Clinical Classification of Cold and Warm Shock: Is there a signal in the noise?

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"Finding patterns is easy in any kind of data-rich environment; that's what mediocre gamblers do. The key is in determining whether the patterns represent noise or signal."

Nate Silver 'The Signal and The Noise'(1)

The 2020 Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-associated Organ Dysfunction in Children(2) share much in common with the 2017 American College of Critical Care Medicine Clinical Practice Parameters for Hemodynamic Support of Pediatric and Neonatal Septic Shock. (3) One notable difference is the change in emphasis away from the bedside clinical classification of warm and cold shock:

Recommendation 25 'We suggest not using bedside clinical signs in isolation to categorize septic shock in children as "warm" or "cold" (weak recommendation, very low quality of evidence). This wording is cautious as is required in such guidelines, informed only by the available evidence. But many of us find this both surprising and uncomfortable. We tend to believe our eyes. We have all spent many hours at the bedside weighing combinations of heart rate, pulse pressure, diastolic pressure, capillary refill time and peripheral temperature or other factors. The recommendation seems to tell us not to believe what we see. Can this really be true?

Existing studies are clear that classification of shock based on bedside examination does not reflect the true hemodynamic state. Clinical estimations of cardiac output (CO) and systemic vascular resistance (SVR) agree very poorly with femoral thermodilution values. (4) Indeed patients maybe more correctly classified as 'warm' or 'cold' shock by the origin of their sepsis (community acquired vs. in-hospital) (5) than by clinical examination.

Maybe the problem is the simple one: doctors behave like humans do in general; our assessments may be flawed because of cognitive biases. We are prone to anchoring and availability biases: we prioritise the first, and most accessible, information we come across. We are all suckers for confirmation biases whereby we ignore subsequent information (e.g stroke volume estimation) that doesn't fit with our prior opinion. All of these may contribute when we are trying to integrate discordant information. For example, what weighting do we give to 'capillary refill time' as compared to 'pulse pressure' in determining shock type? Asking these questions highlights extensive gaps in in our knowledge (Table). Skin blood flow, as assessed by capillary refill time and extremity temperature, may not represent the true state of the circulation. After all muscle, gut, coronary, renal and brain blood flow all have different autoregulation processes.(6) Why do we presume that pressing on a finger or chest wall informs on the average of all of these? Further, the hemodynamic state may vary rapidly with time. Finally, our techniques for measuring cardiac output in children cannot be considered a 'gold standard'.

Walker and colleagues(7) consider some of these uncertainties, specifically the degree of agreement of individual clinical signs with the contemporaneous classification of 'shock type' in children with sepsis. While there are limitations of in the study, (retrospective design, single center, exclusion of children with variable shock types in the first hour, no direct measures of shock type), there are also important strengths (large numbers, systematic assessment on a sepsis pathway, *a priori* standards for each parameter to support a shock type classification, and a rigorous statistical approach). The individual clinical signs of shock type showed poor agreement with each other and variable agreement with the summary variable of 'shock type'. Intriguingly, comparison between the choice of vasoactive and clinical outcome revealed no suggestion that matching vasoactive to the clinical summary state of 'shock type' was beneficial. Elegantly the investigators also report on repeated simulations replacing the clinicians' classification of shock type with a random allocation. These confirmed that extremity temperature, capillary refill, and pulse strength were the factors that drove clinicians to allocate a patient as warm or cold shock. In contrast pulse pressure and diastolic blood pressure did not contribute to this decision. Interestingly, the vasoactive choice was as likely to match the random shock classification as the clinicians' allocation.

These data add weight to the view that we are wasting our time on bedside shock type classification. Maybe. However, this could all be a *'signal-to-noise'* problem.

A short digression: the recent ANDROMEDA-SHOCK study examined the effect of resuscitation targeting standardised assessment of peripheral perfusion vs serum lactate in adults with septic shock. (8) By day 28, 34.9% of the peripheral perfusion group and 43.4% of the lactate group had died (hazard ratio, 0.75 [95% CI, 0.55-1.02]; P = 0.06; risk difference, −8.5% [95% CI, −18.2%-1.2%]). This point estimate suggests an important benefit of targeting capillary refill; however, others would note the confidence interval and p-value as consistent with the binary view of this being a negative trial. Here again we can indulge our confirmation bias and take what we prefer from this experiment. Our conclusion is that in adults, very careful and standardised assessment of peripheral perfusion *may* provide an important additional resuscitation target in high risk patients.

These result conflict with the pediatric data discussed here. Given the confusion highlighted by Walker and colleagues, how would we plan equivalent trials in children? Perhaps we simply haven't filtered out sufficient noise from our vital signs to optimise any signal. For example, we rarely consider heart rate and blood pressure in the formal context of centiles for age or disease states. The opportunity here is to use tools from statistics, computing, mathematics to fill the gap. (9-11) Computational systems which integrate individual patient vital signs with predictive models of physiology at the bedside have the potential to add precision to our clinical decision making. We also know little about the optimal physiological targets for most of the vital signs we record. Such questions are the subject of upcoming randomised trials funded by the UK National Institute of Health Research from the UK Paediatric Intensive Care Society Study Group (Oxy-PICU saturation

targets and PRESSURE mean arterial pressure targets). These approaches may combine to reduce noise and amplify the signal for clinicians at the bedside.

Table: Challenges to defining and treating shock type based on clinical assessment.

CO = Cardiac output SVR = systemic vascular resistance

Challenge	Impact	Mitigation
Little standardisation of clinical examination (e.g central vs. peripheral capillary refill time)	Individual clinicians may assess elements of the clinical examination differently	Standardisation of clinical examination (e.g. peripheral perfusion assessment in ANDROMEDA-SHOCK)(8)
Weighting of elements of clinical examination unknown Individual elements of clinical examination may be discordant	Same findings on examination can lead to different conclusions	Further work similar to Walker et al (7)including direct measures of CO/SVR to determine features most predictive of warm or cold shock including hierarchy of these factors
Skin perfusion may not reflect vital organ perfusion or systemic blood flow	Clinical examination does not reflect the true hemodynamic state.	Definition of factors that confound clinical examination (e.g. a cold room or following prolonged exposure) and incorporate them into robust physiological models
Haemodynamic state can vary rapidly with time and therapy	Choice of vasoactives may be out of date	Beware one-time measures of CO/SVR in a dynamic situation. Consider repeated or continuous measures in high risk cases.
Precise and accurate measures of CO / SVR are not generally available in critically ill children	Incorrect values may misguide treatment	Treat estimates of CO/SVR as broad categorisation (high / medium / low) and as a tool for recognising trends.
Vasoactive medications are not 'clean drugs' (mixed alpha/beta 1 and 2 effects at different doses) Individuals respond differently to similar doses of vasoactive medications	Complex to match intended with unwanted effects.	Constant monitoring and reassessment. Preference for drugs with rapid offset unless hemodynamic state is both well-defined and not varying rapidly
Optimal therapeutic haemodynamic goals in children are unknown.	Potential to cause harm by over- or undertreatment with fluid and vasoactives.	Computational models of vital sign data to define clinical parameters in context of age and disease

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