Caution urged against reinterpreting Surviving Sepsis Campaign fluid bolus recommendations for resource-limited settings.

The recent viewpoint by Ranjit and colleagues[1] review the evidenced-based Surviving Sepsis Campaign (SSC) paediatric guidelines published in 2020 for haemodynamic support[2] indicating challenges in these recommendations in resource-limited settings[1] and, they recommend to individually tailor management and targeting physiological endpoints.

We agree that some of the guideline recommendations are not based on adequate evidence, however there has been one multicentre Phase III randomised controlled trial of fluid bolus trial in African Children (FEAST)[3] which directly informed these guidelines. The current SSC guideline indicates ' *In healthcare systems with no availability of intensive care and in the absence of hypotension, we recommend <u>against</u> bolus fluid administration while starting maintenance fluids (strong recommendation, high quality of evidence)'*[2]. The FEAST trial demonstrated harm in every subgroup (including large groups of sepsis and malaria) and for every definition of shock (except severe hypotension for which there was no control arm).

The authors of the viewpoint indicate that this is hard to implement but provide no evidence to support these statements. Furthermore, they highlight discordant views of the FEAST trial and challenge the secondary analysis of the terminal events. In the FEAST trial adverse events and deaths, possibly related to fluid overload (cerebral/pulmonary oedema), were actively solicited and reviewed by an independent Endpoint Review Committee (ERC), blind to arm. Based on pre-specified criteria, the ERC assigned the mode of death to be due to cardiovascular, respiratory or neurological causes, blind to randomised arm. This robust evidence showed that even a modest bolus of 20 mls/kg given over one hour resulted in excess deaths due to cardiac collapse (Figure) with no excess deaths due to respiratory or neurological events[4].

We are very concerned that this group of specialists included statements in the main body of the viewpoint text indicating '*Administration of an initial fluid bolus is often well tolerated, even in LMIC settings*'. The authors provide no reference to support this statement, and note that this recommendation is counter to what is recommended by the 2020 SSC guideline. We had previously estimated, whilst WHO continued to recommend fluid boluses (and recommendations such as those suggested by Ranjit and colleagues) that in sub-Saharan Africa this would result in an 33,000 excess deaths per million paediatric admissions with shock per year[5]. We recommend our African colleagues to take this into consideration when interpreting this current viewpoint and strongly urge them follow the evidence-based SSC guideline.

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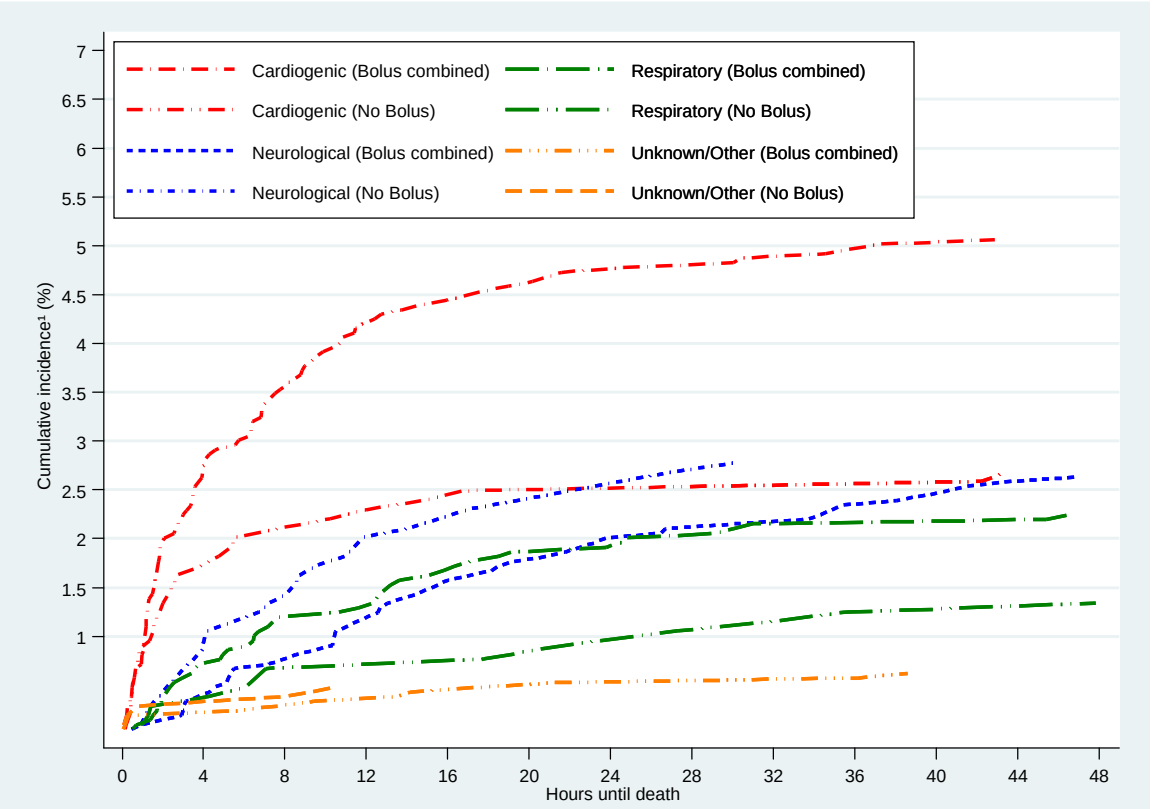
Figure: Cumulative incidence of mortality for bolus combined and no bolus arms by Terminal Clinical Events (TCE) for 297 children who died within 48 hours.



TCE		Randomisation arm					
	Total	Albumin bolus	Saline bolus	*Bolus combined*	No bolus	Sub-hazard ratio[2]	p-value
Total enrolled	3141	1050	1047	*2097*	1044		
Cardiogenic	123 (3.9%)	50 (4.8%)	46 (4.4%)	*96 (4.6%)*	27 (2.6%)	1.79 (1.17-2.74)	0.008
Neurological	63 (2.0%)	19 (1.8%)	25 (2.3%)	*44 (2.1%)*	19 (1.8%)	1.15 (0.67-1.98)	0.61
Respiratory	61 (1.9%)	21 (2.0%)	26 (2.5%)	*47 (2.2%)*	14 (1.3%)	1.68 (0.93-3.06)	0.09
Cardiogenic and Neurological[3]	11 (0.3%)	6 (0.6%)	4 (0.4%)	*10 (0.5%)*	1 (0.1%)	5.00 (0.64-39.04)	0.13
Respiratory and Neurological[3]	21 (0.7%)	8 (0.8%)	3 (0.3%)	*11 (0.5%)*	10 (1.0%)	0.55 (0.23-1.29)	0.17
Unknown/ Other	18 (1.7%)	7 (0.7%)	6 (0.6%)	*13 (0.6%)*	5 (0.5%)	1.30 (0.46-3.63)	0.62

[1]Cumulative probability of death from a specific TCE in the presense of other TCE's.
[2]The sub-hazard ratio for bolus combined vs no bolus takes into account the competing risks.
[3]For clarity in the graph, combined TCEs are redistributed so that cardiogenic and neurological are included with cardiogenic alone and neurological and respiratory (largely terminal lung aspiration in a comatosed child) are included with neurological alone.

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