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ORIGINAL ARTICLE

Paediatric community-acquired septic shock: results from the REPEM network study

P. Van de Voorde · B. Emerson · B. Gomez · J. Willems · D. Yildizdas · I. Iglowstein · E. Kerkhof · N. Mullen · C. R. Pinto · T. Detaille · N. Qureshi · J. Naud · J. De Dooy · R. Van Lancker · A. Dupont · N. Boelsma · M. Mor · D. Walker · M. Sabbe · S. Hachimi-Idrissi · L. Da Dalt · H. Waisman · D. Biarent · I. Maconochie · H. Moll · J. Benito

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Abstract
Introduction and purpose of the study With this study we aimed to describe a "true world" picture of severe paediatric 'community-acquired' septic shock and establish the feasibility of a future prospective trial on early goal-directed therapy in children. During a 6-month to 1-year retrospective screening period in 16 emergency departments (ED) in 12 different countries, all children with

P. Van de Voorde (✉) · J. Willems · S. Hachimi-Idrissi
Paediatric Intensive care and Emergency Medicine, 1K12IC, University Hospital Ghent, De Pintelaan 185, 9000 Ghent, Belgium
e-mail: patrick.vandevoorde@ugent.be

B. Emerson · D. Walker
Paediatric Emergency Medicine, Yale-New Haven Children's Hospital, New Haven, CT, USA

B. Gomez · J. Benito
Paediatric Emergency Medicine, University Hospital Cruces, Barakaldo, Bilbao, Spain

D. Yildizdas
Paediatric Intensive Care Medicine, Çukurova University Hospital, Adana, Turkey

I. Iglowstein
Paediatric Emergency Medicine, Ostschweizer Children's hospital, St Gallen, Switzerland

E. Kerkhof · H. Moll
Paediatric Emergency Medicine, Sophia Children's Hospital, Rotterdam, The Netherlands

N. Mullen · I. Maconochie
Paediatric Emergency Medicine, St Mary's Hospital, London, UK

C. R. Pinto
Paediatric Intensive Care Medicine, Coimbra Children's Hospital CHUC, Coimbra, Portugal

T. Detaille
Paediatric Intensive Care and Emergency Medicine, University Hospital Louvain UCL, Brussels, Belgium

N. Qureshi
Paediatric Emergency Medicine, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia

J. Naud
Paediatric Emergency Medicine–SMUR, University Hospital Pellegrin, Bordeaux, France

J. De Dooy
Paediatric Intensive Care Medicine, Antwerp University Hospital, Antwerp, Belgium

R. Van Lancker · M. Sabbe
Emergency Medicine, University Hospital, Leuven, Belgium

A. Dupont · D. Biarent
Paediatric Intensive Care and Emergency Medicine, University Hospital Queen Fabiola HUDERF, Brussels, Belgium

N. Boelsma · S. Hachimi-Idrissi
Paediatric Intensive Care Medicine, University Hospital Brussels, Brussels, Belgium

M. Mor · H. Waisman
Paediatric Emergency Medicine, Schneider Children's Medical Center of Israel, Petah Tikva, Tel Aviv, Israel

L. Da Dalt
Paediatrics, Cà Foncello Hospital, Treviso, Italy

severe sepsis and signs of decreased perfusion were included.
Results A 270,461 paediatric ED consultations were screened, and 176 cases were identified. Significant comorbidity was present in 35.8 % of these cases. Intensive care admission was deemed necessary in 65.7 %, mechanical ventilation in 25.9 % and vasoactive medications in 42.9 %. The median amount of fluid given in the first 6 h was 30 ml/kg. The overall mortality in this sample was 4.5 %. Only 1.2 % of the survivors showed a substantial decrease in Paediatric Overall Performance Category (POPC). 'Severe' outcome (death or a decrease ≥2 in POPC) was significantly related ($p<0.01$) to: any desaturation below 90 %, the amount of fluid given in the first 6 h, the need for and length of mechanical ventilation or vasoactive support, the use of dobutamine and a higher lactate or lower base excess but not to any variables of predisposition, infection or host response (as in the PIRO (Predisposition, Infection, Response, Organ dysfunction) concept).
Conclusion The outcome in our sample was very good. Many children received treatment early in their disease course, so avoiding subsequent intensive care. While certain variables predispose children to become septic and shocked, in our sample, only measures of organ dysfunction and concomitant treatment proved to be significantly related with outcome. We argue why future studies should rather be large multinational prospective observational trials and not necessarily randomised controlled trials.

Keywords Paediatric · Child · Emergency medicine · Sepsis · Shock · Outcome

Introduction

Sepsis is still an important health problem in children, with a hospital mortality of 3–10 % in 'developed' countries and up to 15–30 % when shock is present [2, 9, 23, 25]. Existing figures rarely include children who die or are fully resuscitated before reaching the paediatric intensive care unit (PICU) or provide information about attributed long-term morbidity [2, 9]. Most often, septic patients present initially to the emergency department (ED), where they should be recognized and where early aggressive resuscitation can make a difference [21].

This study therefore aims to describe an ED picture of severe paediatric community-acquired septic shock. It can serve as a 'true world' baseline, accounting for a potential Hawthorne effect[1] in any subsequent prospective trial and will help in establishing the feasibility of such a trial on, for instance, early goal-directed therapy (EGDT) in children [2, 18].

[1] A temporary change in behaviour or performance in response to a change in the environmental conditions like for instance increased observation or appreciation of that performance.

Methods

This is a retrospective observational study in 16 ED from 12 countries. It was conceived as the first part of a study that will evaluate EGDT guideline compliance and subsequent patient outcomes. Institutional ethics committee approval was obtained in each centre. As data were rendered anonymous before handling, a waiver of consent was granted.

Patients were screened for eligibility backwards from a centre-specific starting date (between September 2011 and May 2010). All centres screened a 1-year period except for three centres that, because of logistics and data quality, only screened a period of 9 and 6 months, respectively (Table 1). Cases were identified using data from ED or secondary transfer logs, microbiology and/or pharmacology registries, in view of local availability, and then evaluated whether they met all inclusion and any exclusion criteria (Table 2).

Data focussed on the first hours of sepsis and are chronological from first symptoms, first participating ED bedside contact [T0] to final outcome at discharge, as defined by the Paediatric Overall Performance Category (POPC): a six-level description of the degree of functional/cerebral disability from normal to death [5]. An operational manual provided definitions and normal values where needed [7]. Case report forms were controlled for eligibility, completeness and internal consistency by the principal investigator (PVDV). Electronic data input was performed centrally (UH Ghent, Belgium) using SNAP software [19].

Primary data analysis

All analyses were performed in StatsDirect software [20]. Unknown data are reported but excluded from further calculations. Nominal data are given as percentages of the total sample. For continuous variables, we calculated mean and standard deviation (SD). To explore the relations between these variables and 'severe' outcome, a 95 % confidence interval (CI) is given for the difference between means, using the unpaired Student's *t* test. We defined 'severe' outcome as death and/or a decrease in POPC of 2 or more. Tests for association between pairs of categorical variables were performed, using the Fisher exact test. For selected variables, we also calculated a 95 % CI for the difference between proportions, using the iterative method of Miettinen and Nurminen [13]. Ordinal data are presented as median and interquartile range (IQR). The hypothesis of equality of medians was tested using a Mann–Whitney *U* test. *P* values smaller than 0.05 were considered significant.

Table 1 Centre specifics and cases included per centre

Centre	Final inclusions	Approx. paediatric non-traumatic ED consults in same time *n*	% Hospital admissions	Sec. transfer, *n*	Severe outcome
AX	15	3,366	27 %	280	1
BW[a]	15	4,341	17 %	32	0
CS	5	13,884	22 %	72	1
DE	9	7,200	10 %	176	1
ER	7	16,681	7 %	260	1
GY	12	2,184	17 %	0	1
TF[a]	19	18,700	17 %	30	0
HP	17	18,000	20 %	–	3
ZM	15	22,000	16 %	0	1
JL	10	48,000	4 %	0	0
LH	3	10,800	11.6 %	10	0
MF	13	15,428	17.4 %	–	1
PS[b]	8	20,680	15 %	–	0
WZ	16	18,900	12 %	25	0
XT	7	42,737	10 %	70	0
BK	6	7,560	21 %	250	0
16	176	270,461	4–27 %	1,205	10

Different centres had sometimes different screening starting points (between May 2010 and September 2011), but all screened backward for a 1-year period consecutively. For each centre, we present the approximate number of paediatric non-trauma cases seen in the ED during the recruitment period and the percentage of hospital admissions in this group, as well as the absolute number of secondary transfers by a team from the participating ED (*en dash* if not retraceable). Finally, we give the absolute number of severe outcome cases per centre, defined as cases that died or had a decrease in POPC of 2 or more

[a] Due to reasons of logistics and data quality, BW and TF only screened for a 9-month period

[b] Due to reasons of logistics and data quality, PS only screened for a 6-month period

Reported *P* values are only exploratory, and hence, no correction for multiple testing was done. Given the low number of 'severe outcome' patients within the sample, we refrained from any further logistic regression analysis [17].

Table 2 Inclusion and exclusion criteria for case selection [2, 7, 25]

Inclusion:

- Children between 44 weeks gestational age and 16 years
- Admission to hospital or death after presenting at the participating ED (<6 h before) or after secondary transport (admitted in the referring hospital <6 h at referral)
- With presumed 'community-acquired' sepsis
  - At least two of four SIRS criteria (as defined by Goldstein et al.) [7]
  - *And the* presumed presence of an infection (suspected or proven)
- And with any sign of decreased perfusion at any moment in the first 6 h of admission: (altered decreased mental status, capillary refill > 2 s or flash, diminished or bounding peripheral pulses, mottled cool extremities, decreased urinary output <1 ml/kg/h)

Exclusion

- Patients who are considered palliative
- Patients who have an uncorrected cyanotic heart disease
- Patients who have a clear other non-infectious cause for the presenting shock or for whom sepsis is not the primary diagnosis, e.g. bronchiolitis, seizure disorder, metabolic and/or cardiac aetiologies
- Insufficient data availability for screening or case report form

Results

Study subjects

Excluding two centres because of low data quality, 16 centres participated to the study (five Belgian, one Dutch, one French, one Saudi, one Turkish, one American, one British, one Spanish, one Portuguese, one Swiss, one Italian, one Israeli). Although most of these were tertiary referral hospitals, the number of children seen in the ED, the percentage of subsequent hospital admissions and the number of secondary transfers varied substantially (Table 1). Ultimately, 176 cases were included, 10.8 % of which after transfer from another hospital. Most cases presented during the day, with only 19.3 % between 22.00 h and 07.00 h. The median age of the sample was 2 years; the number of boys and girls equally distributed (Table 3). Significant comorbidity was present in 35.8 %; the baseline POPC showed moderate disability in 6.2 % and severe disability in 4.5 % of cases.

Table 3 Recognised covariates, grouped by PIRO classification, their total sample value in percentage %, median (+ IQR) or mean (+SD), as well as the values for the group with severe or good outcome and finally their statistical relation to severe outcome

Covariables	TOTAL [*n*=176]: %; mean (SD) or median (IQR)	Unknown, *n*	Severe outcome [*n*=10]	Good outcome [*n*=166]	[95 % CI]
Predisposition					
Age	med. 2 years (0.65–6)	0	0.65 years	2 years	[−0.08; 2.7]
Gender	49.5 % male	1	60 %	55.2 %	[−24.7 %; 30 %]
Severe comorbidity	35.8 %	11	33.3 %	35.9 %	[−24.8 %; 27.6 %]
First contact time T0	14 h (9–18)	2	14.5 h	14 h	[−3; 5]
First symptoms	med. 30 h before T0 (13–72)	9	42 h	30 h	[−24; 20]
Secondary transfer	10.8 %	3	20 %	10.4 %	[−6 %; 41 %]
Infection					
Meningococcal disease	23.6 %	70	14.3 %	24.2 %	[−26.9 %; 27.5 %]
Pneumococcal disease	10.4 %	70	14.3 %	10.1 %	[−10.7 %; 41.5 %]
Toxic shock syndrome	7.2 %	23	11.1 %	7 %	[−6.7 %; 36.9 %]
Site of infection: brain	15 %	23	33.3 %	13.9 %	[−3 %; 51.3 %]
Site of infection: line	5.2 %	23	11.1 %	4.9 %	[−4.2 %; 38.9 %]
Site of infection: urine	9.8 %	23	0 %	10.4 %	[−16.5 %; 19.9 %]
Host response					
White blood cell count	Mean, 13,980/μL (10,955)	8	12,932	14,040	[−6323; 8539]
White blood cell <1,000/μl	14.4 %	9	30 %	13.4 %	[−3.7 %; 47.5 %]
Thrombocytes <100,000/μl	25.9 %	10	44.4 %	24.8 %	[−7.9 %; 46.1 %]
INR (int. normal. ratio)	med. 1.61 (1.3–2)	79	1.71	1.6	[−0.86; 0.2]
Glycaemia	med. 109.5 g/L (90–152)	26	107	110	[−80; 40]
C-reactive protein	mean 18 mg/dl (14.2)	36	23.7	17.8	[−20.2; 8.4]
Organ dysfunction					
Any hypotension first 6 h	47.7 %	0	80 %	45.8 %	**[2.2 %; 51.2 %]***
Any oxygen sat. <90 % first 6 h	33.3 %	17	90 %	29.5 %	**[29.2 %; 72.3 %]*****
Intensive care/HDU admission	65.7 %	1	80 %	62.4 %	[−14.4 %; 34.5 %]
Need for mech. ventilation	25.9 %	0	100 %	21.3 %	**[50.4 %; 84.2 %]*****
Length of mech. ventilation	med. 0 h (0–0)	2	60	0	**[−96;−24]*****
Need for vasoactive medic.	42.9 %	0	100 %	39.2 %	**[32.3 %; 68.1 %]*****
Length of vasoactive support	med. 0 h (0–22)	8	59	0	**[−72; −22]*****
Creatinine	med. 0.47 mg/dl (0.3–0.85)	12	0.7	0.45	**[−0.01; −0.5]***
ALT	med. 48 IU/L (26–117)	89	79	46	[−66; 20]
Base excess (mean)	mean -8 (6.9)	48	−15.8	−7.5	**[−3.5; −13.1]*****
Lactate (mg/dl; mean)	mean 39.8 mg/dl (32.9)	63	77	37	**[17.2; 62.8]*****
Treatments provided					
Total fluid first 6 h	med. 30 ml/kg (18–60)	5	58	30	**[10; 50]****
Total fluid first 24 h	med. 40 ml/kg (19–66)	11	68	35	**[10; 65]****
Total fluid first 6 h>40 ml/kg	43.3 %	5	90 %	40.4 %	**[18.3 %; 61.7 %]****
Total fluid first 24 h>40 ml/kg	50 %	10	90 %	47.4 %	**[11.2 %; 55 %]***
Additional fluid bolus after 6 h	20.4 %	14	20 %	20.4 %	[−16.9 %; 31.3 %]
Total fluid first h>20 ml/kg	73.7 %	5	100 %	72 %	[−0.4 %; 35.4 %]
Any colloid bolus first 24 h	18.2 %	0	50 %	16.3 %	**[6.5 %; 60.8 %]***
Any blood products first 24 h	22.7 %	0	60 %	20.5 %	**[9.9 %; 63.8 %]***
Any packed red cells first 24 h	16.6 %	1	60 %	13.9 %	**[16.7 %; 70 %]***
Any plasma transf. first 24 h	11.4 %	0	30 %	10.2 %	[−0.3 %; 50.5 %]
Any platelet transf. first 24 h	7.4 %	0	20 %	6.6 %	[−1.8 %; 44.7 %]
Dopamine in first 24 h	29 %	0	60 %	27.1 %	**[3.1 %; 57.3 %]***
Dobutamine in first 24 h	15.9 %	0	60 %	13.2 %	**[17.4 %; 70.7 %]****

Table 3 (continued)

Covariables	TOTAL [n=176]: %; mean (SD) or median (IQR)	Unknown, n	Severe outcome [n=10]	Good outcome [n=166]	[95 % CI]
Noradrenaline in first 24 h	18.2 %	0	40 %	16.9 %	[−1.1 %; 52.6 %]
Adrenaline in first 24 h	13.6 %	0	40 %	12 %	**[4 %; 57.2 %]***
Any corticosteroids in first 24 h	14.9 %	2	40 %	13.4 %	**[2.5 %; 55.9 %]***

Covariates are presented with the units or groupings used. For each variable, the number of cases is given in which that variable is 'unknown' (not measured, not retraceable). For hypotension, we use the definitions from Goldstein et al. [7]. Fluid boluses are summated without taking into account maintenance fluids. For biochemical values, the worst value on day 1 counts. Causative agents or infectious sites are positive if proven biochemically, by culture or PCR. Depending on the properties of the variables, a Fisher exact, Student's t or Mann–Whitney U test is used for statistical inference. The 95 % confidence intervals [CI] are given for the differences between proportions, medians or means, respectively (see "Methods" section)

Significant relations are presented in bold

*P values <0.05, **P<0.01, ***P<0.001 are indicated here and are two-sided

Severity and outcome of paediatric community-acquired septic shock

Out of 176 cases, 5.7 % ended with severe outcome, either death (n=8) or survival with a decrease in POPC of two or more (n=2). Significant comorbidity was present in three of the eight deaths (acute lymphoblastic leukaemia (n=1), lymphoproliferative syndrome (n=1), severe pulmonary hypertension (n=1)), giving a mortality of 5.1 % in the group of children with significant comorbidity. Cardiopulmonary resuscitation (CPR) was performed in three children during the first hour of presentation and all died. In another three children, CPR was performed on PICU; one child died, but the other two survived with good outcome. Overall, 50 % of deaths happened in the first 48 h after presentation.

Although all cases had severe sepsis and signs of decreased perfusion, they differed in severity and were thus more or less likely to need medical interventions and/or end up with severe outcome (Table 3). For instance, hypoxemia was seen in 33.3 % and hypotension for age in 47.7 % [7]. Admission to PICU or a high dependency unit (HDU) was deemed necessary in 65.7 % of cases, and the median length of stay was 4 days. Total length of stay in hospital was far longer, ranging from 0 to 71 days, with a median of 7 days. A 7.5% were discharged to another hospital. Mechanical ventilation and vasoactive medications were initiated in 25.9 % and 42.9 % of cases, respectively. The median amount of fluid given in the first 6 h (excluding maintenance) was 30 ml/kg, with 16.9 % receiving less then 10 ml/kg bolus and 43.3 % 40 ml/kg or more. Only 20.4 % of patients received further fluid boluses after these 6 h. Colloids were given in 18.2 % of cases and blood products in 22.7 %. In addition, corticosteroids were given in 14.9 % and intravenous immunoglobulin in 5.7 %.

Pneumonia was diagnosed in 27.5 % and meningitis in 15 % of cases. A diagnosis of toxic shock syndrome was made in 7.2 %. Overall, a solitary viral aetiology was presumed or proven in 30 children; in the remaining, sepsis was mixed or rather bacterial in origin (proven by culture or polymerase chain reaction (PCR) or presumed based on typical clinical presentation). Table 4 summarizes the bacteria and viruses most frequently isolated. Antibiotics were started in all but six children (96.6 %), and this almost always within 3 h after T0. Antibiotic treatment was considered suboptimal (too late or not adequate for focus or patient history) in only six of the 176 cases. This had no impact on outcome in our sample, as all these cases survived with good outcome.

Table 4 Bacteria or viruses effectively isolated, in absolute numbers, as well as the respective number of severe outcome cases

Gram-positive, n=37		Severe outcome
Streptoccocus A	5	0
Streptoccocus B	3	1
Streptoccocus pneumoniae	11	1
Staphylococcus aureus	5	1
Staphylococcus epidermidis	7	1
Other Gram-positives	6	0
Gram-negative, n= 61		
Neisseria meningitidis	25	1
Escherichia coli	15	0
Klebsiella spp.	4	1
Pseudomonas spp.	6	1
Other Gram-negatives	11	0
VIRAL n= 19		
Influenza H1N1	5	0
Proven viral origin	14	0
Multiple virus and/or bacteria isolated, n= 9		
Unknown, n=70 (of which presumed viral n=15)		3

In some children, more than one type of bacteria and/or virus was isolated (most often two, but in two cases and three different agents). In others, a bacterial or viral infection was presumed on presentation but not identified in cultures or PCR (unknown)

Covariates and their relation with severe outcome

We used standard parametric and non-parametric testing to explore the relations between individual variables and the defined severe outcome (Table 3). Variables were grouped according to the PIRO classification: Predisposition [P], Infection [I], Response [R], Organ dysfunction [O] [15]. In addition, variables related to treatments initiated were described.

We only included variables for which sufficient data were recorded. Arterial oxygenation ($pa0_2$) was rarely available in the first hours, so oxygen saturation by pulse oximetry was used instead. A decreased consciousness was reported very frequently, but only in 91 cases was a Glasgow Coma Scale available. Overall, biochemical values were often missing, sometimes because they were irretrievable, but most often because they were not measured. Mixed venous saturation was reported in only 41 cases and then only from the PICU period. Recombinant activated protein C was started in one 2-year-old child with meningococcemia. Renal replacement therapy was initiated in five children, all of them survived with good outcome. Intravenous immunoglobulin was given in eight cases, with a severe outcome in one case.

Discussion

The current study aimed to describe a true baseline state, with parts of the resuscitation guidelines already being implemented and without any Hawthorne effect. On its own, this study is only exploratory in nature. With diminishing mortality and a long list of influencing variables, more than 2,000 children per group are easily needed to draw any strong conclusions [2, 7, 17]. Importantly, this will also depend on how severe sepsis and septic shock is actually defined [2, 7, 10, 24]. We used an 'early' definition of shock, based on signs of perfusion, allowing thus less severely ill patients into the sample. It is probably in these patients that timely and adequate treatment can make the largest difference. Severe sepsis is a spectrum of diseases and likewise treatments and outcomes will differ between patients and settings [1, 6, 12].

Outcome of community-acquired septic shock and the impact of selected covariables

The mortality in this sample was low. Moreover, only 1.2 % of the survivors showed a substantial decrease in POPC. One of the eight children who died did so before PICU admission and would have been missed if PICU had been the point of entry. As expected, the eventual patient outcome is strongly influenced by the case severity. Defining this severity is always difficult and flawed by issues of data availability, measurement accuracy, definitions and differences in local practice. For instance, first-hour intubation can be an indication of severe cardio-respiratory failure but can also be related to local protocols of early intubation in case of fluid resuscitation or secondary transfer. We used the PIRO classification to identify factors of influence in sepsis severity, need for therapy and final outcome [15].

By means of an elaborate CRF, we attempted to capture as much of the patient history as possible. The retrospective design precluded any definite conclusions regarding for instance time delays, since this might be equally related to decision making as to disease progression. The majority of children presented within 24 h of first disease symptoms and the majority of their medical interventions were done within the first 6 h after presentation. Time delays between onset of shock and first treatments have shown a clear relation with outcome [3, 14, 25]. In our data, no significant effect of any time measure on outcome was detected, perhaps because the overall quality of care provided was high.

None of the a priori patient characteristics (P), not even severe comorbidity, proved to be statistically related to outcome (Table 3). This clearly differs from previous studies, where mortality in children with chronic disease was sometimes more than twofold [2, 25]. Interestingly, both in these studies as in ours, the number of children with a chronic disease was well above 30 %. The nature of infection [I] also did not influence outcome. As in the study of Herrero et al., meningococcemia was by far the most frequent bacteria involved in our sample but not significantly associated with severe outcome [8].

Why some children eventually had a severe outcome is the result of a complex interaction between very different factors. Without doubt, there is a significant impact of the degree of host response [R], but for the variables we investigated we could not confirm this. However, we did see a significant relation between variables and outcome for those concerning organ dysfunction [O] or provided treatments. Treatments in turn are initiated depending on (the perception of) disease severity and the degree of organ dysfunction at that moment, thus only indirectly influencing outcome. A positive impact on outcome has been shown repeatedly for EGDT, but the question definitely remains which part of the proposed protocol really matters [4, 18]. In the meantime, the overall compliance with EGDT in adult and paediatric ED remains low. For instance, in our sample, only one in six cases had mixed venous saturation measured. Early vasoactive support and mechanical ventilation was started in 42.9 % and 25.9 %, respectively, and the length of both was significantly related with severe outcome. Again, this most likely reflects disease severity, rather than being a true treatment effect. This observation as such makes any treatment evaluation difficult. When we compared our data for instance with Larssen et al. who saw a positive effect on outcome if certain practice parameters

were met (antibiotics within first 3 h, lactate measured and 20 ml/kg saline bolus in first hour), we could not confirm their results [11]. The overall compliance rate with these parameters was very similar (55 %) and was almost always related to the absence of lactate measurement. However, in our population, the more severe cases (and definitely those with a severe outcome) actually received more fluid in the first hours, had lactate measured and timely antibiotics given. Lactate, often obtained from venous blood gas analysis, proved a good predictor for outcome in our sample and might prove a less invasive way of guiding therapy.

Strengths and weaknesses

With diminishing mortality and better overall quality of care, it will be increasingly difficult to study paediatric septic shock, owing to sample size, selection bias and ethical issues. Existing studies are not easy to compare due to differences in definitions, inclusion criteria, time to presentation, comorbidity, health care system and treatment variations [4, 6, 10, 12]. Having the ED as the point of entry, this study aimed to capture as well cases that died or were resuscitated before admission. In this sample, this is not a small group. In attempting to describe a 'true' picture of paediatric community-acquired sepsis, by using tertiary referral centres, the design may have induced selection bias. This was in part corrected by including secondary transfer cases. The screening in each participating centre had a different sensitivity, depending on data availability. Despite a tendency to 'over'-include patients, other cases (probably the less severe ones) could have been missed. The high accessibility of health care in most participating countries might further have induced very early medical intervention—avoiding the development of 'severe sepsis'—or early admission with sepsis development only on the ward. In this study, two deaths have not been included as they were referred after more than 6 h in the initial hospital. We chose a 6-h limit to avoid including hospital-acquired sepsis or non-sepsis-related shock and/or having problems with data quality [4]. Due to this approach, we might have missed cases that developed septic shock later in their disease course or were merely referred (too) late. Finally, while we included cases that were transported directly to ICU after a pre-hospital intervention by a team from the participating ED, most likely, we will have missed cases when, as is the habit in some centres, patients with chronic comorbidity directly go to the ward or ICU from home and so bypass our screening.

Due to the retrospective study nature, there were often incomplete fields in the CRF, sometimes because they were not retraceable but more often because they were not measured. While the general medical management was quite similar in the majority of centres, there were sometimes important differences in the amount of monitoring and tests ordered (for instance, blood tests, cultures or PCR). This might have induced bias when evaluating the relation between these tests and outcome as well as selection bias (case identification). Standard severity scores (e.g. PIM, PRISM) and end points used in other trials (e.g. shock reversal) are difficult to calculate or define in this setting. Importantly, both PIM or PRISM and shock reversal are highly influenced by these unknown data (e.g. arterial blood gas) as well as by treatment decisions made (e.g. timing of intubation). Treatment decisions in turn are equally related to disease severity and the local system of health-care organization.

This study was intended as a first part of a subsequent prospective trial. It identified however several problems that might preclude such a randomized control trial (RCT). The relatively low prevalence and high number of identified covariates will make it difficult to sufficiently power any trial. The differences in patient trajectory between regions and centres further complicate patient identification, thus inducing selection bias. Importantly, sepsis and shock are still poorly defined entities with different cut-offs used in different studies. Even with a similar clinical presentation, clearly, not every shock is the same and should be treated the same way [12]. Ideally, cases with too low or too high probability of survival should be excluded, but in that situation too strict inclusion criteria would generate results that cannot be extrapolated to the 'true world'. By doing this retrospective study, we tried to account for bias from unblinding and Hawthorne effects, but these will definitely be of influence in a prospective RCT. Finally, the already existing evidence for certain treatments (e.g. early appropriate antibiotics) might make it ethically difficult to withhold them in any control group, where on the other hand the costs of a large RCT likely to fail makes this study design also disputable [16].

It is thus our opinion that, although having their own confounders and difficulties, large prospective observational studies are more feasible and have the possibility to adequately describe these complex clinical problems [22].

Conclusion

Having the ED as the point of entry, this study of children with community-acquired septic shock aimed to also capture cases who died or were resuscitated before admission. Indeed, many children were seen and received treatment early in their disease course, thus avoiding any subsequent intensive care admission. In the majority of cases, most or all medical interventions were performed within the first 6 h of contact.

Overall, the outcome in this true world sample was very good. Several factors, as described within the PIRO classification, are presumed to be of influence. Where certain variables predispose children to become septic and shocked, we could

only confirm an impact on severe outcome for covariates that concern organ dysfunction or provided treatments.

This study served as a first exploratory part of a potential prospective RCT. We however argue why we think that such a trial might not be feasible. In our opinion, a large prospective observational study, if high in quality and using clear definitions and inclusion criteria, can provide important information to understand the problem of septic shock in children. A broad international paediatric emergency medicine research network should provide the necessary framework to initiate this.

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References

1. Becker JU, Theodosis C, Jacob ST, Wira CR, Groce NE (2009) Surviving sepsis in low-income and middle-income countries: new directions for care and research. Lancet Infect Dis 9:577–582
2. Brierley J, Carcillo JA, Choong K et al (2009) Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine. Crit Care Med 37:666–688
3. Cruz AT, Perry AM, Williams EA et al (2011) Implementation of goal-directed therapy for children with suspected sepsis in the emergency department. Pediatrics 127:e758–e766
4. de Oliveira CF, de Oliveira DS, Gottschald AF et al (2008) ACCM/PALS haemodynamic support guidelines for paediatric septic shock: an outcomes comparison with and without monitoring central venous oxygen saturation. Int Care Med 34:1065–1075
5. Fiser DH (1992) Assessing the outcome of pediatric intensive care. J Pediatr 121:68–74
6. Fisher JD, Nelson DG, Beyersdorf H (2010) Clinical spectrum of shock in the Pediatric Emergnecy Department. Ped Em Care 26:622–625
7. Goldstein B, Giroir B, Randolph A, Members of the international consensus conference panel (2005) International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med 6:2–8
8. Herrero M, Alcalde M, Gomez B et al (2012) Invasive bacterial infections in a paediatric emergency department in the era of the heptavalent pneumococcal conjugate vaccine. Eur J Em Med 19:89–94
9. Inwald DP, Tasker RC, Peters MJ, Nadel, PICS Study Group (2009) Emergency management of children with severe sepsis in the United Kingdom: the results of the Paediatric Intensive Care Society sepsis audit. Arch Dis Child 94:348–353
10. Klein Klouwenberg PMC, Ong DSY, Bonten MJC, Cremer OL (2012) Classification of sepsis, severe sepsis and septic shock: the impact of minor variations in data capture and definition of SIRS criteria. Intensive Care Med 38:811–819
11. Larsen GY, Mecham N, Greenberg R (2011) An emergency department septic shock protocol and care guideline for children initiated at triage. Pediatrics 127:e1585–e1592
12. Maitland K, Kiguli S, Opoka RO et al (2011) Mortality after fluid bolus in African children with severe infection. N Engl J Med 364:2483–2495
13. Miettinen OS, Nurminen M (1985) Comparative analysis of two rates. Stat Med 4:213–2
14. Ninis N, Phillips C, Bailey L et al (2005) The role of healthcare delivery in the outcome of meningococcal disease in children: case–control study of fatal and non-fatal cases. BMJ 330:1475–1481
15. Opal SM (2005) Concept of PIRO as a new conceptual framework to understand sepsis. Pediatr Crit Care Med 6(3 suppl):555–560
16. Paul M, Shani V, Muchtar E et al (2010) Systematic review and meta-analysis of the efficacy of appropriate empiric antibiotic therapy for sepsis. Antimicrob Agents Chemother 54:4851–4863
17. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR (1996) A simulation study of the number of events per variable in logistic regression analysis. J Clin Epid 49:1373–1379
18. Rivers PE (2010) Point: adherence to early goal-directed therapy: does it really matter? Yes. After a decade the scientific proof speaks for itself. Chest 138:476–480
19. SNAP 8.0 professional campus edition. Mercator Ltd., Bristol UK. ©2004
20. StatsDirect statistical software, version 2.7.8. StatsDirect Ltd. ©1990–2010
21. Stroud MH, Prodhan P, Moss MM, Anand KJ (2008) Redefining the golden hour in pediatric transport. Pediatr Crit Care Med 9:435–437
22. Vincent JL (2010) We should abandon randomized controlled trials in the intensive care unit. Crit Care Med 38(suppl):S534–S538
23. Watson SR, Carcillo JA, Linde-Zwirble WT et al (2003) The epidemiology of severe sepsis in children in the United States. Am J Respir Crit Care Med 167:695–701
24. Weiss SL, Parker B, Bullock ME et al (2012) Defining pediatric sepsis by different criteria: discrepancies in populations and implications for clinical practice. Pediatr Crit Care Med 13:e219–e226
25. Wolfler A, Silvani P, Musicco M et al (2008) Incidence of and mortality due to sepsis, severe sepsis and septic shock in Italian pediatric intensive care units: a prospective national survey. Int Care Med 34:1690–1697