused participation (for geographical reasons or lack of interest). Seven patients' data were missing due to language problems or incomplete questionnaires. Fifty (77%) of these 65 children completed the questionnaires. No statistically significant differences were found between patient characteristics (age of child at PICU admission and follow-up study, gender, length of stay, length of artificial ventilation, risk of mortality, highest creatinine and lactate, and physical sequelae) of participants (n = 50) and nonparticipants (n = 32) (data not shown). Mean follow-up time was 6.5 yrs (range, 1.5–10.1 yrs). No statistically significant differences were found between participants and nonparticipants with regard to causative organisms and number, duration and dosages of vasoactive agents (data not shown).

Table 1. HRQoL of survivors of septic shock compared with Dutch norm data

	Child (n = 31) M ± SD	Effect Size	Norm (n = 641) M ± SD	Adolescent (n = 19) M ± SD	Effect Size	Norm (n = 1270) M ± SD
Physical well-being	59.2 ± 11.2	0.2	57.3 ± 9.5	52.5 ± 13.8	0.1	50.4 ± 9.4
Psychological well-being	60.5 ± 9.1	0.5	55.7 ± 9.1	57.3 ± 9.2	0.6	51.9 ± 8.4
Moods and emotions	56.4 ± 11.1	0.4	52.5 ± 9.5	52.5 ± 9.1	0.2	50.5 ± 9.6
Self-perception	61.6 ± 9.8	0.4	57.4 ± 9.8	51.0 ± 9.4	0.1	49.9 ± 9.3
Autonomy	56.2 ± 9.5	0.0	56.5 ± 8.6	55.7 ± 7.3	0.2	53.5 ± 9.1
Parent relations and home life	58.4 ± 8.6	0.3	55.5 ± 8.4	54.8 ± 6.7	0.3	52.3 ± 9.3
Financial resources	51.9 ± 10.7	0.1	51.4 ± 10.6	56.1 ± 7.0	0.4	52.7 ± 9.2
Peers and social support	55.0 ± 10.8	0.2	53.1 ± 9.1	55.0 ± 7.1	0.4	51.7 ± 9.4
School environment	59.0 ± 11.1	0.1	58.4 ± 10.2	53.0 ± 9.7	0.3	50.7 ± 8.7
Bullying	48.0 ± 11.4	0.0	48.1 ± 11.0	47.0 ± 9.0	0.2	48.8 ± 10.1

HRQoL, health-related quality of life; Mean ± SD, mean ± standard deviation.
$p < .005$ study group vs. norm data. Higher scores represent better HRQOL.

HRQoL

Fifty children completed the KIDSCREEN-52. No statistically significant differences were found in HRQoL in the 31 children and the 19 adolescents compared with age-related Dutch norm populations. Moderate effect sizes were found in the psychological well-being domain in both age groups; the study group was shown to have better psychological well-being than the norm group. Effect sizes for the other domains were small (Table 1).

Psychological Function

Fifty children (n = 23 girls, 27 boys) completed the anxiety questionnaire and 48 children (n = 22 girls, 26 boys) completed the depression questionnaire. Overall good psychological function was determined. No statistically significant differences were found in the anxiety scores, except in girls surviving septic shock. They reported less anxiety compared with the Dutch norm population. Statistically significant differences were found in all depression scores, except in boys attending secondary school (≥13 yrs of age). Children surviving septic shock reported less depression compared with the Dutch norm population. Moderate and large effect sizes were found for all anxiety and depression scores, except for anxiety scores in boys attending secondary school (Table 2).

Cognitive Function

Fifty children completed the cognitive scale of the TNO-AZL Children's Quality of Life Questionnaire Child Form. However, only 45 children (≤15 yrs) were compared with norm data. Children had significantly worse cognitive function compared with the norm population. Adolescents reported scores comparable with the norm population (Table 2). Twenty (44%) of the 45 children scored <25th percentile of the norm population, indicating cognitive problems.

Education. Thirty-seven participants (n = 15 girls, 22 boys) attended primary school at the time of the follow-up study, whereas 13 (n = 8 girls, 5 boys) attended secondary school. Five (14%) of the primary school students and two (15%) of the secondary school students visited schools for special education. In total, seven (14%) of 50 children attended special education schools and five (71.4%) of these seven children had cognitive problems (<25th percentile). In the Dutch population, generally 3% of children and 3.5% of adolescents attend special education schools (data from Dutch Health Statistics, www.cbs.nl). The number of children attending special education at primary school ($t = 1.845$, $df = 36$, $p = .073$) and adolescents at secondary school

Table 2. Anxiety, depression, and cognitive function compared with Dutch norm data

	n	All Children With Septic Shock M ± SD	Effect Size	Norm Mean ± SD
Anxiety[a]				
Girls	23	28.3 ± 6.7[e]	0.7	33.0 ± 6.5
Primary school	15	29.1 ± 7.2	0.6	33.4 ± 6.5
Secondary school	8	26.9 ± 5.8	0.9	32.5 ± 6.7
Boys	27	28.2 ± 6.1	0.3	30.0 ± 6.0
Primary school	22	27.6 ± 6.3	0.7	31.2 ± 5.5
Secondary school	5	31.0 ± 4.1	0.4	28.7 ± 6.4
Depression[b,c]				
Girls	22	5.1 ± 4.1[e]	0.6	9.3 ± 6.5
Primary school	15	5.4 ± 4.4[e]	0.5	8.9 ± 6.5
Secondary school	7	4.5 ± 3.5[e]	1.0	10.5 ± 6.5
Boys	26	5.5 ± 4.1[e]	0.5	8.2 ± 5.7
Primary school	21	5.5 ± 4.5[e]	0.5	8.4 ± 5.9
Secondary school	5	5.4 ± 2.1	0.5	7.7 ± 4.9
Cognitive function[d]				
Child	31	25.2 ± 4.9[e]	0.8	28.4 ± 3.9
Adolescent	19	27.3 ± 3.0	0.1	27.6 ± 4.1

Mean ± SD, mean ± standard deviation.

[a]Anxiety scores range from 20–60; higher scores represent more anxiety; [b]depression scores range from 0–54; higher scores represent more depression; [c]one girl and one boy did not fill in the depression questionnaire; [d]cognitive function scores range from 0–32; higher scores represent better HRQOL; [e]$p < .005$ study group vs. norm data.

Table 3. Patient characteristics of children with and without self-reported cognitive problems

	Children With Cognitive Problems (n = 20) Median (Range)	Children Without Cognitive Problems (n = 25) Median (Range)	p
Age of child at PICU admission, yrs	1.8 (0.0–7.0)	5.0 (0.1–17.0)[a]	.00
Length of stay in PICU, days	6.5 (2.0–15.0)	4.0 (2.0–35.0)	.19
Length of artificial ventilation, days	5.0 (0.0–14.0)	2.0 (0.0–25.0)	.35
Risk of Mortality, PIM2, %	9.2 (1.1–26.2)	6.5 (1.0–26.1)	.18
Age of child at follow-up study, yr	9.7 (8.1–13.0)	12.0 (8.0–20.4)	.03
Highest creatinine in PICU, μmol/L	60.0 (18.0–227.0)	55.5 (26.0–296.0)	.78
Highest lactate in PICU, mmol/L	3.1 (0.7–16.4)	3.0 (0.8–23.0)	.60
	n (%)		
Female	10 (50.0)	9 (36.0)	.35
Physical sequelae (yes)	9 (45)	6 (24)	.16
Artificial ventilation (yes)	15 (75.0)	17 (68.0)	.60

PICU, pediatric intensive care unit; PIM, Pediatric Index of Mortality.

[a]$p < .005$ children with self-reported cognitive problems compared with children without self-reported cognitive problems. Children with cognitive problems scored <25% of the norm population.

($t = 1.172$, $df = 11$, $p = .266$) did not differ significantly from the general Dutch population.

Risk Factors for Cognitive Problems. Children who reported cognitive problems were significantly younger at PICU admission compared with children without cognitive problems (Table 3). A backward regression analysis for cognitive function showed a final model ($R^2 = .13$, $F = 6.5$, $p = .015$) with one significant risk factor: age of the child at PICU admission (B = 0.59, 95% confidence interval, 0.1–1.1; $p = .015$).

Relationship Between Cognitive Function and HRQoL, Anxiety, and Depression. Children and adolescents who reported worse cognitive function had significantly more negative emotions, more problems with their parents, and reported significantly more bullying, higher anxiety, and depression scores compared with children who had better cognitive function (Table 4).

Follow-up Time. No statistically significant correlations were found between follow-up time and HRQoL, anxiety, depression, and cognitive function (data not shown).

DISCUSSION

This is one of the first follow-up studies to describe self-reported HRQoL, psychological function, and cognitive function of children surviving septic shock. HRQoL, anxiety, and depression scores of children who survived septic shock are on average better or similar to the scores of children and adolescents of the same age and gender in the general Dutch population. However, cognitive function, as reported by the children themselves, is worse in septic shock survivors compared with the norm population. A younger age child at PICU admission is associated with lower cognitive function. In addition, a larger number of septic shock-surviving children, although not significant, attend special education schools.

Studies in adult survivors of severe sepsis and septic shock showed HRQoL outcomes similar to those in other adults surviving ICU admission, but lower than the general population (2). Studies focusing on HRQoL after surviving pediatric septic shock are scarce (13, 14). In contrast with our findings, HRQoL was decreased on the physical domains of these studies. The severity of illness and chronic complaints negatively affected HRQoL (13, 14). One study focusing on HRQoL in children surviving bacterial meningitis showed a lower HRQoL compared with the general population, especially in children with worse cognitive function due to the meningitis (21). Because most effect sizes were small-to-moderate in this study, the clinical importance of these differences in HRQoL is relative. Similar to our findings, several studies in pediatric oncology show better or comparable HRQoL, anxiety, and de-

Table 4. Correlations between cognitive function and HRQoL domains, anxiety, and depression

	Cognitive Function	
n = 45	Correlations	p
HRQoL		
Physical well-being	0.351	.02
Psychological well-being	0.375	.01
Moods and emotion	0.568[a]	.00
Self-perception	0.335	.02
Autonomy	0.363	.02
Parents relation and home life	0.483[a]	.00
Financial resources	0.274	.09
Peers and social support	0.396	.01
School environment	0.367	.02
Bullying	0.610[a]	.00
Anxiety	−0.359	.02
Depression	−0.581[a]	.00

HRQoL, health-related quality of life.

[a]Significant at $p < .005$.

pression scores compared with the norm population (35, 36).

Few studies describe psychological adjustment in PICU survivors after discharge (16, 37). PICU admission is associated with emotional, behavioral, and psychiatric symptoms. In contrast with these findings, anxiety and depression scores in our study group were similar to or even better than normative data from the Dutch population. Our results are difficult to compare with these earlier studies, considering the differences in follow-up time.

In short, HRQoL, anxiety, and depression in these septic shock survivors are equal to or slightly better than in the age-related Dutch norm population. Patients confronted with a life-threatening disease are faced with the necessity to accommodate to the illness. Two mechanisms describing adaptation to stressful events give a possible explanation for this positive outcome: 1) the concept of posttraumatic growth, defined as "the experience of significant positive change arising from the struggle with a major life crisis"; and 2) the concept of response shift, defined as "the experience of hardship changing the internal standard of patients, resulting in changes in the meaning of self-evaluation and hence in a possibly different experience of problems and values" (38, 39). These two mechanisms describe a process of adaptation to stressful events, leading to a possible change for better-perceived HRQoL and decreased scores for anxiety and depression questionnaires. We do not know how parental perceptions of the child surviving influences children's psychological function. More detailed studies focusing on these mechanisms are needed in children surviving critical illnesses.

Almost half (44%) of the children studied reported cognitive function problems and 14% of the children attended special education schools. Survivors of septic shock seem to be at risk for adverse neurodevelopmental outcomes also affecting academic performance. These findings are in accordance with a recent pilot study on neuropsychological function in children following PICU admission (40). Results suggest impaired memory and attention in these children, and a specific deficit in children with septic illness. Also, earlier reports on survivors of traumatic brain injury, bacterial meningitis, or meningococcal disease show neurologic deficits (19, 21, 41). Future research should consider whether these deficits are disease-specific or present in PICU children in general, and examine risk factors like hypoperfusion, age at time of illness, delirium, hypoxia, sepsis, and inflammation (20, 42).

Because we did not include a control group, it is not clear whether there is an association between cognitive problems and sepsis in our patients. We performed another follow-up study on HRQoL in a small heterogeneous group of PICU survivors. No cognitive impairment was found in 27 children (aged 8–15 yrs) admitted for a broad range of diseases (e.g., asthma, trauma, meningococcal disease, cardiac failure). Because of the small number of children in this study, we could not analyze differences in cognitive functioning in children admitted with different diseases (12). Our studies and the study of Elison et al suggest that children with septic shock are at risk for developing cognitive problems (40).

In our study, cognitive function problems were especially reported by children who were younger at the time of PICU admission. Follow-up studies after pediatric brain injury and in animal studies indicate that the younger brain may be more vulnerable for the development of cognitive problems (43, 44). Possibly other risk factors, such as meningitis and pathophysiologic mechanisms mediating cognitive dysfunction, need to be analyzed in larger populations in future studies (20).

Cognitive function problems, as evaluated by the children themselves, are associated with more depressive moods, bullying, and depression in the current study despite the fact that HRQoL and depression in the whole study group were comparable with the norm population. Children with cognitive function problems may adapt less well to stressful events and may be more vulnerable to other problems than children without cognitive function problems. Prospective follow-up studies with adequate neuropsychological testing are necessary to evaluate cognitive function and risk factors (before, during, and after PICU admission) for cognitive function problems (45, 46). Awareness of long-term sequelae may result in supportive programs after discharge, as is the case for neonatal and trauma patients (47, 48).

A number of limitations to this study should be taken into account. First, this is a retrospective study in one center with no control group. The response rate of our study was 77%. Although other follow-up studies in the PICU have had similar response rates, this may have biased our results. In addition, no statistically significant differences were found between patient characteristics of participants and nonparticipants. However, there is a trend ($p < .1$) that the majority of the participating children were younger and admitted for a longer period compared with the nonparticipating children. This could have resulted in a selection bias by excluding the older cases admitted for a shorter stay. Second, the number of studied children is relatively small, and due to different ages, gender, and follow-up times, strong conclusions are difficult. Therefore, a case control study matched on age, gender, follow-up time, and hospital or PICU admission would be interesting. Third, seven children were excluded because they did not complete the Dutch questionnaire adequately due to language barrier. Our results therefore cannot be extrapolated to all ethnic and cultural groups living in the Amsterdam region. Fourth, in the present study, cognitive function was measured with a short self-report questionnaire. Yet, diagnostic clarification and grading of clinical severity of cognitive disorders should be evaluated by comprehensive neuropsychological testing. These tests are designed to examine a variety of cognitive abilities, including speed of information processing, attention, memory, language, and executive functions.

In addition, younger children (<8 yrs of age) were not evaluated. Future research should evaluate cognitive function in all pediatric septic shock survivors with standardized neuropsychological tests. Besides, premorbid health status is likely an important factor but is difficult to assess (49). Finally, the definition of children as being "at risk" for a cognitive problem was based on the value of the 25th percentile of the domain in the norm population. Because there is no gold standard comparison, the cutoff point may seem arbitrary. This method, however, compared with contrasting means, reveals clear differences between our study group and healthy controls.

Despite these limitations, this is one of the few studies that provides insight into psychosocial behavior of pediatric septic shock survivors. We found that the majority of these survivors matches or even surpasses the general population in HRQoL, anxiety, and depression scores, and cognitive problems. These findings

are noteworthy and require further discussion and research.

Suggestions for Future Research

Cohort and case-control studies of PICU survivors evaluating patient outcomes (physical, psychological, and cognitive sequelae, and quality of life) and risk factors for sequelae (before, during, and after PICU admission) are essential. Awareness of long-term sequelae and their risk factors may result in changes in treatment during the acute phase and in supportive programs after discharge (50, 51). Long-term follow-up clinics of PICU survivors and rehabilitation programs comparable with follow-up care in neonatal and trauma patients should be developed to detect, support, and treat children with cognitive, developmental, and psychological problems. These programs are expected to improve daily life and minimize the impact on children's well-being and future development (47, 48).

CONCLUSION

In this group of septic shock survivors, HRQoL, anxiety, and depression were better or equal compared with the age-related Dutch norm population. Apparently, children are able to overcome the stressful experience of septic shock. Children admitted at a younger age especially reported cognitive function problems. Prospective follow-up studies with adequate neuropsychological testing and information on risk factors, such as meningitis, are warranted to evaluate the association between septic shock, cognitive function, and risk factors for cognitive problems.

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