Intensive Care Med (2020) 46:1264–1266
https://doi.org/10.1007/s00134-020-05946-2

EDITORIAL

Sometimes more is not always better: $ScvO_2$ monitoring in pediatric sepsis

Matthew D. Taylor[1] and Shane M. Tibby[2*]

Continuous central venous oxygen saturation ($ScvO_2$) monitoring became standard of care in adult septic shock following Rivers' 2001 study on goal-directed therapy [1]. Over the subsequent decade, care in adult sepsis improved significantly to the point where large multinational trials failed to replicate these results [2], likely because adults with sepsis are now recognized sooner and resuscitated early and more aggressively, such that $ScvO_2$ is largely normalized by the time of trial enrollment [3]. In comparison, pediatric studies using $ScvO_2$ goal-directed therapy are sparse, but have shown improvement in mortality, indicating continued utility of $ScvO_2$ [4, 5]. However, the pediatric studies are primarily in resource-limited settings, and are characterized by a high mortality in the control arms (Table 1) [4, 5]. The reasons for this are unclear, but may include late presentation, comorbidity (especially malnutrition), and a delay in recognition of signs of shock in children (who may be assessed initially by adult-trained frontline clinicians).

The preferred method of monitoring $ScvO_2$, intermittent vs continuous, remains debatable [4, 5]. Adult studies have compared predominantly continuous vs no monitoring (Table 1), whilst the few pediatric studies have used both intermittent and continuous. Although seemingly attractive, adoption of continuous $ScvO_2$ monitoring in young children has been hampered by lack of equipment, cost, and the need for a dedicated monitoring lumen in small central venous catheters (i.e., resulting in only double lumen catheters being available). In the January edition of *Intensive Care Medicine*, Sankar et al. present results from a randomized trial examining whether intermittent $ScvO_2$ monitoring is non-inferior to continuous monitoring in pediatric septic shock [6]. If proven non-inferior, this would justify preferential use of intermittent monitoring. The primary endpoint, reversal of shock at 6 h, was achieved in 19% (intermittent) and 36% (continuous), respectively. The authors failed to show non-inferiority, as the lower bound of the 95% confidence interval crossed the non-inferiority margin of − 20% (95% CI for absolute difference − 32% to − 4%). Thus, intermittent monitoring is not non-inferior to continuous. However, given that the upper margin of 95% CI did not cross zero (i.e., − 4%), can we postulate that continuous is actually superior to intermittent $ScvO_2$ monitoring? Current guidance suggests that it may indeed be justifiable to also interpret a non-inferiority trial in terms of a superiority design in certain scenarios [7]. Applying a standard, two-sided test of superiority (*prtesti*, StataCorp Texas) yields $P = 0.015$, consistent with evidence of superiority for continuous monitoring in Sankar's study.

Thus, is this evidence from a single study strong enough to recommend continuous over intermittent $ScvO_2$ monitoring in children? We would suggest "no, not yet", based upon two key areas: methodological aspects of the current study and generalizability.

Methodological aspects

The authors have conducted a challenging study to a very high standard. The non-inferiority design is appropriate, in that they are asking whether a cheaper option (intermittent) is no worse than the more expensive and technologically challenging option (continuous). However, the a priori acceptable limit for non-inferiority of − 20% could be considered as too liberal, and likely represents a trade-off between adequate power and deliverability. In comparison, as alluded to by the authors, an alternative design utilizing a non-inferiority margin of − 10% (which perhaps is more clinically relevant), with 80% power would require approximately 594 patients! This is

*Correspondence: shane.tibby@gstt.nhs.uk
[2] Evelina London Children's Hospital, London, UK
Full author information is available at the end of the article

Table 1 Relevant studies examining $ScvO_2$ monitoring in sepsis

Study	Year	Type of $ScvO_2$ Monitoring	*N*	Patient population	Mortality rate (%) (EGDT vs standard)	Positive impact	High-income country
EGDT [1]	1997–2000	Continuous	263	Adults USA	30.5 vs 46.5	Yes	Yes
ARISE [2]	2008–2014	Continuous	1600	Adults Australia	18.6 vs 18.6	No	Yes
ProMISE [2]	2011–2014	Continuous	1260	Adults UK	29.5 vs 29.2	No	Yes
ProCESS [2]	2008–2013	Continuous	1341	Adults USA	19.5 vs 18.9	No	Yes
SPROUT* [9]	2013–2014	Measured in 35% of patients	569	Children Six continents	25% (cohort study)	N/A	Mixed, but predominantly high income
Continuous $ScvO_2$ [4]	2004–2005	Continuous	102	Children Brazil	11.8 vs 39.2	Yes	No
Intermittent** $ScvO_2$ [5]	2010–2012	Intermittent	120	Children India	33.3 vs 54	Yes	No
Current study [6]	2015–2018	Continuous vs intermittent	152	Children India	43 vs 47 (continuous vs intermittent)	No	No

All bar two (*, **) are randomized controlled trials

*Point prevalence study

**Prospective cohort study

challenging: to provide context, the RESOLVE study in pediatric sepsis recruited 477 patients from 104 sites in 18 countries over 2.5 years [8].

A second methodological issue concerns potential for bias. This trial was unblinded, and the primary monitoring tool, $ScvO_2$, also forms part of the primary endpoint (one of eight components that must be met to define shock resolution). Of note, the shock variables yielding the largest differences between the two trial arms at 6 h were: tachycardia resolution (13%), capillary refill time normalization (8%) and $ScvO_2$ normalization (6%). Continuous $ScvO_2$ monitoring creates a potential for "intervention bias", in that the more a variable is measured, the higher probability of finding an abnormality and hence intervening in an attempt to normalize the variable. Of course, part of the point of continuous monitoring is to create more intervention, again creating a challenge in study design faced by the authors. The authors have helpfully re-analyzed the data on composite shock resolution at 6 h after excluding $ScvO_2$; this now produces a reduced difference of 11% (35% versus 46%) in favor of continuous group, which is no longer significant ($P = 0.17$).

Generalizability

The primary endpoint (shock resolution), is sensible; however, the observed 6-h shock resolution difference of 17% (19 versus 36%) in the current study did not translate into perhaps more clinically meaningful "hard" endpoints, such as mortality, length of stay, need for mechanical ventilation, renal replacement therapy or inotrope duration.

A second point impacting generalizability of this, and of all three pediatric $ScvO_2$ studies, is the high rate of mortality in the control groups: 39–54% [4–6]. These results are different from a large, multinational point prevalence study of pediatric sepsis (SPROUT) in 569 children from 128 PICU sites spanning 6 continents [9]. The SPROUT mortality rate was 25%, and did not differ between developed and resource-limited countries. More recent data from Europe have suggested that the mortality from septic shock is even lower, at 10%, further limiting generalizability [10].

Sankar et al. are to be commended for completing a well-designed study in a challenging setting and adding to the knowledge base for sepsis monitoring and treatment [6]. Unfortunately, as the results from this study are far from conclusive, this begs the obvious question: where to from here for future studies?

In settings where baseline mortality is high, a more detailed examination of factors contributing to mortality may be helpful. For example, the two groups in Sankar's study received broadly similar therapies; however, there was a suggestion that the continuous group received more fluid and inotropes early on (albeit not reaching statistical significance). Is it thus possible that survivors, regardless of study group allocation, received more components of a recognized sepsis bundle earlier [11]? If so, sustained health education and bundle compliance

monitoring could provide a cheaper alternative to $ScvO_2$ monitoring. In lower-mortality settings, evaluation of the "added value" for $ScvO_2$ monitoring, regardless of intermittent/continuous mode, is more problematic. The effect size for any hard endpoint is likely to be miniscule and any study would likely be hopelessly underpowered. Alternatives may include mechanistic endpoints (e.g., microvascular assessment), or avoidance of harm (e.g., does $ScvO_2$-guided resuscitation increase fluid overload). We certainly do not claim to have the answers here, and will defer back to the reader….answers on a postcard, please.

Author details
[1] Cohen Children's Medical Center, New Hyde Park, New York, USA. [2] Evelina London Children's Hospital, London, UK.

Compliance with ethical standards

Conflicts of interest
On behalf of all authors, the corresponding author (ST) states that there is no conflict of interest.

Publisher's Note

Received: 16 November 2019 Accepted: 21 January 2020
Published online: 11 February 2020

References

1. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M, Early Goal-Directed Therapy Collaborative Group (2001) Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 345:1368–1377
2. Angus DC, Barnato AE, Bell D, Bellomo R, Chong CR, Coats TJ, Davies A, Delaney A, Harrison DA, Holdgate A, Howe B, Huang DT, Iwashyna T, Kellum JA, Peake SL, Pike F, Reade MC, Rowan KM, Singer M, Webb SA, Weissfeld LA, Yealy DM, Young JD (2015) A systematic review and meta-analysis of early goal-directed therapy for septic shock: the ARISE, ProCESS and ProMISe Investigators. Intensive Care Med 41:1549–1560. https://doi.org/10.1007/s00134-015-3822-1
3. Nguyen HB, Jaehne AK, Jayaprakash N, Semler MW, Hegab S, Yataco AC, Tatem G, Salem D, Moore S, Boka K, Gill JK, Gardner-Gray J, Pflaum J, Domecq JP, Hurst G, Belsky JB, Fowkes R, Elkin RB, Simpson SQ, Falk JL, Singer DJ, Rivers EP (2016) Early goal-directed therapy in severe sepsis and septic shock: insights and comparisons to ProCESS, ProMISe, and ARISE. Crit Care 20:160. https://doi.org/10.1186/s13054-016-1288-3
4. de Oliveira CF, de Oliveira DS, Gottschald AF, Moura JD, Costa GA, Ventura AC, Fernandes JC, Vaz FA, Carcillo JA, Rivers EP, Troster EJ (2008) ACCM/PALS haemodynamic support guidelines for paediatric septic shock: an outcomes comparison with and without monitoring central venous oxygen saturation. Intensive Care Med 34:1065–1075. https://doi.org/10.1007/s00134-008-1085-9
5. Sankar J, Sankar MJ, Suresh CP, Dubey NK, Singh A (2014) Early goal-directed therapy in pediatric septic shock: comparison of outcomes "with" and "without" intermittent superior vena caval oxygen saturation monitoring: a prospective cohort study. Pediatr Crit Care Med 15:e157–e167. https://doi.org/10.1097/PCC.0000000000000073
6. Sankar J, Singh M, Kumar K, Sankar MJ, Kabra SK, Lodha R (2019) 'Intermittent' versus 'continuous' ScvO2 monitoring in children with septic shock: a randomised non-inferiority trial. Intensive Care Med 46(1):82–92. https://doi.org/10.1007/s00134-019-05858-w
7. European Medicines Agency (2000) Points to consider on switching between superiority and non-inferiority https://www.ema.europa.eu/en/documents/scientific-guideline/points-consider-switching-between-superiority-non-inferiority_en.pdf Accessed 12 Nov 2019
8. Nadel S, Goldstein B, Williams MD, Dalton H, Peters M, Macias WL, Abd-Allah SA, Levy H, Angle R, Wang D, Sundin DP, Giroir B, REsearching severe Sepsis and Organ dysfunction in children: a gLobal perspective (RESOLVE) study group (2007) Drotrecogin alfa (activated) in children with severe sepsis: a multicentre phase III randomised controlled trial. Lancet 369:836–843. https://doi.org/10.1016/S0140-6736(07)60411-5
9. Weiss SL, Fitzgerald JC, Pappachan J, Wheeler D, Jaramillo-Bustamante JC, Salloo A, Singhi SC, Erickson S, Roy JA, Bush JL, Nadkarni VM, Thomas NJ, Sepsis Prevalence, Outcomes, and Therapies (SPROUT) Study Investigators and Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network (2015) Global epidemiology of pediatric severe sepsis: the sepsis prevalence, outcomes, and therapies study. Am J Respir Crit Care Med 191:1147–1157. https://doi.org/10.1164/rccm.201412-2323OC
10. Boeddha NP, Schlapbach LJ, Driessen GJ, Herberg JA, Rivero-Calle I, Cebey-López M, Klobassa DS, Philipsen R, de Groot R, Inwald DP, Nadel S, Paulus S, Pinnock E, Secka F, Anderson ST, Agbeko RS, Berger C, Fink CG, Carrol ED, Zenz W, Levin M, van der Flier M, Martinón-Torres F, Hazelzet JA, Emonts M, EUCLIDS Consortium (2018) Mortality and morbidity in community-acquired sepsis in European pediatric intensive care units: a prospective cohort study from the European Childhood Life-threatening Infectious Disease Study (EUCLIDS). Crit Care 22:143
11. Samransamruajkit R, Limprayoon K, Lertbunrian R, Uppala R, Samathakanee C, Jetanachai P, Thamsiri N (2018) The utilization of the surviving sepsis campaign care bundles in the treatment of pediatric patients with severe sepsis or septic shock in a resource-limited environment: a prospective multicenter trial. Indian J Crit Care Med 22:846–851