Fluid resuscitation in diabetic ketoacidosis and the BSPED guidelines: what we still don't know

Mark J Peters 1,2

¹Great Ormond Street Institute of Child Health, UCL, London, UK

²PICU, Great Ormond Street Hospital For Children NHS Foundation Trust, London, UK

Correspondence to

Dr Mark J Peters, Great Ormond Street Institute of Child Health, UCL, London WC1N 3JH, UK; mark.peters@ucl.ac.uk

Received 17 October 2020

Revised 20 November 2020

Accepted 10 February 2021

Published Online First

19 March 2021

The 2020 British Society for Paediatric Endocrinology and Diabetes (BSPED) guideline differs from the previous iteration and the more conservative National Institute of Health and Care Excellence 2016 guideline for diabetic ketoacidosis in children and young people (2015). It recommends a more liberal approach to initial fluid resuscitation and a reduced enthusiasm for using inotropes. This contrasts with shock resuscitation guidance elsewhere. In septic shock acute fluid resuscitation is now recommended to be more selective and conservative, and the early use of vasoactive drugs is supported.¹

So why did BSPED make a new recommendation for diabetic ketoacidosis (DKA)? Recent correspondence² suggests that it arose from: (A) expert interpretation of physiological data suggesting hypoperfusion as the precursor to cerebral oedema; (B) the Pediatric Emergency Care Applied Research Network (PECARN) fluid in DKA randomised controlled trial³ and (C) regional audit data. Such evidence is not compelling.

Physiological and imaging data suggest cerebral hypoperfusion may *not* be present at baseline. In 1948, Kety *et al*⁴ measured cerebral blood flow (CBF) in adults with DKA: *none* had CBF below the normal range and several were hyperaemic. Glaser *et al*⁵ interpreted MRI scans of patients in DKA as suggesting *increased* CBF. Some of this excess may have resulted from treatment. If concern about hypoperfusion is key, it is not clear why increasing perfusion with inotropes rather than fluid is discounted. Inotropes have the advantage of not reducing osmolarity, and rapid falls in osmolarity probably contribute to cerebral oedema. The PECARN study³ was prompted by concerns about this mechanism. It compared high and lower volume and tonicity fluid regimens in children

with DKA. There was no difference in the primary outcome of significant neurological deterioration. Children at high risk of cerebral oedema at baseline were excluded, and clinically evident brain injury was so rare: 12 episodes (0.9%) that the study was not powered to inform on relative risk. Last, use of unpublished audit data in the development of guidelines is unconventional. Most guidelines state the methodologies in advance and specifically avoid the use of non-peer-reviewed data as a potential source of bias.

Perhaps something more fundamental needs to be considered when discussing intravenous fluid resuscitation. This is a very difficult area to study. There is no high-performing, or universally accepted, definition of shock in children; hypotension definitions are problematic, and the severity of shock does not always relate to the probability of a poor outcome; positive acute physiological responses (improvements in heart rate and perfusion) correlate poorly with outcomes, the risks and benefits of fluid resuscitation are highly sensitive to the *cause* of shock (eg, myocarditis less benefit than hypovolaemia), the timing (early resuscitation more benefit than late resuscitation) and the healthcare system in which the resuscitation is being provided (greater risk when no access to positive pressure ventilation, lower risk on an intensive care unit).¹ Defining shock is especially problematic in DKA. Acidosis and hypocarbia cause a range of clinical features *independent* of tissue oxygen delivery, for example, tachycardia, tachypnoea and reduced skin perfusion,^{6,7} and adaptive metabolism (eg, raised serum lactate⁸) that can easily be misinterpreted as signs of shock.

The degree of physiological disturbance with severe acidosis, tachypnoea and poor perfusion would be associated with very

<http://dx.doi.org/10.1136/edpract-2020-320076>

<http://dx.doi.org/10.1136/edpract-2020-320077>

<http://dx.doi.org/10.1136/edpract-2021-321669>

Check for updates

© Author(s) (or their employer(s)) 2021. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Peters MJ. *Arch Dis Child Educ Pract Ed* 2021;**106**:223–225.

Figure 1 Randomised controlled trials of liberal versus conservative fluids resuscitation: relative risk of mortality in the more liberal group is shown against the mortality in the more conservative fluid group. There is a strong ($r=0.69$) correlation between the log of the relative risk and the conservative group mortality with the equation $y=0.69e^{0.026x}$ that is unlikely to be due to chance ($p=0.02$). In other words, fluid resuscitation is effective in shock with a high mortality risk but harmful in low-risk populations.^{10 11 13–16} DKA is a very low-risk population.

poor prognosis *if* it resulted from septic shock or other systemic insults. DKA is different. How different can be illustrated with the physiologically based scoring system the Paediatric Index of Mortality 3. The values of a base excess -30 mmol/L, with an arterial partial pressure for oxygen (PaO_2) of 10 kPa in 25% oxygen and a systolic blood pressure of 100 mm Hg estimates a risk of mortality of 9.7% *without* DKA but only 1.2% *with* DKA.⁹ This estimate fits with the reported mortality of DKA (0.5%–2%).

‘What is the risk of death *from shock*?’ should be the key question when balancing the risks and benefits of fluid resuscitation. Trial evidence illustrates this point (figure 1). ‘Early-goal directed therapy’ (EGDT) describes an approach of increased monitoring for subclinical shock. EGDT results in more aggressive fluid resuscitation and dramatically improved outcome in randomised trials in adults and children. However, this effect is *only* seen when the control group mortality is very high (39%–49%).^{10 11} When similar trials were repeated in lower risk populations (control group mortality 18%–22%), they offered no net benefit.^{12–14} Indeed, the only large high-quality trial of fluid resuscitation in children observed that fluid *increased* mortality in acute infective illness. Maitland’s Fluid Expansion as Supportive Therapy study had a ‘no fluid bolus group’ mortality of 7% and fluid resuscitation *increased* this to $>10\%$.¹⁵ So, the ‘space’ for fluid resuscitation to improve outcomes was relatively limited, and the potential for harm was high. Of relevance to the management of fluids in DKA is that it carries a low risk of mortality—only a tiny subset of whom die from shock—on the continuum shown in the exploratory plot (figure 1). Therefore, potential opportunities for aggressive fluid resuscitation to improve outcomes are limited, and the potential for

harm appears high. An aim for future guidelines might be a more approach stratified for the specific risks of cerebral oedema versus shock in an individual case.

What we don’t yet know about the BSPED guidelines is: why they choose to recommend more aggressive resuscitation in a low-risk situation? Fluids carry a potentially important risk of harm even in the absence of the predominant additional risk of cerebral oedema. The general principle should be that we do not intervene without evidence. We don’t yet know where the balance of risks and benefits sits for early volume expansion in DKA. But any change requires a justification than can be considered by the potential users of the guideline.

Twitter Mark J Peters @pus27

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Commissioned; externally peer reviewed.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iD

Mark J Peters <http://orcid.org/0000-0003-3653-4808>

REFERENCES

- Weiss SL, Peters MJ, Alhazzani W, *et al.* Surviving sepsis campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. *Intensive Care Med* 2020;46:10–67.
- Wright N, Thomas R. Response to: management of fluids in paediatric diabetic ketoacidosis: concerns over new guidance. *Arch Dis Child* 2020;105:1020–1.

- 3 Kuppermann N, Ghetti S, Schunk JE, *et al.* Clinical trial of fluid infusion rates for pediatric diabetic ketoacidosis. *N Engl J Med* 2018;378:2275–87.
- 4 Kety SS, Polis BD, Nadler CS, *et al.* The blood flow and oxygen consumption of the human brain in diabetic acidosis and coma 1. *J Clin Invest* 1948;27:500–10.
- 5 Glaser NS, Wootton-Gorges SL, Marcin JP, *et al.* Mechanism of cerebral edema in children with diabetic ketoacidosis. *J Pediatr* 2004;145:164–71.
- 6 Lillie J, Boot E, Tibby SM, *et al.* Management of fluids in paediatric diabetic ketoacidosis: concerns over new guidance. *Arch Dis Child* 2020;105:1019–20.
- 7 Mitchell JH, Wildenthal K, Johnson RL. The effects of acid-base disturbances on cardiovascular and pulmonary function. *Kidney Int* 1972;1:375–89.
- 8 Cox K, Cocchi MN, Saliccioli JD, *et al.* Prevalence and significance of lactic acidosis in diabetic ketoacidosis. *J Crit Care* 2012;27:132–7.
- 9 Straney L, Clements A, Parslow RC, *et al.* Paediatric index of mortality 3: an updated model for predicting mortality in pediatric intensive care*. *Pediatr Crit Care Med* 2013;14:673–81.
- 10 Rivers E, Nguyen B, Havstad S, *et al.* Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001;345:1368–77.
- 11 de Oliveira CF, de Oliveira DSF, Gottschald AFC, *et al.* ACCM/PALS haemodynamic support guidelines for paediatric septic shock: an outcomes comparison with and without monitoring central venous oxygen saturation. *Intensive Care Med* 2008;34:1065–75.
- 12 ARISE Investigators, ANZICS Clinical Trials Group, Peake SL, *et al.* Goal-Directed resuscitation for patients with early septic shock. *N Engl J Med* 2014;371:1496–506.
- 13 The ProCESS Investigators. A randomized trial of protocol-based care for early septic shock. *N Engl J Med* 2014;370:1683–93.
- 14 Mouncey PR, Osborn TM, Power GS, *et al.* Trial of early, goal-directed resuscitation for septic shock. *N Engl J Med* 2015;372:1301–11.
- 15 Maitland K, Akech SO, Russell EC. Mortality after fluid bolus in African children. *N Engl J Med* 2011;365:1348–53.
- 16 Hjortrup PB, Haase N, Bundgaard H, *et al.* Restricting volumes of resuscitation fluid in adults with septic shock after initial management: the classic randomised, parallel-group, multicentre feasibility trial. *Intensive Care Med* 2016;42:1695–705.