Intensive Care Med (2017) 43:1686–1689
DOI 10.1007/s00134-017-4800-6

WHAT'S NEW IN INTENSIVE CARE

Paediatric sepsis: old wine in new bottles?

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The recent year marked a milestone in the field of sepsis in adults, with the revised Sepsis-3 definitions [1] and the updated Surviving Sepsis Campaign [2] published. But what about paediatric sepsis: how does Sepsis-3 fit in with what we know on paediatric sepsis and can we relate it to the way we treat children with sepsis?

First of all, what is sepsis in children? The 2005 consensus definition of paediatric sepsis required the presence of systemic inflammatory response syndrome (SIRS) in a child with suspected or proven infection. In view of the high mortality seen with sepsis, the importance of early recognition and intervention was emphasized. However, SIRS criteria are easily met in children with non-infectious diseases, and even infected children meeting these criteria often have nil organ dysfunction.

The Sepsis-3 definitions prompt clinicians and researchers to consider three key aspects when confronted with a patient evaluated for sepsis: (1) presence of *infection*, (2) development of a dysregulated response to infection leading to *organ dysfunction*, and (3) progression to severe disease associated with a substantial *increase in mortality*. From this perspective, a part of previous sepsis awareness programs in children were effectively centred around recognition of *infection* and early initiation of antimicrobial treatment, which remains one of the most powerful interventions to prevent disease progression. With regards to *organ dysfunction*, the Sequential Organ Failure Assessment (SOFA) score allows application to adults with pre-existing organ dysfunction, taking into account severity and number of organ dysfunctions. Unfortunately, SOFA was neither designed nor adapted for the paediatric age group. The Pediatric Logistic Organ Dysfunction Score-2 (PELOD-2) [3] currently represents the closest scoring system to SOFA, but remains to be validated prospectively in children with sepsis outside ICU. With regards to defining subsets of paediatric sepsis patients at substantially greater *mortality* risk, patterns characterizing paediatric sepsis have to be taken into account. First, a large proportion of sepsis deaths in previously healthy children occur within the first 48 h of PICU admission [4]. Ideally, sepsis severity definitions should thus capture patients at high risk of mortality as soon as possible after admission to Emergency Departments (ED) or PICUs. Second, hyperlactataemia may be the most powerful single routine clinical laboratory marker discriminating children at higher mortality risk, both in ED and PICU settings, with lactate levels at presentation >4 mmol/l seen in patients with a mortality of 10% and higher [5, 6]. Third, arterial hypotension remains a late sign of paediatric septic shock, and the triad of hyperlactataemia, hypotension, and vasopressor requirement is initially only present in a minority of children at time of ICU admission. Fourth, clinicians are exposed to an increasingly challenging cohort of children with complex comorbidities, who remain at substantial risk of death even if they survived the initial septic shock. Such late deaths may represent missed opportunities for damage control, pertinent to aspects such as source control, fluid management, and prevention of hospital-acquired secondary infections.

So where are we with treatment for paediatric sepsis? Prevalence and mortality of severe sepsis have become comparable to adults, yet, despite large campaigns addressing sepsis awareness, outcome improvement has been moderate at best. Interestingly, the reduction in sepsis mortality in PICU observed over the past decade is almost identical to that of children requiring PICU for non-infectious causes [7], suggesting that this survival

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Table 1 Review of studies assessing the impact of bundles of care in children with severe sepsis or septic shock

Author Journal, Year, Location, Ref no.	Design	Population Sample size	Intervention	Results on bundle performance	Results on patient outcome
Balamuth F Pediatr Crit Care Med, 2016 Philadelphia, US [8]	Retrospective Single centre	189 Children 56 days to 18 years With severe sepsis or septic shock	Protocolized sepsis guideline	121 children treated with the sepsis protocol 68 were treated with usual care	Children treated according to protocol were more likely to be organ dysfunction-free on day 1 (RR = 4.4, 95% CI: 2.0–9.7) and on day 2 (RR = 5.2, 95% CI: 2.5–10.8)
Cruz AT Pediatrics, 2011 Texas, US [9]	Prospective Quality Improvement program Single centre	191 encounters in 167 patients with suspected sepsis	Septic shock protocol Computerized triage tool Electronic alert High risk classification	Reduced median time from triage to first bolus from 56 to 22 min ($p < 0.001$) Reduced median time to first antibiotics from 130 to 38 min ($p < 0.001$)	Not assessed
Larsen GY Pediatrics, 2011 Utah, US [10]	Prospective Quality Improvement program Single center 2005–2007 Before 2008–2009 After	345	Septic shock protocol and care guideline Educational program Triage tool: VSs and physical examination Feedback	Compliance with 3 bundles care (20 mL/kg IVF within 60′, lactate assessment, and antibiotics within 3 h) increased with time: from 5% (before period) to 54% (after period)	Decreased of median hospital LOS from 181 to 140 h ($p < 0.05$) No difference on mortality rate
Paul R Pediatrics, 2014 Boston, US [11]	Prospective quality improvement program Single centre 2009–2011 Before 2011–2013 After	242 126 before intervention, 116 after intervention	Bundle of 5 time-specific goals (recognition of SS, vascular access, IVF, vasopressors, antibiotics) Plan-do-act-study-act cycles	100% adherence Reduced median time to IVF from 83 (43–145) to 33 min (0–68) Reduced median time to vasoactive agents from 90 (51–164) to 35 (14–86)	Increase of the number of cases between each death from severe sepsis and septic shock
Workman JK Pediatr Crit Care Med, 2016 Utah, US [12]	Prospective single center	321 met screening inclusion criteria	Care in compliance with SSC guidelines (117 children, 36%)	Shorter time to antibiotics administration (44 vs. 94 min, $p < 0.01$), Shorter time to vasoactive infusion (47.5 vs. 130 min, $p < 0.01$)	No difference on NP-MODS
Lane RD Pediatrics, 2016 Utah, US [13]	Prospective Quality improvement program (2007–2014) Single centre	1278 children with severe sepsis screening criteria	Septic shock pathway, screening tool/algorithm Compliance to bundle: timely antibiotics, IVF for signs of SS	Mean bundle adherence improved from 73 to 84%	Lower mortality in the bundle compliant group (1.2% vs. 4.2%, OR = 0.20 IQR (0.07–0.53))
Paul R Pediatrics, 2012 Boston, US [14]	Prospective quality improvement program Single centre 2009–2011 Pre	126 severe sepsis or septic shock	Bundle of 5 time-specific goals (recognition of SS, vascular access, IVF, vasopressors, antibiotics)	19% adherence to the global bundle	Reduced ICU and hospital LOS: 6.8 vs. 10.9 days, $p = 0.009$ and 5.5 vs. 6.8, $p = 0.035$ respectively

CI confidence interval, *IQR* interquartile range, *IVF* intravenous fluid, *LOS* length of stay, *NP-MODS* new or progressive –multi organ dysfunctions, *OR* odd ratio, *RR* relative risk, *SS* septic shock, *SSC* survival sepsis campaign, *VSs* vital signs

increase is likely due to a combination of improved practices. While randomized controlled pharmaceutical trials have consistently failed to demonstrate survival benefit, there is hope that the era of personalized medicine may help to identify subgroups of patients, where benefit will exceed harm of previously studied interventions. At this stage, getting the basics done right remains the best we can do, and scepticism as to how well we are performing is warranted, considering that audits often reveal median times from hospital presentation to first antibiotics exceeding the 1-h benchmark proposed in the Surviving Sepsis Guidelines [8]. Implementation of a sepsis protocol results in shorter time to first intravenous fluid and antibiotics administration as well as reduced time to vasoactive infusion [9–12]. Management of children with a sepsis protocol, based on SCCM-PALS guidelines, aiming to timely deliver antibiotics, adequate intravenous fluid resuscitation and vasoactive agents, has been shown to be associated with a decreased mortality [13, 14], a reduced length of hospital and PICU stay [10, 14], and a reduced number of children with organ dysfunction (Table 1) [8]. Increased compliance with sepsis bundles in paediatric emergency departments was associated with improved outcomes, highlighting the importance of bundle implementation and maintenance for performance metrics [15]. Although most studies in children were not powered to assess mortality as an outcome, the aggregate evidence strongly supports institutions to implement pediatric sepsis bundles, and screen tools for sepsis, as part of best practice-as recommended by the 2017 guidelines for adults [2].

So where to from here then? Future sepsis interventions need to identify the patient group most likely to respond to a specific intervention. First of all, is the patient actually suffering from an infection and can we speed up time to diagnosis allowing earlier appropriate antimicrobial treatment using molecular diagnostics? Second, can we develop faster, easily accessible markers and scoring systems to reliably identify children with dysregulated immune response? Can these help us to discriminate subgroups that benefit from more/less aggressive fluid resuscitation, early inotropes, and therapeutic adjuncts such as antitoxin therapy, immune modulators and extracorporeal life support? Third, maybe one of the most important paradigm changes the Early Goal Directed study promoted, was the realization that ED and ICU represent a care continuum rather than two separate entities. Using early serial observations to discriminate responders from non-responders to the initial sepsis bundle will help to develop powerful tools to rapidly identify patients who should receive early ICU support.

In conclusion, re-shaping our approach to infection, sepsis, and sepsis severity in children is not just an academic exercise but is key to developing screening tools for early recognition and designing trials addressing the right target groups. Thanks to the creation of large international paediatric research networks, these questions can now be addressed in collaborative studies.

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Acknowledgements
The authors would like to thank the section Infection, Inflammation and Sepsis and scientific members of the European Society of Paediatric and Neonatal Intensive Care (ESPNIC).

Compliance with ethical standards

Conflicts of interest
None of the authors has declared a conflict of interest.

Received: 13 March 2017 Accepted: 11 April 2017
Published online: 22 April 2017

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