

## PEER REVIEW HISTORY

BMJ Paediatrics Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Update and harmonisation of guidance for the management of diabetic ketoacidosis in children and young people in the UK.
<b>AUTHORS</b>	Rugg-Gunn, Charlotte EM Deakin, Mark Hawcutt, Daniel B

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Reviewer name: Dr. Gerald Jaspers Institution and Country: Radboudumc, Netherlands Competing interests: None
<b>REVIEW RETURNED</b>	11-Mar-2021

<b>GENERAL COMMENTS</b>	<p>My biggest concern: it is a nice summary of the better concordance and the differences of 2 UK guidelines on DKA. However this article is submitted as a review article and it should contain (as the author guideline states): the pros and cons of any contentious or uncertain aspect should be described. the difference between the 2 UK guidelines are described, there is however no pro/con argumentation. It is more of a short practical summary and background for physicians with little experience in treatment of DKA.</p> <p>2. What I would add to the discussion (from an international perspective): why are there 2 national guidelines? I take it the BSPED is involved in the development of the NICE guideline. I would argue that it is in a waste of effort, money and time that 2 major guidelines were developed.</p> <p>3. Key message 1 is not a key message from the article, it is part of the introduction to the subject.</p> <p>4. Key message 4 is not a key message, but more of a general statement. I too hope that adherence to guidelines contribute to a reduction of death of cerebral edema, but this article provides no evidence to support this. I would rephrase to something like 'Careful monitoring and adherence to these national guidelines is recommended and hopefully contributes to a reduction in deaths secondary to cerebral edema'.</p> <p>5. Key message 5 'further research...' is a message without meaning in my opinion. Further research is always necessary. Advise: rephrase to where future research should be focussed on. In my opinion it should not be focussed on efficacy (it will probably be efficacious for the greatest part of the DKA population). It should be focussed on its efficacy in preventing cerebral edema from developing, especially compared to previous the version of the guidelines.</p> <p>6. the ISPAD guideline is mentioned several times. It should be added to the reference list.</p> <p>7. the additional learning points: these are important points in the treatment of DKA. However they seem rather randomly picked and do not focus on the essence of the review: fluid management in DKA, but rather reflect a wide range in the treatment of DKA (initial stage and final stage) and there is no debate regarding the pro's and con's of their strength (again review argument).</p> <p>8. quite a number of references on the list are not in the text, at least: 9, 10, 13, 14, 15, 16 17 are not mentioned.</p>
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	9. the title doesn't cover the message: it is a comparison of 2 major UK guidelines. Harmonisation of DKA management in children and young people: comparing 2 updated UK guidelines
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<b>REVIEWER</b>	Reviewer name: Dr. Stephen Tomlin Institution and Country: Great Ormond Street Hospital for Children, United Kingdom of Great Britain and Northern Ireland Competing interests: None
<b>REVIEW RETURNED</b>	19-Mar-2021

<b>GENERAL COMMENTS</b>	<p>This paper does what it says on the tin and is a review of how 2 standards have now "thankfully" come together. It is set out totally logically, highlighting how and why the changes have come together, commenting on the few minor differences still remaining and pointing out what the changes mean to practice.</p> <p>I think it will be a good read to many involved in paediatric care at all levels on a topic that has caused real issues for many years and without the resolution could be deemed to have endangered lives and been an unethical scenario in practice.</p> <p>I only have 2 points to raise:</p> <ol style="list-style-type: none"> <li>1. Saline is described in 3 ways through out the document - Saline, NACL and Sodium Chloride. Can I suggest that we have harmonisation of this nomenclature and use the standard of Sodium Chloride 0.9% throughout.</li> <li>2, One of the key messages (line 28) is to have "close supervision by seniors". I think this needs a little more definition. This is alluded to through out the document and uses other statements: seniors; senior paediatricians; responsible senior paediatricians and senior, experienced paediatricians. It is not clear what is being alluded to - either directly in this document or f</li> </ol>
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<b>REVIEWER</b>	Reviewer name: Dr. Nicola Heddy Institution and Country: Great Ormond Street Hospital for Children, United Kingdom of Great Britain and Northern Ireland Competing interests: None
<b>REVIEW RETURNED</b>	21-Mar-2021

<b>GENERAL COMMENTS</b>	<p>Overall good summary of new guidelines and the importance to treating clinicians and their patients of guideline harmonisation. Important recognition of the lack of data on cerebral oedema and importance of collecting this. Minor amendments suggested as below primarily for clarity.</p> <p>Page 3. Line 20. Discordance does have potential to increase risk of cerebral oedema but more directly causes problems with guideline adherence and agreement between clinicians in practice as you note in your conclusion/recommendations.</p> <p>Page 3. Line 19. Consider mentioning ISPAD guidelines at this point as it is referenced later.</p> <p>Page 4. Line 47. Agree that PECARN has been key in changing the guidelines but would suggest the rationale was that there was no significant difference in the groups of rapid and slower fluid administration rather than the points listed although these are true.</p> <p>Page 5. Line 4-8. Consider re-phrasing for clarity.</p> <p>Page 5. Line 11. H-S Formula is not used to calculate deficit but maintenance.</p> <p>Page 5. Line 31. Suggest use full words sodium chloride not NaCl</p> <p>Page 5. Line 43. 'perhaps an adolescent' sounds like there is doubt about whether the patient is an adolescent rather than that the doubt lies in whether the higher rate should be used. Consider re-phrase for clarity.</p> <p>Page 5. Line 43. 'pump' consider stating 'insulin pump' or more accurately 'continuous subcutaneous insulin infusion' or using quotation marks.</p>
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	<p>Page 5. BSPED does not state that it should be continued but that it may be continued. NICE also states to think about this in conjunction with a specialist.</p> <p>Page 6. 0.9% saline. In some places you use NaCL, some sodium chloride, some saline. Should be standardised.</p> <p>Page 6. Line 3. Inotropes considered, not necessarily given.</p> <p>Page 6. Line 4. BSPED also state maximum of 97th centile for age – more likely to be encountered clinically and easy to miss.</p> <p>Page 6. Consider role of 'additional learning points' section – doesn't flow well with remainder of article in my opinion.</p> <p>Page 6. Line 58. Important point, shame to leave it at the end?</p>
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## VERSION 1 – AUTHOR RESPONSE

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C.Rugg-Gunn@student.liverpool.ac.uk

Prof. Saskia de Wildt  
Associate Editor, BMJ Paediatrics Open

Dear Prof. de Wildt,

Thank you for your kind consideration of our manuscript entitled "Update and harmonisation of guidance for the management of diabetic ketoacidosis in children and young people". We greatly appreciate the reviewers' very helpful and constructive comments.

We have carefully considered all the comments and amended the manuscript accordingly. We believe that the manuscript has improved significantly as a result, and we are grateful to you for further considering publication in BMJ Paediatrics Open.

The reviewer comments below have been indented and the response to each comment follows. Any changes made to the manuscript have been highlighted in bold font.

Editor in Chief comments:

1. Title

Add "in the UK"

We agree that this provides greater clarity to the audience. The title has been amended to reflect this, "Update and harmonisation of guidance for the management of diabetic ketoacidosis in children and young people in the UK".

Create a new table highlighting key recommendations of both guidance

We have introduced a new table, with important comparators taken from both guidelines. We have structured this in the form of a single guideline for the management in a bid to provide further understanding of the similarities and differences between the two guidelines. It is referenced in the main text in Updated Guidance and it is detailed below.

Table 1: Flowchart identifying the similarities and differences between the updated 2020 guidelines

NICE(1)

BSPED(2)

If in shock - 20ml/kg bolus of 0.9% sodium chloride.

Not in shock – 10ml/kg bolus of 0.9% sodium chloride.

When calculating the total fluid replacement, subtract any initial bolus volumes from the total fluid deficit (if in shock – do not include the bolus volumes).

In shock – bolus given as soon as possible.

Not in shock – bolus given over 30 minutes. In shock – bolus given over 15 minutes.  
 Reassess and further boluses of 10ml/kg up to a total of 40ml/kg – then consider inotropes.  
 Not in shock - bolus given over 60 minutes.  
 Fluid requirement = Deficit + Maintenance  
 Hourly rate = ((Deficit – any initial bolus) / 48 hours) + Maintenance per hour  
 Mild to moderate DKA (blood pH 7.1 or above) = 5% dehydration.  
 Severe DKA (blood pH below 7.1) = 10% dehydration. Mild DKA (venous pH 7.2-7.29 or bicarbonate <15 mmol/l) = 5% dehydration.  
 Moderate DKA (venous pH 7.1-7.19 or bicarbonate <10mmol/l) = 7% dehydration.  
 Severe DKA (venous pH less than 7.1 or bicarbonate <5 mmol/l) = 10% dehydration.  
 Fluid maintenance: 0.9% sodium chloride without added glucose, Holliday-Segar formula.  
 (100mg/kg for the first 10kg, 50ml/kg for the second 10kg, and 20ml/kg for each subsequent kg)  
 Given over 48 hours  
 Maximum weight of 75kg in the Holliday-Segar formula Maximum weight of 80kg or 97th centile weight for age (whichever is lower) in the Holliday-Segar formula  
 All fluids (except any initial boluses) contain 40mmol/litre (or 20mmol/500ml) potassium chloride, unless they have renal failure or hyperkalaemia. Do not delay potassium replacement.  
 Monitor serum sodium levels - they should rise as DKA is treated. Falling serum sodium is a sign of possible cerebral oedema. Use corrected sodium values = measured sodium + ((glucose-5.6)/3.5).  
 Start intravenous insulin infusion 1-2 hours after beginning intravenous fluid therapy, disconnect continuous subcutaneous insulin infusion (CSII).  
 Use a soluble insulin infusion at a dosage between 0.05 and 0.1 units/kg/hour. Do not give bolus doses of intravenous insulin. 0.05 units/kg/hour would be sufficient in most cases, but consider 0.1 units/kg/hr in severe DKA.  
 When plasma glucose concentration falls below 14mmol/litre change fluids to 0.9% sodium chloride with 5% glucose and 40mmol/litre potassium chloride.  
 Once ketones <1.0mmol/l, consider switching from intravenous to subcutaneous insulin.

Additional learning points should be earlier in the article.

The learning points have been reviewed and key components restructured within the “Updated guidance” section of the article. On the advice of the reviewers, we have removed the learning points with limited relevance.

Expand your paper considerably as suggested by reviewers.

We have taken into consideration all comments submitted and have expanded the paper.

Associate Editor comments:

Also please check other non-UK guidelines for DKA and compare these as well. Dependent on your findings this may also guide your conclusion.

We have reviewed non-UK guidelines and expanded upon the comparison between these and the UK based guidelines. Where conflict still remains between the NICE and BSPED guidelines, these additional guidelines may provide some clarity and ultimately guide healthcare professionals to a conclusion. Subsequently, we have reviewed the consensus guidelines for the International Society for Pediatric and Adolescent Diabetes (ISPAD) and the European Society for Paediatric Endocrinology and the Lawson Wilkins Pediatric Endocrine Society (ESPE/LWPES) guidelines and The Royal Children’s Hospital Melbourne (RCH) on diabetic ketoacidosis in children and adolescents. These were chosen due to their wide-reaching global impact with respect to the ISPAD and ESPE/LWPES guidance, and RCH for their comparable demographics and healthcare systems to the UK. The additional paragraphs have now been added under an additional subheading entitled “Comparison to International Guidance” and is also given below.

“The new guidelines released by both NICE and BSPED read similarly to those of non-UK based origin. The 2018 consensus guidelines released by ISPAD in conjunction with the European Society for Paediatric Endocrinology and the Lawson Wilkins Pediatric Endocrine Society (ESPE/LWPES) are used globally as standard guidelines for paediatric DKA management. Although the updated NICE and BSPED guidelines are very similar, as reviewed in Figure 2, the BSPED guidelines appear to be most similar to the ISPAD guidelines on fluid resuscitation and electrolyte balance, with very few differences between

the two.

The most pertinent similarities between the BSPED and ISPAD guidelines include giving a bolus for shock (20mL/kg), using the Holliday-Segar formula to determine the maintenance fluid requirements, using a maximum of 80kg in weight for these calculations and stratifying the severity of DKA (into mild, moderate and severe) compared to the two classifications used by NICE (mild/moderate and severe).

In contrast to the NICE and BSPED guidelines which state a 0.9% sodium chloride solution must be used when considering fluid requirements, in the ISPAD guidance, either a 0.45% or 0.9% sodium chloride or a balanced salt solution (Ringer's lactate, Hartmann's solution or PlasmaLyte) may be used. This is secondary to recent findings from randomised control trials (RCTs) showing no difference in cerebral injury in patients rehydrated at different rates with either 0.45% or 0.9% saline.<sup>(3)</sup> Additionally, for those not in shock, these fluids should be infused over 30 to 60 minutes which falls between the two 2020 guidelines (NICE states to give fluids over 30 minutes, BSPED states over 60 minutes). Regarding the fluid bolus for those in shock, as with the NICE 2020 guidelines, the ISPAD guidelines state that it should be given "as soon as possible".<sup>(3)</sup> Conversely, BSPED says this should be over 15 minutes. However, in practice this difference in nomenclature is likely to be negligible. Also in agreement with the NICE 2020 guidelines, the ISPAD guidelines recommend the prescription of insulin at between 0.05 and 0.1 units/kg/hour, where 0.05 units/kg/hour is usually sufficient in mild DKA. When assessing glucose introduction, the ISPAD guidance recommends that healthcare professionals "consider adding glucose before 17 mmol if falling rapidly. Otherwise 5% glucose should be added when the plasma glucose falls to approximately 14 to 17 mmol/L." This is in contrast to the NICE and BSPED guidelines which only introduce 5% glucose when it has fallen below 14mmol/L.

The Royal Children's Hospital in Melbourne (RCH) Clinical Practice Guidelines for Diabetic Ketoacidosis, last updated in November 2018, have been adapted for statewide use with the support of the Victorian Paediatric Clinical Network. Although broadly similar, there are a few distinct differences between the RCH guidelines and those of NICE, BSPED and ISPAD. For those in shock, a 10mL/kg 0.9% sodium chloride bolus can be given, half the volume of 20mL/kg recommended by the other guidelines. Although initial fluid rates are based on a degree of dehydration (with the RCH stratifications varying from the other guidelines – mild = <4%, moderate = 4-7% and severe = >7%), maintenance fluids are not calculated using the Holliday-Segar formula. Instead a detailed table is used, with the fluid requirements classified according to the different degrees of dehydration up to a maximum of 70kg.

However, as with the other guidelines, 40mmol/L of potassium chloride is added to the fluid, as long as the child is not anuric or a serum potassium  $\geq 5.5$  mmol/L. If required, these can be increased to a maximum of 60mmol/L, which is not specified in the other guidelines. Additionally, 5% glucose is added if the blood glucose is  $\leq 15$  mmol/L, which is comparable, although this can be increased to 10% glucose if blood glucose is falling rapidly or  $\leq 5$  mmol/L. Insulin infusion rate of 0.1 units/kg/hour is recommended unless treating children under 5 years, children undergoing inter-hospital transfer (where limited access to biochemical monitoring) or children with blood glucose <15 mmol/L at the time of commencement of the insulin infusion. This is placed at the upper end of the bracket of the other guidelines, where 0.1 units/kg/hour is recommended for those with severe DKA, adolescence or unresolved ketosis."

What I miss in your review is the use of effective osmol and urinary ketones to reduce the risk of cerebral edema? Are these aspects already similar across these guidelines?

The update in the 2020 guidelines from both NICE and BSPED centred on fluid therapy and there was little alteration to the monitoring of ketones as these were identical and in line with international guidance. Using near-patient ketone testing every 1-2 hours to confirm that ketone levels are falling adequately is considered sufficient to observe for risk of cerebral oedema. Subsequently both BSPED and NICE recommend increasing insulin infusion after 6-8 hours to 0.1 units/kg/hour or greater as well as consulting senior paediatricians or intensivists if ketone levels are not observed to be falling.<sup>(1, 2)</sup>

Reviewer 1 comments:

My biggest concern: it is a nice summary of the better concordance and the differences of 2 UK guidelines on DKA. However, this article is submitted as a review article and it should contain (as the author guideline states): the pros and cons of any contentious or uncertain aspect should be described. The difference between the 2 UK guidelines are described, there is however no pro/con argumentation. It is more of a short practical summary and background for physicians with little experience in treatment of DKA.

We are grateful to the reviewer for highlighting this issue. We have assessed the contentious aspects of the two guidelines and have included discussion of these including pros and cons to improve this article. The changes are listed under "Updated guidance" in the paper and below.

"Although these guidelines now have greater cohesion, a number of minor differences remain:(1, 6)

- Regarding fluid replacement, NICE have included 2 levels of severity of DKA, whilst BSPED have subdivided the stratification to include 3 discrete categories for severity and subsequent dehydration status, as outlined in Table 1.
- This remains a challenge due to the absence of continuity across the two guidelines. The impact could be great due to the difference between 5% dehydration and 7% dehydration when calculating fluid deficit, and thus risk the development of cerebral oedema. Given that the maximum weight considered for each is 75kg for NICE and 80kg for BSPED, the maximum difference in deficit fluids could be 1,850ml ( $5\% \times 75\text{kg} = 3750\text{ml}$  for NICE compared to  $7\% \times 80\text{kg} = 5600\text{ml}$ ). However, the difference only affects those in the "moderate DKA" category as those with mild DKA are assumed to have 5% dehydration and severe DKA 10% dehydration in both guidelines.
- For patients who are clinically dehydrated, but not in shock, an IV 10 ml/kg bolus of 0.9% sodium chloride is recommended on admission. This should be administered over 30 minutes (NICE) or 60 minutes (BSPED). This volume is included in the fluid replacement when calculating the total fluid deficit. NICE recommend discussing with a paediatrician experienced in DKA management before giving more than one IV bolus. A second bolus should only be considered if needed to improve tissue perfusion and this must be done after reassessing their clinical status.
- Although the bolus provided is identical, administering it over double the period of time recommended by NICE (in the case of the BSPED guidelines) could increase the risk of cerebral oedema secondary to prolonged dehydration. Given that there is a lack of clear evidence about whether the risk of CO is increased secondary to greater fluid administration, it is probable that they are being cautious. However, it must be ensured that this does not result in inadequate fluid resuscitation, which could further increase the risk of CO. Guidance from the ISPAD consensus released in 2018 states that this should be administered between 30-60 minutes which falls between the two UK guidelines. Therefore, aiming to administer the fluid rapidly but observing for signs of potential deterioration and adjusting the rate accordingly will provide the best outcome for patients.
- In the presence of hypovolaemic shock both NICE and BSPED recommend an IV 0.9% sodium chloride bolus of 20ml/kg. BSPED recommend repeating these infusions over 15 minutes to a maximum of 40ml/kg, followed by inotropes, whilst NICE recommends administering it as soon as possible. In both guidelines, the bolus for shock is not subtracted from total fluid deficit.
- Whilst the nomenclature varies between these two guidelines, in practice it is likely that these will represent similar time frames. Administering a 20ml/kg 0.9% sodium chloride bolus to treat shock as quickly as possible should provide the best therapy for the patient.
- When calculating fluid replacement, the NICE guidelines recommend a maximum weight of 75kg whereas BSPED recommend a maximum weight of 80kg or 97th centile weight for age (whichever is lower).
- This discrepancy is unlikely to be encountered on a frequent basis in general paediatric practice. However, if the weight greatly exceeds 75kg it may be more appropriate for young people to be managed according to adult guidelines due to their increased body habitus. Additionally, identifying a CYP on the 97th centile can be difficult, especially in an emergency setting, and therefore this may be missed."

What I would add to the discussion (from an international perspective): why are there 2 national guidelines? I take it the BSPED is involved in the development of the NICE guideline. I would argue that it is a waste of effort money and time that 2 major guidelines were developed.



Thank you for raising this point. The BSPED guideline evolved from the NICE guideline due to concerns over the limited evidence that was used to develop the management. Whilst there were a number of dual-serving board members, the additional expertise from the BSPED special interest group in diabetic ketoacidosis, and further evidence used to contribute to the BSPED guidance was thought to increase its safety. Both guidelines have changed considerably since their conception and it could be argued that now, due to their similarities, there is little requirement for both guidelines. The following section has been added to the discussion.

"The BSPED guideline evolved from the NICE guideline in 2009 due to concerns over limited evidence that was used for its development. Whilst there were a number of dual-serving board members, the additional interest from the BSPED special interest group in DKA, and appropriate evidence was thought to increase its safety."

"As both guidelines have changed considerably since their conception, and now have only minor differences, it could be argued that there is no benefit of two guidelines."

Key message 1 is not a key message from the article, it is part of the introduction to the subject

We agree with this statement and have removed it from the list of key messages.

Key message 4 is not a key message, but more of a general statement. I too hope that adherence to guidelines contribute to a reduction of death of cerebral edema, but this article provides no evidence to support this. I would rephrase to something like 'Careful monitoring and adherence to these national guidelines is recommended and hopefully contributes to a reduction in deaths secondary to cerebral edema'.

This sentence has been altered and now reads "Careful monitoring and adherence to these national guidelines is recommended and will hopefully contribute to a reduction in deaths secondary to cerebral oedema."

The ISPAD guideline is mentioned several times. It should be added to the reference list.

Thank you for identifying this. It has been added to the list of references.

The additional learning points: these are important points in the treatment of DKA. However, they seem rather randomly picked and do not focus on the essence of the review: fluid management in DKA, but rather reflect a wide range in the treatment of DKA (initial stage and final stage) and there is no debate regarding the pro's and con's of their strength

We agree with this statement and have reviewed their inclusion. Learning points that were ascertained to be relevant to the topic of review have been debated with pro/con argumentation whilst others were discarded as they were of reduced benefit.

Quite a number of references on the list are not in the text, at least: 9, 10, 13, 14, 15, 16, 17 are not mentioned.

Thank you for highlighting this error. All references are now complete.

The title doesn't cover the message: it is a comparison of 2 major UK guidelines. Harmonisation of DKA management in children and young people: comparing 2 updated UK guidelines

We have updated the title in line with both this comment and that of the Editor in chief. It now reads

"Update and harmonisation of guidance for the management of diabetic ketoacidosis in children and young people in the UK."

Reviewer 2:

Saline is described in 3 ways throughout the document – Saline, NaCl and Sodium Chloride. Can I suggest that we have harmonisation of this nomenclature and use the standard of Sodium Chloride 0.9% throughout.

We are grateful to the reviewer for highlighting this oversight. We have reviewed the nomenclature used throughout the article and have harmonised all uses to "Sodium Chloride 0.9%".

One of the key messages (line 28) is to have "close supervision by seniors." I think this needs a little more definition. This is alluded to throughout the document and uses other statements: seniors; senior paediatricians; responsible senior paediatricians and senior, experienced paediatricians. It is not clear what is being alluded to- either directly in this document or from the 2 review documents. I believe this is worth defining if it is going to be a key message.

We have reviewed this statement and identified the most appropriate senior clinicians to consult when this arises in a hospital setting. We hope that the unified phrasing of "experienced paediatricians" provides clarity.

Reviewer 3:

Page 3. Line 20. Discordance does have potential to increase risk of cerebral oedema but more directly causes problems with guideline adherence and agreement between clinicians in practice as you note in your conclusions/recommendations.

On the advice of Reviewer 1 we have removed this key message due to its lack of importance as a key message.

Page 3. Line 19. Consider mentioning ISPAD guidelines at this point as it is referenced later.

Thank you for highlighting this. We have introduced the following into the beginning of Page 4 Line 19.

"Whilst internationally the International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines(3) are widely used..."

Page 4. Line 47. Agree that PECARN has been key in changing the guidelines but would suggest the rationale was that there was no significant difference in the groups of rapid and slower fluid administration rather than the points listed although these are true.

We agree that this should be included and have expanded upon the findings of the PECARN study which provided rationale for the guideline change.

"The rationale for this was based on new evidence from the PECARN DKA fluid trial, which suggested that there was no significant difference in the groups of rapid and slower fluid administration."



Page 5. Line 4-8. Consider re-phrasing for clarity.

These lines have now been rephrased.

"The fluid protocols followed in the PECARN study were fundamental to these updates,(4) as "neither the rate of administration nor the sodium chloride content of intravenous fluids significantly influenced neurologic outcomes in children with diabetic ketoacidosis."(4) Therefore, restrictions to the fluid administration which were recommended in the 2015 NICE guidance "were not necessarily required".(5)

Page 5. Line 11. H-S Formula is not used to calculate deficit but maintenance.

Thank you for highlighting this error. We have corrected this.

Page 5. Line 31. Suggest use full words sodium chloride, not NaCl

Page 6. 0.9% saline. In some places you use NaCl, some sodium chloride, some saline. Should be standardised.

This was also noted by Reviewer 2 and we have harmonised all terms to "Sodium Chloride 0.9%".

Page 5. Line 43. 'perhaps an adolescent' sounds like there is doubt about whether the patient is an adolescent rather than that the doubt lies in whether the higher rate should be used. Consider re-phrase for clarity.

We appreciate the insight and this sentence has been altered and now reads "unless the patient is suffering from severe DKA or is an adolescent".

Page 5. Line 43. 'pump' consider stating 'insulin pump' or more accurately 'continuous subcutaneous insulin infusion' or using quotation marks

We have corrected this terminology to "continuous subcutaneous insulin infusion".

Page 5. BSPED does not state that it should be continued but that it may be continued. NICE also states to think about this in conjunction with a specialist.

We agree with this and have reviewed and amended accordingly. The sentence now reads "...and for patients already on long-acting insulin, it may be continued, and in new patients consider commencing long-acting subcutaneous insulin alongside IV. Similarly, the NICE guidelines state that continuing subcutaneous basal insulin in a child or young person who was using a basal insulin before DKA may be continued in discussion with a diabetes specialist."

Page 6. Line 3. Inotropes considered, not necessarily given.

We thank the reviewer for highlighting this error. We have adjusted accordingly.

Page 6. Line 4. BSPED also state maximum of 97th centile for age – more likely to be encountered clinically and easy to miss.

Thank you very much for this addition, we have introduced this to the discussion and have commented upon the potential for it to be missed.

"...maximum weight of 80kg or 97th centile weight for age (whichever is lower). This can be difficult to identify, especially in an emergency situation, and therefore this may be missed."

Page 6. Consider the role of 'additional learning points' section – doesn't flow well with remainder of article in my opinion.

This concern has been raised by multiple reviewers and we have subsequently questioned its beneficence and place within the article. We have taken the relevant points and restructured them within the main body of the article.

Page 6. Line 58. Important point, shame to leave it at the end?

We agree that this is an important point and have subsequently embedded it into the introduction and conclusion.

We would like to thank you once more for considering our paper, and look forward to hearing from you shortly.

Yours sincerely,

Charlotte Rugg-Gunn

1. Diabetes (type 1 and type 2) in children and young people: diagnosis and management: NICE guideline NG18; 2020 [Available from: <https://pathways.nice.org.uk/pathways/diabetes-in-children-and-young-people/diabetic-ketoacidosis-in-children-and-young-people#content=view-node%3Anodes-recognition-referral-and-diagnosis>.
2. Integrated care pathway for the management of children and young people with Diabetic Ketoacidosis: British Society for Paediatric Endocrinology and Diabetes; 2020 [Available from: [https://www.bsped.org.uk/media/1742/dka-icp-2020-v1\\_1.pdf](https://www.bsped.org.uk/media/1742/dka-icp-2020-v1_1.pdf).
3. Wolfsdorf JJ, Glaser N, Agus M, Fritsch M, Hanas R, Rewers A, et al. ISPAD Clinical Practice Consensus Guidelines 2018: Diabetic ketoacidosis and the hyperglycemic hyperosmolar state. *Pediatr Diabetes*. 2018;19 Suppl 27:155-77.
4. Kuppermann N, Ghetti S, Schunk JE, Stoner MJ, Rewers A, McManemy JK, et al. Clinical Trial of Fluid Infusion Rates for Pediatric Diabetic Ketoacidosis. *N Engl J Med*. 2018;378(24):2275-87.
5. Diabetes (type 1 and type 2) in children and young people: diagnosis and management. Evidence reviews for fluid therapy for the management of diabetic ketoacidosis. Guideline version (Draft). National Institute for Health and Care Excellence; 2020.

## VERSION 2 – REVIEW

<b>REVIEWER</b>	Reviewer name: Dr. Gerald Jaspers Institution and Country: Radboudumc, Netherlands Competing interests: None
<b>REVIEW RETURNED</b>	06-May-2021

<b>GENERAL COMMENTS</b>	<p>Thank you for the complete and elaborate response to the review. In my opinion this text is a considerable improvement</p> <p>A short annotation in advance: the outlining of numbers and lines is somewhat skewed (at least in my browser). If the line-numbers in my comments do not seem to correspond fully, please check the neighbouring lines.</p> <p>I only have minor comments</p> <p>1. page 12, line 42. I would add '(differences in)' between 'establish'</p>
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	<p>and 'their'. This is what would be very interesting: is there an impact on outcome between both guidelines. Furthermore I would change mortality rate (which is very, very low and unlikely to differ) to 'the risk of CO'</p> <p>2. I am missing the goal of this article at the end of the introduction. Consider deleting the last sentence of the introduction and inserting the goal of this article</p> <p>3. page 12, line 54. Consider changing ' the groups of' to 'outcomes between'</p> <p>4. page 13, line 11. 'less cautious fluid restriction' is a difficult to interpret sentence. In my opinion 'more liberal fluid administration' is clearer.</p> <p>5. page 13, line 45 it says 'calculate sodium'. Is corrected sodium meant?</p> <p>6. page 14, 2nd bullet. The text mentions that this is a challenge. I agree that it is a difference between guidelines, which leads to a considerable difference in the calculated amount of fluid (in an adolescent; as is stated in the example), however, I doubt whether this has a major impact on the risk of CO (considering both PECARN and that this concerns moderate DKA). I suggest simply stating the difference, including the calculation.</p> <p>7. Page 14, 3rd bullet (line 22-33). To my knowledge there is no evidence to favour either bolus speed. I would rephrase and make it more concise: just stating the balance between the risk of osmolar shift vs the risk of dehydration on CO and that ISPAD recommends 30-60min is enough.</p> <p>8. Thank you for considering my point on why 2 UK guidelines? and discussing this point in the discussion. I would consider to even put it stronger: both guidelines are almost similar: why waste time, effort and money on maintenance of both: it is time for these 2 guidelines to merge to come to a nationwide UK guideline for the sake of the aforementioned and the sake of clarity.</p>
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## VERSION 2 – AUTHOR RESPONSE

University of Liverpool Medical School,  
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L69 3GE

C.Rugg-Gunn@student.liverpool.ac.uk

8th May 2021

Prof. Saskia de Wildt  
Associate Editor, BMJ Paediatrics Open

Dear Prof. de Wildt,

Thank you for your kind consideration of our manuscript entitled "Update and harmonisation of guidance for the management of diabetic ketoacidosis in children and young people in the UK". We greatly appreciate the reviewers' very helpful and constructive comments.

We have carefully considered all the updated comments and amended the manuscript accordingly. We believe that the manuscript has improved significantly as a result, and we are grateful to you for further considering publication in BMJ Paediatrics Open.

The reviewer comments below have been indented and the response to each comment follows. Any changes made to the manuscript have been highlighted in italic font.

Editor comments:

Editor(s)' Comments to Author (if any):

1. Key message: please refer to: TWO UK guidelines. this piece needs to stand on its own, and BMJ P

Open has a broader audience than the UK (!). Similarly, add this also to the abstract.  
Thank you for highlighting this oversight, we have amended the text accordingly.

Reviewer 1:

1. page 12, line 42. I would add '(differences in)' between 'establish' and 'their'. This is what would be very interesting: is there an impact on outcome between both guidelines. Furthermore I would change mortality rate (which is very, very low and unlikely to differ) to 'the risk of CO'

Thank you for the notes. We have introduced the changes you have suggested and agree with your points about the outcomes associated with both guidelines, it must be assessed in further research.

2. I am missing the goal of this article at the end of the introduction. Consider deleting the last sentence of the introduction and inserting the goal of this article

We have added additional sentences at the end of the introduction in line with this, "This article aims to highlight the considerable alterations made to the two main UK guidelines. Alongside these updates, this article will provide clinical context to paediatricians and junior doctors who are likely to treat these vulnerable groups."

3. page 12, line 54. Consider changing 'the groups of' to 'outcomes between'  
This further clarifies the point and thus we have adjusted it to read "outcomes between".

4. page 13, line 11. 'less cautious fluid restriction' is a difficult to interpret sentence. In my opinion 'more liberal fluid administration' is clearer.

We agree that this is clearer and have adjusted the sentence accordingly.

5. page 13, line 45 it says 'calculate sodium'. Is corrected sodium meant?

In this instance, calculating sodium levels was the primary objective however as this has raised some doubt, we have altered the sentence to read, "Initially assess for presence of hyponatraemia, continue to monitor throughout treatment and treat as soon as blood glucose falls. It is important to monitor for both hyponatraemia and rapid hypernatraemia as these can both be signs of CO."

6. page 14, 2nd bullet. The text mentions that this is a challenge. I agree that it is a difference between guidelines, which leads to a considerable difference in the calculated amount of fluid (in an adolescent; as is stated in the example), however, I doubt whether this has a major impact on the risk of CO (considering both PECARN and that this concerns moderate DKA). I suggest simply stating the difference, including the calculation.

Thank you for your comments. We have amended the bullet to reflect only on the potential difference rather than discussion over the unlikely chance of this impacting on the risk of CO in the patient.

"A difference remains between the maximum weight considered by the guidelines when calculating fluid deficit. Given that the maximum weight considered for each is 75kg for NICE and 80kg for BSPED, the maximum difference in deficit fluids could be 1,850ml ( $5\% \times 75\text{kg} = 3750\text{ml}$  for NICE compared to  $7\% \times 80\text{kg} = 5600\text{ml}$  for BSPED.)"

7. Page 14, 3rd bullet (line 22-33). To my knowledge there is no evidence to favour either bolus speed. I would rephrase and make it more concise: just stating the balance between the risk of osmolar shift vs the risk of dehydration on CO and that ISPAD recommends 30-60min is enough.

Thank you for identifying this important point. We have rephrased the bullet point and believe that this provides clarity to the situation.

"A delicate balance between increasing the risk of osmolar shift secondary to rapid fluid administration with the risk of dehydration and subsequent CO due to slower fluid administration is the foundation for the initial discrepancy between the two guidelines. Guidance from the 2018 ISPAD consensus states that this should be administered between 30-60 minutes, which falls between the two UK guidelines, was found to be adequate for fluid administration.(1) Therefore, aiming to administer the fluid rapidly but observing for signs of potential deterioration and adjusting the rate accordingly will provide the best outcomes for patients."

8. Thank you for considering my point on why 2 UK guidelines? and discussing this point in the discussion. I would consider to even put it stronger: both guidelines are almost similar: why waste time, effort and money on maintenance of both: it is time for these 2 guidelines to merge to come to a

nationwide UK guideline for the sake of the aforementioned and the sake of clarity.  
 Thank you for the continued discussion. It is a challenging conversation and therefore we have introduced the following into the manuscript:  
 "The existence of two guidelines in the UK is primarily historical, with both guideline-producing groups having good reason to be interested in this area. However the UK would, in our opinion, be better served with a single set of guidance to avoid confusion and harmonise practice."

We would like to thank you once more for considering our paper, and look forward to hearing from you shortly.

Yours sincerely,

Charlotte Rugg-Gunn

1. Wolfsdorf JJ, Glaser N, Agus M, Fritsch M, Hanas R, Rewers A, et al. ISPAD Clinical Practice Consensus Guidelines 2018: Diabetic ketoacidosis and the hyperglycemic hyperosmolar state. *Pediatr Diabetes*. 2018;19 Suppl 27:155-77.

### VERSION 3 – REVIEW

<b>REVIEWER</b>	Reviewer name: Dr. Gerald Jaspers Institution and Country: Radboudumc, Netherlands Competing interests: None
<b>REVIEW RETURNED</b>	20-May-2021.
<b>GENERAL COMMENTS</b>	thank you for answers to my suggestions. I have no further comments.

### VERSION 3 – AUTHOR RESPONSE