National Institute for Health and Care Excellence

Guideline version (Draft)

Diabetes (type 1 and type 2) in children and young people: diagnosis and management

[A] Evidence reviews for fluid therapy for the management of diabetic ketoacidosis

NICE guideline NG18

Evidence reviews underpinning recommendations x to y and research recommendations in the NICE guideline

[September 2020]

Draft for Consultation

These evidence reviews were developed by Guidelines Update Team

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ISBN:

Contents

1 Fluid therapy for the management of diabetic ketoacidosis

1.1 Review question

In children and young people with diabetic ketoacidosis:

- What is the appropriate route of fluid administration for rehydration?
- What fluids (including additives) should be used for rehydration?
- At what rate, including volume of fluid should children and young people be rehydrated?

1.1.1 Introduction

Diabetic ketoacidosis (DKA) is a life-threatening condition that can occur in children and young people with type 1 diabetes. It can also affect some children and young people with type 2 diabetes. Management of DKA involves the replacement of fluids and electrolytes. The 2015 NICE guidance on the diabetes (type 1 and type 2) in children and young people: diagnosis and management included recommendations on fluid therapy that covered the route of administration, types of fluids and additives that should be given as well as the volume and rate of fluid administration.

The topic was reviewed by NICE's surveillance team and new evidence was identified which prompted a partial update of the guideline. The aim of this review is to determine the optimal route of administration, type of fluid (including additives) and rate and volume for rehydration in children and young people with DKA.

1.1.2 Summary of the protocol

PICO Table	
Population	Children and young people with type 1 or type 2 diabetes with diabetic ketoacidosis (although the diabetes may not yet have been recognised, for example, if the child or young person is presenting for the first time with DKA)

Intervention	Route of administration:
	• Oral
	• Intravenous
	
	Type of fluids:
	• Any isotonic fluid that can be taken orally
	• Fluids administered intravenously:
	  ○ Saline (sodium chloride) solution at different concentrations (e.g. 0.45% or 0.9%)
	  ○ Hartmann's solution
	  ○ Ringer's lactate solution
	  ○ IV fluid with additives:
	  ○ Glucose
	  ○ Potassium
	  ○ Bicarbonate
	  ○ Phosphate

PICO Table	
	Volume and rate of rehydration: Oral: • Different volumes e.g. high volume or low volume (as defined by author) IV: • Different rates e.g. rapid rate, fast rate or slow rate (as defined by author) • Different volumes e.g. high volume or low volume (as defined by author)
Comparator	Route of administration: • Oral vs IV Type of fluids: • Different oral fluids compared to each other • Different intravenous fluids compared to each other • Different additives compared to each other • Additives compared to no additives. Volume and rate of rehydration: • Oral fluids: • Different volumes compared to each other (low volume vs. high volume) IV fluids: • Different rates compared to each other (e.g. slow rate vs. rapid rate) • Different volumes compared to each other (low volume vs. high volume)
Outcomes	• Mortality • Incidence of cerebral oedema (this could cause morbidity or mortality), to include participants with symptoms or signs suggestive of cerebral oedema (for example, development of unconsciousness) provided these are reported as being related to cerebral oedema • Time to resolution of dehydration • Rate of change of blood glucose concentration or resolution of hyperglycaemia • Resolution of acidosis/ resolution of ketosis • Serum chloride concentration • Serum sodium concentration • Healthcare utilisation (for example, duration of admission, requirement for ventilation [as a proxy for severity of DKA or presence of cerebral oedema]) • Acute cases of renal failure • Neurologic status - decline in neurological status measured using validated scores such as the Glasgow Coma Scale score (e.g. magnitude of decline or the duration of time in which GCS was less than 14) • IQ (assessed using validated scales such as the Wechsler Preschool and Primary School Scale of Intelligence short form)

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and appendix B.

Four studies were identified that focused on children and young people with type 1 diabetes while the remaining studies did not specify type of diabetes. The committee highlighted that the management of DKA in children with type 1 or type 2 diabetes does not differ. Therefore, these studies were not downgraded for indirectness.

Additionally, some studies included children and young people with severe to moderate DKA whilst the majority of studies included children with all severities of DKA. Therefore, evidence has been presented by severity of DKA.

Declarations of interest were recorded according to NICE's conflicts of interest policy (2018).

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

A total of 1,191 RCTs and systematic reviews and 1,456 observational studies were identified in the search. After removing duplicate references, 677 RCTs and systematic reviews and 861 observational studies were screened at title and abstract stage. 10 additional studies (1 RCT and 9 observational studies) were identified from the 2015 NICE guidance on diabetes (type 1 and type 2) in children and young people: diagnosis and management. Overall, a total of 1,548 studies were screened.

Following title and abstract screening, 30 studies (12 RCTs and systematic reviews and 18 observational studies) were included for full text screening. These studies were reviewed against the inclusion criteria as described in the review protocol (Appendix A). Overall, 12 studies were included (6 RCTs and 6 retrospective cohort studies).

Route of administration

Studies which compared route of administration were not identified.

Type of fluids – oral fluids

Studies which compared different oral fluids were not identified.

Type of fluids – IV fluids

7 studies (4 RCTs, and 3 retrospective cohort studies) were identified which examined the type of fluid for rehydration:

- 3 studies examined the type of fluid that should be used as the initial IV fluid in children and young people with DKA. The following IV fluids were examined:
  - 0.9% saline vs Hartmann's solution
  - 0.9% saline vs Plasma-Lyte-A
  - 0.9% saline vs hypertonic saline (3% NaCl)
- 1 study examined the type of fluid that should be used for the replacement of deficit in children and young people with DKA. The following IV fluids were examined:
  - 0.9% saline vs 0.45% saline

- 1 study examined the type of fluid that should be used as post bolus rehydration fluid in children and young people with DKA. The following IV fluids were examined:
    - 0.9% saline vs 0.45% saline
- 1 study examined the type of fluid that should be used as after initial rehydration in children and young people with DKA. The following IV fluids were examined:
    - 74 mEq/L NaCl vs 100 mEq/l of NaCl
- 1 retrospective cohort study compared the use of normal saline vs Ringer's lactate in children and young people with DKA.

IV fluids + additives

- 1 retrospective cohort study compared the use of IV fluid (lactate Ringers or lactate Ringers with saline) and sodium carbonate with IV fluid alone.
- 1 retrospective cohort study compared the use of IV fluids (not defined) with sodium bicarbonate with no sodium bicarbonate.

Rate of rehydration

3 studies (2 RCTs, and 1 retrospective cohort study) were identified which examined the rate of rehydration:

- 1 RCT compared fast rate with slow rate of rehydration in children and young people with DKA
- 1 RCT compared rapid rate with slower rate of rehydration in children and young people with T1DM presenting with DKA
- 1 retrospective study compared fast rate with slow rate of rehydration in children and young people with T1DM presenting with DKA

Volume of fluid

- 1 RCT compared high volume of IV fluid with low volume of IV for rehydration in children and young people with T1DM presenting with DKA.

An MHRA search was also conducted. However, no recent drug safety alerts or recalls were identified.

See appendix E for evidence tables and reference section.

1.1.4.2 Excluded studies

Overall, 18 studies were excluded. See appendix L for list of excluded studies.

1.1.5 Summary of studies included in the effectiveness delivery evidence

Type of fluids - IV fluids

Reference	Study type	Population	Intervention	Comparator	Outcomes	Further notes
Basnet 2014	Retrospective cohort study	Children between the age of 1 and 18 years with initial serum pH <7.3 and serum bicarbonate <15 meq/L with hyperglycaemia and ketonuria	**0.9% saline** Used a post-bolus re-hydration fluid during the recovery phase of DKA	**0.45% saline** Used a post-bolus re-hydration fluid during the recovery phase of DKA	• Healthcare utilisation - Mean PICU stay (hours) • Change in corrected sodium (meq/L) • Rate of change of glucose (mg/dL/h)	• Intervention used for post-bolus rehydration fluid • Includes participants with all severities of DKA
Bergmann 2018	Retrospective cohort study	Children aged 0 to 17 years discharged from inpatient, observation, or emergency department (ED) care with a diagnosis of diabetes with	**Normal saline** No information provided on DKA protocols used.	**Ringer's lactate** No information provided on DKA protocols used.	• Cerebral oedema • Length of stay (days) • Healthcare utilisation - Mechanical ventilation	• DKA protocols not defined • Includes participants with all severities of DKA

Reference	Study type	Population	Intervention	Comparator	Outcomes	Further notes
		ketoacidosis, type I (International Classification of Diseases, Ninth Revision [ICD-9] codes 250.11 and 250.13), between January 1, 2005, and September 30, 2015				
Kupperman 2018	RCT	Children aged between 0 and 18 years of age and had a diagnosis of diabetic ketoacidosis	**0.45% sodium chloride solution** **Standard initial bolus:** 10 ml per kilogram bolus of 0.9% sodium chloride solution. **Additional intravenous fluid bolus:** • 10 ml per kilogram of 0.9% sodium chloride solution (fast administration). • No additional bolus (slow administration)	**0.9% sodium chloride solution** **Standard initial bolus:** 10 ml per kilogram bolus of 0.9% sodium chloride solution. **Additional intravenous fluid bolus:** • 10 ml per kilogram of 0.9% sodium chloride solution (fast administration) • No additional bolus (slow administration)	• Confirmed decline in Glasgow Come Scale Score • Clinically apparent brain injury • IQ • Renal failure • Death • Time to DKA resolution • Time to hospital discharge (hours)	• Intervention used for replacement of deficit • Study also compares different rate of fluid (2x2 factorial design) Includes participants with all severities of DKA

Reference	Study type	Population	Intervention	Comparator	Outcomes	Further notes
			Assumed deficit: • 10% of body weight (fast administration) • 5% of body weight (slow administration) **Process of replacement of deficit:** • During the initial 12 hours, replace half the fluid deficit, plus maintenance fluids. Then replace remaining deficit, plus maintenance fluids, during the subsequent 24 hours (fast administration) • Replace deficit, plus maintenance fluids, evenly during a period of 48 hours (slow administration) **Fluid used for replacement of deficit:** 0.45% sodium chloride solution.	**Assumed deficit:** • 10% of body weight (fast administration) • 5% of body weight (slow administration) **Process of replacement of deficit:** • During the initial 12 hours, replace half the fluid deficit, plus maintenance fluids. Then replace remaining deficit, plus maintenance fluids, during the subsequent 24 hours (fast administration) • Replace deficit, plus maintenance fluids, evenly during a period of 48 hours (slow administration) **Fluid used for replacement of deficit:** 0.9% sodium chloride solution.		
Savaş-Erdeve 2011	Retrospective	Patients younger than 18 years of	**75 mEq/L Sodium Chloride**	**100 mEq/L Sodium Chloride**	• Cerebral oedema • Blood glucose levels (mg/dL)	• Intervention used after

Reference	Study type	Population	Intervention	Comparator	Outcomes	Further notes
	cohort study	age who were admitted to the paediatric intensive care unit from 2002 to 2009	Initial rehydration was performed with isotonic solutions in the first hour of treatment. The total volume to be given was calculated assuming a 10% deficit plus maintenance fluid. Amounts of fluids used in the initial resuscitation were subtracted from the total volume calculated for 48 hours and the infusion rate was adjusted accordingly. The patients in Group I had received IV fluids with a Na concentration of 75 mEq/L (1/2 isotonic NaCl plus 1/2 5% dextrose).	Initial rehydration was performed with isotonic solutions in the first hour of treatment. The total volume to be given was calculated assuming a 10% deficit plus maintenance fluid. Amounts of fluids used in the initial resuscitation were subtracted from the total volume calculated for 48 hours and the infusion rate was adjusted accordingly. The patients in Group II had received IV fluids with a Na concentration of 100 mEq/L (2/3 isotonic NaCl plus 1/3 5% dextrose).	• Sodium concentration (mEq/L)	initial rehydration • Includes participants with type 1 diabetes with all severities of DKA
Shafi 2018	RCT	Subjects with age ≤18 years with a diagnosis of DKA were screened for the inclusion in the study and were included if they met the	**0.9% normal saline** Children randomised to the 0.9% saline received 20 ml/kg of solution during the initial 1 hour of fluid therapy. The rest of the fluid and management was per the written DKA management protocol	**Hypertonic Saline (3% NaCl)** Children randomised to the hypertonic saline (3% NaCl) received 20 ml/kg of solution during the initial 1 hour of fluid therapy. The rest of the fluid and management was per the	• Cerebral oedema • Chloride concentration (mEq/L) • Time needed for the correction of hyperglycaemia • Time needed for the resolution of acidosis	• Intervention used as initial fluid • Includes participants with severe to moderate DKA

Reference	Study type	Population	Intervention	Comparator	Outcomes	Further notes
		criteria for having moderate-severe DKA	followed by the treating unit, which is based on the ISPAD clinical practice consensus guidelines.	written DKA management protocol followed by the treating unit, which is based on the ISPAD clinical practice consensus guidelines.		
Williams 2020	RCT	All consecutive children > 1 month to < 12 years who presented to the paediatric emergency room with DKA as defined by the International Society of Paediatric and Adolescent Diabetes (ISPAD-2014) were enrolled into the study	**0.9% normal saline** Volume calculated based on deficit (6.5-10%) and maintenance fluid as per Holliday Segar. Fluids given over 48 hours as hourly infusion. Eligible children who presented in shock [perfusion abnormalities with or without hypotension (blood pressure < 5th centile for age)], received trial fluid bolus of 20 ml/kg over an hour.	**Plasma-Lyte-A** Volume calculated based on deficit (6.5-10%) and maintenance fluid as per Holliday Segar. Fluids given over 48 hours as hourly infusion. Eligible children who presented in shock [perfusion abnormalities with or without hypotension (blood pressure < 5th centile for age)], received trial fluid bolus of 20 ml/kg over an hour.	• Incidence of acute kidney injury (AKI) • Healthcare utilisation - Need for renal replacement therapy (RRT) • Healthcare utilisation- Need for ventilation • Mortality in hospital • Cerebral oedema • Healthcare utilisation- Length of intensive care unit (ICU) stay • Healthcare utilisation - length of hospital stay	• Intervention used as initial fluid • Includes participants with all severities of DKA
Yung 2017	RCT	Children with moderate to severe DKA	**Hartmann's solution**	**0.9% normal saline**	• Minimum sodium concentration	• Intervention used as initial fluid

Reference	Study type	Population	Intervention	Comparator	Outcomes	Further notes
		admitted to the paediatric intensive care unit (PICU) or high-dependency unit with DKA were eligible.	After resuscitation, subjects were randomised to Hartmann's solution as their initial fluid for at least 12 hours.	After resuscitation, subjects were randomised to 0.9% normal saline as their initial fluid for at least 12 hours.	• Maximum chloride concentration • Altered conscious state • Acute renal failure • Healthcare utilisation-Paediatric intensive care unit (PICU) or high-dependency unit (HDU) stay	• Includes participants with moderate to severe DKA

1 **IV fluids + Additives**

Reference	Study type	Population	Intervention	Comparator	Outcomes	Further notes
Green 1998	Retrospective cohort study	Children aged 15 years or younger with a hospital diagnosis of severe DKA	**Sodium bicarbonate** Children received standard DKA therapy with hydration and intravenous insulin infusion. Adjunctive bicarbonate therapy was administered by treating physicians in doses ranging from 7 to 238 mEq and from 0.53 to 7.37 mEq/kg (mean 2.08, median 1.66 mEq	**No sodium bicarbonate** Children received standard DKA therapy with hydration and intravenous insulin infusion.	• Cerebral oedema • Duration of hospitalisation	• Children with severe DKA DKA protocol not defined. • Includes participants with severe DKA
Mar 1981	Retrospective cohort study	Children with diabetes with DKA with at least one episode of DKA	**Sodium bicarbonate and saline and lactate Ringers or sodium bicarbonate and Lactate Ringers**	**Lactate Ringers or Lactate Ringers with saline** No sodium bicarbonate No information about DKA protocol provided.	• Length of stay (days) • Duration of acidosis (hours)	• DKA protocol not defined. • Includes participants with all severities of DKA

Reference	Study type	Population	Intervention	Comparator	Outcomes	Further notes
			IV solution with sodium bicarbonate No information about DKA protocol provided.			

1

2 **Rate of rehydration**

Reference	Study type	Population	Intervention	Comparator	Outcomes	Further notes
Felner 2001	Retrospective cohort study	Patients within insulin-dependent diabetes mellitus who received DKA therapy under a traditional fluid protocol (group 1)were identified from a list of patients at Children's Medical Centre of Dallas who has discharge diagnoses of 'diabetic ketosis/ ketoacidosis" and admission	**Fast rate** The fluid deficit was calculated by multiplying the percentage of dehydration (7-10%, determined clinically on initial presentation) by the patient's weight. The fluid deficit was added to 1.5 times the patient's total fluid requirement. Half of the total required fluid was ordered over the first 12 hours of treatment and the remaining 50% over the next 24 hours.	**Slow rate** Total fluids were delivered at 2.5 times the maintenance rate regardless of the degree of dehydration. Fluid were decreased to 1 to 1.5 times the maintenance rate after 24 hours of treatment (or earlier if acidosis resolved) until urine ketones were negative.	• Time acidosis resolved (hours) • Change in sodium concentration • Change in chloride concentration	• Participants with type 1 diabetes with all severities of DKA • Type of fluid used in the two arms was different.

Reference	Study type	Population	Intervention	Comparator	Outcomes	Further notes
		dates from September 1st 1994 to June 30th 1997, whereas patients treated under the revised fluid protocol (group 2) were identified from a list of patients admitted from July 1st 1997 to March 31st 2000.				
Glaser 2013	RCT	Children aged 8 to 18 years old, were diagnosed with type 1 diabetes and had DKA	**Rapid rate** **Intravenous fluid bolus**: 20 mL/Kg **Assumed fluid deficit:** 10% of body weight **Rate of deficit replacement:** Two-thirds over first 24 h; One-third over next 24 h **Urine output replacement:** Half of urine vol replaced while serum glucose level is >250 mg/dL **Fluid type:** 0.9% saline while serum glucose is	**Slower rate** **Intravenous fluid bolus:** 10 mL/Kg **Assumed fluid deficit:** 7% of body weight **Rate of deficit replacement:** Evenly over 48 h **Urine output replacement:** None **Fluid type:** 0.9% saline while serum glucose is >250 mg/dL, followed by 0.45% saline.	• Treated for suspected cerebral oedema • Risk of cerebral oedema	• Intravenous fluid bolus is different in both arms. • Participants with type 1 diabetes with all severities of DKA

Reference	Study type	Population	Intervention	Comparator	Outcomes	Further notes
			>250 mg/dL, followed by 0.45% saline.			
Kuppermann 2018	RCT	Children aged between 0 and 18 years of age and had a diagnosis of diabetic ketoacidosis	**Fast administration of sodium chloride** **Process of replacement of deficit:** During the initial 12 hours, replace half the fluid deficit, plus maintenance fluids. Then replace remaining deficit, plus maintenance fluids, during the subsequent 24 hours. **Fluid used for replacement of deficit:** 0.45% and 0.9% sodium chloride (data available separately for different solution)	**Slow administration of sodium chloride** **Process of replacement of deficit:** Replace deficit, plus maintenance fluids, evenly during a period of 48 hours. **Fluid used for replacement of deficit:** 0.45% and 0.9% sodium chloride (data available separately for different solution)	• Confirmed decline in Glasgow Come Scale Score • Clinically apparent brain injury • IQ • Renal failure • Death • Time to DKA resolution • Time to hospital discharge (hours)	• Rate of replacement deficit • Study also compares different fluids (2x2 factorial design) • Includes participants with all severities of DKA

1 **Volume of rehydration**

Reference	Study type	Population	Intervention	Comparator	Outcomes	Further notes
Bakes 2016	RCT	Children were eligible for	**High volume IV fluid**	**Low volume IV fluid**	• Cerebral oedema	• Participants with type 1 diabetes

Reference	Study type	Population	Intervention	Comparator	Outcomes	Further notes
		participation if they were between 0 and 18 years of age, had type 1 diabetes mellitus plus the presence of DKA	The high-volume IV fluid group, received a 20 mL/kg of IV 0.9% saline bolus over the first hour followed by 0.675% saline + potassium replacement at 1.5 times maintenance.	Low-volume IV fluid group, received a 10 mL/kg of IV 0.9% saline bolus over the first hour followed by 0.675% saline + potassium replacement at 1.25 times maintenance.	• Time to metabolic normalisation • Healthcare utilisation - length of treatment • Time to discharge	with all severities of DKA • Replacement rate varies between arms.

1 See appendix E for full evidence reviews.

2 **1.1.6 Summary of the effectiveness evidence**

3 **Type of fluid - IV fluids**

4 ***Moderate to severe DKA***

5 *0.9% Saline vs Hartmann's solution as initial IV fluid*

6 **Outcomes during treatment of DKA**

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Minimum sodium concentration – MD greater than 1 favours 0.9% saline					
Yung 2017	RCT	77	MD: 0.00 (-1.47, 1.47)	High	Could not differentiate between IV fluids
Maximum chloride concentration – MD greater than 1 favours 0.9% saline					
Yung 2017	RCT	77	MD: 2.00 (-0.27, 4.27)	Moderate	Could not differentiate between IV fluids
Altered conscious state (defined as deterioration in Glasgow Coma Scale (CGS))– RR less than 1 favours 0.9% saline					
Yung 2017	RCT	77	RR: 2.92 (0.12, 69.64)	Low	Could not differentiate between IV fluids

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Acute renal failure - RR less than 1 favours 0.9% saline					
Yung 2017	RCT	77	RR: 2.92 (0.12, 69.64)	Moderate	Could not differentiate between IV fluids

0.9% Saline vs hypertonic saline (3% NaCl) as initial IV fluid

Outcomes during 1 hour of treatment

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Chloride concentration (mEq/L) - MD less than 1 favours 0.9% saline					
Shafi 2018	RCT	40	MD -5.70 (-9.81, -1.59)	Low	**0.9% saline =favoured**

Outcomes during 12 hours of treatment

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Cerebral oedema - RR less than 1 favours 0.9% saline					
Shafi 2018	RCT	40	RR: 1.00 (0.07, 14.90)	Low	Could not differentiate between IV fluids

All severities of DKA

0.9% Saline vs Plasma-Lyte A as initial IV fluid

Outcomes during 24 hours of treatment

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Incidence of acute kidney injury (AKI) (defined with either KDIGO or pRIFLE criteria)– RR less than 1 favours 0.9% saline					
Williams 2020	RCT	66	RR: 0.80 (0.19, 3.29)	Low	Could not differentiate between IV fluids

Outcomes during 48 hours of treatment

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Incidence of acute kidney injury (AKI) (defined with either KDIGO or pRIFLE criteria)– RR less than 1 favours 0.9% saline					

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Williams 2020	RCT	66	RR: 0.35 (0.04, 3.23)	Low	Could not differentiate between IV fluids

1 **Outcomes till discharge**

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Healthcare utilisation – Need for renal replacement therapy - RR less than 1 favours 0.9% saline					
Williams 2020	RCT	66	RR: 0.21 (0.01, 4.26)	Low	Could not differentiate between IV fluids
Healthcare utilisation – Need for ventilation - RR less than 1 favours 0.9% saline					
Williams 2020	RCT	66	RR: 0.53 (0.05, 5.58)	Low	Could not differentiate between IV fluids
Mortality in hospital - RR less than 1 favours 0.9% saline					
Williams 2020	RCT	66	RR: 0.21 (0.01, 4.26)	Low	Could not differentiate between IV fluids
Cerebral oedema - RR less than 1 favours 0.9% saline					
Williams 2020	RCT	66	RR: 0.35 (0.01, 8.38)	Very low	Could not differentiate between IV fluids

2 *0.9% Saline vs. 0.45% saline for replacement of deficit*

3 **Outcomes during treatment of DKA**

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Confirmed decline in Glasgow Coma Scale score to <14 - RR less than 1 favours 0.9% saline					
Kuppermann 2018	RCT	1361	RR: 1.27 (0.72, 2.22)	Moderate	Could not differentiate between IV fluids
Confirmed decline in Glasgow Coma Scale score to <14 - RR less than 1 favours 0.9% saline – fast rate					
Kuppermann 2018	RCT	682	RR: 1.07 (0.46, 2.50)	Moderate	Could not differentiate between IV fluids
Confirmed decline in Glasgow Coma Scale score to <14 - RR less than 1 favours 0.9% saline– slow rate					
Kuppermann 2018	RCT	679	RR: 1.44 (0.68, 3.06)	Moderate	Could not differentiate between IV fluids
Confirmed decline in Glasgow Coma Scale score to <14 - RR less than 1 favours 0.9% saline - in people with severe DKA (defined as with initial pH in the lowest quartile of the study group (pH <7.0))					

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Kuppermann 2018	RCT	282	RR: 1.66 (0.81, 3.38)	Moderate	Could not differentiate between IV fluids
Confirmed decline in Glasgow Coma Scale score to <14 - RR less than 1 favours 0.9% saline - in people with severe DKA (defined as with initial pH in the lowest quartile of the study group (pH <7.0))- fast rate					
Kuppermann 2018	RCT	131	RR: 1.62 (0.50, 5.27)	Moderate	Could not differentiate between IV fluids
Confirmed decline in Glasgow Coma Scale score to <14 - RR less than 1 favours 0.9% saline - in people with severe DKA (defined as with initial pH in the lowest quartile of the study group (pH <7.0))- slow rate					
Kuppermann 2018	RCT	151	RR: 1.68 (0.69, 4.10)	Moderate	Could not differentiate between IV fluids
Clinically apparent brain injury - RR less than 1 favours 0.9% saline					
Kuppermann 2018	RCT	1389	RR: 0.70 (0.22, 2.21)	Low	Could not differentiate between IV fluids
Clinically apparent brain injury - RR less than 1 favours 0.9% saline – fast rate					
Kuppermann 2018	RCT	695	RR: 0.98 (0.14, 6.92)	Low	Could not differentiate between IV fluids
Clinically apparent brain injury - RR less than 1 favours 0.9% saline – slow rate					
Kuppermann 2018	RCT	694	RR: 0.59 (0.14, 2.46)	Low	Could not differentiate between IV fluids
Clinically apparent brain injury - RR less than 1 favours 0.9% saline - in people with severe DKA (defined as with initial pH in the lowest quartile of the study group (pH <7.0))					
Kuppermann 2018	RCT	303	RR: 1.03 (0.26, 4.02)	Low	Could not differentiate between IV fluids
Clinically apparent brain injury - RR less than 1 favours 0.9% saline - in people with severe DKA (defined as with initial pH in the lowest quartile of the study group (pH <7.0))- fast rate					
Kuppermann 2018	RCT	141	RR: 0.96 (0.06, 15.02)	Low	Could not differentiate between IV fluids
Clinically apparent brain injury - RR less than 1 favours 0.9% saline - in people with severe DKA (defined as with initial pH in the lowest quartile of the study group (pH <7.0))- slow rate					
Kuppermann 2018	RCT	162	RR: 1.05 (0.22, 5.05)	Low	Could not differentiate between IV fluids
Mortality- RR less than 1 favours 0.9% saline					
Kuppermann 2018	RCT	485	RR: 0.31 (0.01, 7.45)	Moderate	Could not differentiate between IV fluids
Mortality- RR less than 1 favours 0.9% saline – fast rate					
Kuppermann 2018	RCT	238	RR: 0.31 (0.01, 7.45)	Moderate	Could not differentiate between IV fluids

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Mortality- RR less than 1 favours 0.9% saline – slow rate					
Kuppermann 2018	RCT	247	RR not estimable due to zero event in both arms	Low	Not applicable as treatment effect could not be estimated
Renal failure - RR less than 1 favours 0.9% saline					
Kuppermann 2018	RCT	1389	RR not estimable due to zero event in both arms	Low	Not applicable as treatment effect could not be estimated

1 **2 to 6 months after hospitalisation**

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
IQ (in children aged 3 to 5 years) - MD greater than 0 favours 0.9% saline					
Kuppermann 2018	RCT	54	MD: -2.90 (-10.22, 4.41)	Moderate	Could not differentiate between IV fluids
IQ (in children aged 3 to 5 years) - MD greater than 0 favours 0.9% saline – fast rate					
Kuppermann 2018	RCT	30	MD: -4.00 (-13.19, 5.19)	Moderate	Could not differentiate between IV fluids
IQ (in children aged 3 to 5 years) - MD greater than 0 favours 0.9% saline – slow rate					
Kuppermann 2018	RCT	24	MD: -1.00 (-13.09, 11.09)	Low	Could not differentiate between IV fluids
IQ (in children aged 6 to 18 years) - MD greater than 0 favours 0.9% saline					
Kuppermann 2018	RCT	768	MD:0.48 (-1.33, 2.28)	High	Could not differentiate between IV fluids
IQ (in children aged 6 to 18 years) - MD greater than 0 favours 0.9% saline- fast rate					
Kuppermann 2018	RCT	388	MD: 0.00 (-2.49, 2.49)	High	Could not differentiate between IV fluids
IQ (in children aged 6 to 18 years) - MD greater than 0 favours 0.9% saline- slow rate					
Kuppermann 2018	RCT	380	1.00 (-1.61, 6.61)	Moderate	Could not differentiate between IV fluids

1 *0.9% Saline vs 0.45% saline post-bolus re-hydration fluid*

2 **Outcomes during treatment of DKA**

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Healthcare utilisation- Mean PICU length of stay (hours) -MD less than 0 favours 0.9% saline					
Basnet 2014	Retrospective cohort study	88	MD: 2.00 (-1.01, 5.01)	Low	Could not differentiate between IV fluids
Rate of change of glucose (mg/dL/h) - MD greater than 0 favours 0.9% saline					
Basnet 2014	Retrospective cohort study	88	MD: -7.70 (-18.02, 2.62)	Low	Could not differentiate between IV fluids
Change in corrected sodium from baseline (meq/L) -MD less than 0 favours 0.9% saline					
Basnet 2014	Retrospective cohort study	88	MD:3.50 (1.43, 5.57)	Low	**0.45% saline favoured**

3 *Normal saline vs Ringer's lactate*

4 **Outcomes during treatment of DKA**

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Healthcare utilisation – mechanical ventilation – RR less than 1 favours normal saline					
Bergmann 2018	Retrospective cohort study	45603	RR: 0.93 (0.59, 1.46)	Very low	Could not differentiate between IV fluids
Cerebral oedema – RR less than 1 favours normal saline					
Bergmann 2018	Retrospective cohort study	45603	RR: 4.53 (3.68, 7.65)	Very low	**Favours Ringer's lactate**

Type 1 diabetes - All severities of DKA

75 mEq/L NaCl vs 100 mEq/L NaCl after initial rehydration

Outcomes during 1 hour of treatment

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Blood glucose levels – MD less than 0 favours 75 mEq/L of NaCl					
Savaş-Erdeve 2011	Retrospective cohort study	32	MD: 0.10 (-113.06, 113.26)	Very low	Could not differentiate between IV fluids

Outcomes during 24 hours of treatment

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Change in corrected sodium from baseline (meq/L) – MD greater than 0 favours 75 mEq/L of NaCl					
Savaş-Erdeve 2011	Retrospective cohort study	32	MD: -1.00 (-3.40, 1.40)	Low	Could not differentiate between IV fluids
Cerebral oedema – RR less than 1 favours 75 mEq/L of NaCl					
Savaş-Erdeve 2011	Retrospective cohort study	32	RR not estimable due to zero event in both arms	Very low	Not applicable as treatment effect could not be estimated

IV+ additives

Severe DKA

IV fluid (not specified) with sodium bicarbonate vs IV fluid (not specified) with no sodium bicarbonate

Outcomes till discharge

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Duration of hospitalisation (hours) – MD less than 0 favours IV +sodium carbonate					

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Green 1998	Retrospective cohort study	106	MD: 16.00 (0.73, 31.27)	Very low	**No sodium bicarbonate favoured**
Cerebral oedema – RR less than 1 favours IV +sodium carbonate					
Green 1998	Retrospective cohort study	106	RR: 0.86 (0.06, 13.39)	Very low	Could not differentiate between additives and no additives

1 ***All severities of DKA***

2 *IV fluid (Lactate Ringers or Lactate Ringers with saline) with sodium bicarbonate vs IV fluid (Lactate Ringers or Lactate Ringers with saline) alone*

3 **Outcomes during treatment of DKA**

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Duration of acidosis – MD less than 0 favours IV +sodium carbonate					
Mar 1981	Retrospective cohort study	49	MD: -1.16 (-5.53, 3.21)	Very low	Could not differentiate between additives and no additives
Length of hospital stay – MD less than 0 favours IV +sodium carbonate					
Mar 1981	Retrospective cohort study	49	MD: 2.05 (-2.52, 6.62)	Very low	Could not differentiate between additives and no additives

Rate of rehydration

All severities of DKA

Fast rate (defined as replacement of half fluid deficit plus maintenance during initial 12 hours followed by the replacement of remaining deficit plus maintenance fluid during subsequent 24 hour) vs slow rate (defined as replacement of deficit plus maintenance fluids evenly during a period of 48 hours) for the replacement of deficit

Outcomes during treatment of DKA

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Confirmed decline in Glasgow Coma Scale score to <14 - RR less than 1 favours fast rate					
Kuppermann 2018	RCT	1361	RR: 0.77 (0.44, 1.35)	Moderate	Could not differentiate between rates
Confirmed decline in Glasgow Coma Scale score to <14 - RR less than 1 favours fast rate – 0.45% Saline					
Kuppermann 2018	RCT	675	RR: 0.91 (0.39, 2.12)	Moderate	Could not differentiate between rates
Confirmed decline in Glasgow Coma Scale score to <14 - RR less than 1 favours 0.9% saline– slow rate					
Kuppermann 2018	RCT	686	RR: 0.68 (0.32, 1.44)	Moderate	Could not differentiate between rates
Confirmed decline in Glasgow Coma Scale score to <14 - RR less than 1 favours fast rate - in people with severe DKA (defined as with initial pH in the lowest quartile of the study group (pH <7.0))					
Kuppermann 2018	RCT	282	RR: 0.69 (0.34, 1.41)	Moderate	Could not differentiate between rates
Confirmed decline in Glasgow Coma Scale score to <14 - RR less than 1 favours fast rate - in people with severe DKA (defined as with initial pH in the lowest quartile of the study group (pH <7.0))- 0.45% saline					
Kuppermann 2018	RCT	141	RR: 0.71 (0.22, 2.31)	Moderate	Could not differentiate between rates
Confirmed decline in Glasgow Coma Scale score to <14 - RR less than 1 favours fast rate - in people with severe DKA (defined as with initial pH in the lowest quartile of the study group (pH <7.0))- 0.9% saline					
Kuppermann 2018	RCT	141	RR: 0.68 (0.28, 1.66)	Moderate	Could not differentiate between rates
Clinically apparent brain injury - RR less than 1 favours fast rate					
Kuppermann 2018	RCT	1389	RR: 0.50 (0.15,1.65)	Low	Could not differentiate between rates
Clinically apparent brain injury - RR less than 1 favours fast rate – 0.45% NaCl					

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Kuppermann 2018	RCT	689	RR: 0.40 (0.08, 2.05)	Low	Could not differentiate between rates
Clinically apparent brain injury - RR less than 1 favours fast rate – 0.9% NaCl					
Kuppermann 2018	RCT	700	RR: 0.66 (0.11, 3.94)	Low	Could not differentiate between rates
Clinically apparent brain injury - RR less than 1 favours fast rate - in people with severe DKA (defined as with initial pH in the lowest quartile of the study group (pH <7.0))					
Kuppermann 2018	RCT	303	RR: 0.38 (0.08, 1.87)	Low	Could not differentiate between rates
Clinically apparent brain injury - RR less than 1 favours fast rate - in people with severe DKA (defined as with initial pH in the lowest quartile of the study group (pH <7.0))- 0.45% NaCl					
Kuppermann 2018	RCT	152	RR: 0.40 (0.04, 3.77)	Low	Could not differentiate between rates
Clinically apparent brain injury - RR less than 1 favours fast rate - in people with severe DKA (defined as with initial pH in the lowest quartile of the study group (pH <7.0))- 0.9% NaCl					
Kuppermann 2018	RCT	151	RR: 0.37 (0.04, 3.44)	Low	Could not differentiate between rates
Mortality- RR less than 1 favours fast rate					
Kuppermann 2018	RCT	485	RR: 3.10 (0.13, 75.42)	Moderate	Could not differentiate between rates
Mortality- RR less than 1 favours fast rate – 0.45% NaCl					
Kuppermann 2018	RCT	238	RR: 3.10 (0.13, 75.42)	Moderate	Could not differentiate between rates
Mortality- RR less than 1 favours 0.9% saline – slow rate					
Kuppermann 2018	RCT	247	RR not estimable due to zero event in both arms	Low	Not applicable as treatment effect could not be estimated
Renal failure - RR less than 1 favours 0.9% saline					
Kuppermann 2018	RCT	1389	RR not estimable due to zero event in both arms	Low	Not applicable as treatment effect could not be estimated

1 **2 to 6 months after hospitalisation**

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
IQ (in children aged 3 to 5 years) - MD greater than 0 favours fast rate					
Kuppermann 2018	RCT	54	MD: 2.87 (-4.50, 10.23)	Moderate	Could not differentiate between rates
IQ (in children aged 3 to 5 years) - MD greater than 0 favours fast rate – 0.45% NaCl					
Kuppermann 2018	RCT	30	4.00 (-5.34, 13.34)	Moderate	Could not differentiate between rates
IQ (in children aged 3 to 5 years) - MD greater than 0 favours fast rate – 0.9% NaCl					
Kuppermann 2018	RCT	24	MD: 1.00 (-10.98, 12.98)	Low	Could not differentiate between rates
IQ (in children aged 6 to 18 years) - MD greater than 0 favours fast rate					
Kuppermann 2018	RCT	768	MD: -0.49 (-2.29, 1.32)	High	Could not differentiate between rates
IQ (in children aged 6 to 18 years) - MD greater than 0 fast rate- 0.4% NaCl					
Kuppermann 2018	RCT	388	MD: 0.00 (-2.52, 2.52)	High	Could not differentiate between rates
IQ (in children aged 6 to 18 years) - MD greater than 0 favours 0.9% saline- slow rate					
Kuppermann 2018	RCT	380	MD: -1.00 (-3.58, 1.58)	High	Could not differentiate between rates

2 ***Type 1 diabetes – All severities of DKA***

3 *Rapid rate (two-thirds over first 24 hours, one-third over next 24 hours) vs slower rate (evenly over 48 hours)*

4 **Outcomes during treatment of DKA**

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Treated for suspected cerebral oedema – RR less than 1 favours rapid rate					
Glaser 2013	RCT	18	RR: 3.67 (0.17, 79.54)	Very low	Could not differentiate between rates
High risk of cerebral oedema (High risk defined as SUN in the upper quartile (≥27 mg/dL) and/ or pH in the lower quartile (≤6.97))– RR less than 1 favours rapid rate					
Glaser 2013	RCT	18	RR: 2.08 (0.70, 6.19)	Very low	Could not differentiate between rates

Fast rate (half of total required fluid over the first 12 hours of treatment and the remaining 50% over the next 24 hours) vs slow rate(total fluids delivered 2.5 times the maintenance rate and decreased to 1 to 1.5 times the maintenance rate after 24 hours

Outcomes during treatment of DKA

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Time in which acidosis resolved (hours) – MD less than 0 favours fast rate					
Felner 2001	Retrospective cohort study	60	MD: 4.10 (0.79, 7.47)	Very low	Could not differentiate between rates
Change in sodium concentration (mmol/L)– MD greater than 0 favours fast rate					
Felner 2001	Retrospective cohort study	60	MD: 0.20 (-1.93, 2.33)	Very low	Could not differentiate between rates
Change in chloride concentration (mmol/L)– MD greater than 0 favours fast rate					
Felner 2001	Retrospective cohort study	60	MD: -0.40 (-3.72. 2.92)	Very low	Could not differentiate between rates

Volume of rehydration

Type 1 diabetes – All severities of DKA

High volume vs low volume

Outcomes during treatment of DKA

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Metabolic normalisation – HR greater than 1 favours high volume					
Bakes 2016	RCT	50	HR: 2.00 (1.01, 3.95)	Very low	**High volume favoured**
Length of treatment - HR less than 1 favours high volume					
Bakes 2016	RCT	50	HR: 0.80 (0.41, 1.55)	Very low	Could not differentiate between volumes
Hospital discharge (hours) - HR less than 1 favours high volume					

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Bakes 2016	RCT	50	HR: 0.80 (0.41, 1.55)	Very low	Could not differentiate between volumes
Cerebral oedema – RR less than 1 favours high volume					
Bakes 2016	RCT	50	RR not estimable due to zero event in both arms	Very low	Not applicable as treatment effect could not be estimated

1 See appendix H for full GRADE tables

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1.1.7 Economic evidence

1.1.7.1 Included studies

334 papers were identified for title and abstract screening, 0 were included for full text screening.

1.1.7.2 Excluded studies

See appendix F for excluded studies list.

1.1.8 Summary of included economic evidence

No economic evidence was identified for this review question.

1.1.9 Economic model

This question was not prioritised for health economic modelling.

1.1.10 Evidence statements

Evidence was also identified for which GRADE could not be applied as the evidence was presented in the form of median and interquartile range. This evidence is presented in Appendix G and summarised narratively here.

IV fluids

Moderate to severe DKA

0.9% Saline vs Hartmann's solution as initial IV fluid – Outcomes during treatment of DKA

- Paediatric intensive care unit (PICU) or high dependency unit (HDU) stay was lower in children and young people treated with Hartmann's solution compared to 0.9% saline solution.

0.9% Saline vs Hypertonic saline (3% NaCl) as initial IV fluid - Outcomes during treatment of DKA

- Could not differentiate average time needed for the correction of hyperglycaemia and time needed for the resolution of acidosis between children and young people who received 0.9% saline and those who received hypertonic saline.

All severities of DKA

0.9% Saline vs Plasma-Lyte-A as initial IV fluid - Outcomes during treatment of DKA

- Could not differentiate length of intensive care unit stay and length of hospital stay between children and young people who received 0.9% saline and those who received Plasma-Lyte-A.

0.9% Saline vs 0.45% saline for replacement of deficit - Outcomes during treatment of DKA

- Could not differentiate time to resolution of DKA or time to hospital discharge between children and young people who received 0.9% saline and those who received 0.45% saline.

Normal saline vs Ringers lactate - Outcomes during treatment of DKA

- Could not differentiate length of hospital stay between children and young people treated with normal saline and those who received Ringers lactate.

IV fluids

Mixed population

Fast rate vs slow rate - Outcomes during treatment of DKA

- Could not differentiate time to resolution of DKA or time to hospital discharge between children and young people who received fast rate of fluids and those who received slow rate of fluids.

1.1.11 The committee's discussion and interpretation of the evidence

1.1.11.1. The outcomes that matter most

The committee highlighted that if DKA is not managed effectively with fluid therapy, cerebral oedema can occur which can lead to mortality. Based on this knowledge, the committee identified outcomes such as incidence of cerebral oedema and mortality as important outcomes.

1.1.11.2 The quality of the evidence

In this review, a combined search was conducted to identify studies which explored route of fluid administration for rehydration, type of fluids (including additives) that should be used for rehydration and the rate and volume these fluids should be administered. Overall, 12 studies (6 RCTs and 6 retrospective cohort studies) were included. Both RCTs and comparative observational studies started as high-quality evidence.

Overall, 7 studies (4 RCTs and 3 retrospective cohort studies) were identified which compared different IV fluids. Evidence from these studies ranged from high to very low quality. Two retrospective cohort studies were identified which compared different additives and the evidence from these studies were of very low quality. Furthermore, 3 studies were identified (2 RCTs and 1 retrospective cohort study) which compared different rates of rehydration and evidence from these studies ranged from high to very low quality. Additionally, 1 RCT was identified which compared different volumes of fluid and evidence from this study was of very low quality. These studies were downgraded through GRADE for risk of bias due to baseline differences in the 2 study arms and for not specifying DKA protocols followed. Studies were also downgraded for indirectness if the DKA protocols followed by the 2 arms of the study were different.

The review protocol specified that studies with a mixed population (children and young people with type 1 and type 2 diabetes) would be included but would be downgraded for indirectness if the data was not reported separately. Overall, 4 studies were identified (Bakes 2016, Glaser 2013, Felner 2001 and Sava-Erdeve 2011) which included participants with

type 1 diabetes. The remaining studies included did not explicitly specify the patient characteristics in relation to type of diabetes and did not provide evidence split by the type of diabetes. However, the committee highlighted that DKA is rare in people with type 2 diabetes and management of DKA would not differ based on the type of diabetes. Therefore, studies which did not separate out data by type of diabetes were not downgraded. Furthermore, specific recommendations were not made based on type of diabetes.

Subgroup analysis for different age groups (children under 5, school age children and adolescents) was planned during the review protocol stage. However, evidence was not identified for different age groups. Therefore, no specific recommendations were made based on age.

1.1.11.3 Benefits and harms

The committee noted the current recommendations on route of administration of fluids were ambiguous as in practice IV fluids are preferred in children with DKA. IV fluids can also be switched to oral fluids when the child or young person is alert and not nauseated or vomiting. Based on their clinical understanding, the committee retained the existing recommendation which states that DKA should be treated with intravenous fluids and intravenous insulin if the child or young person is not alert, is nauseated or vomiting or is clinically dehydrated. They also retained an existing recommendation that states that oral fluids should not be given to a child or young person who is receiving IV fluids for DKA unless ketosis is resolving, they are alert and they are not nauseated or vomiting. The committee also expanded on another existing recommendation and stated that clinicians can think about stopping IV fluid therapy for DKA in a child or young person if ketosis is resolving, their pH has reached 7.3, they are alert, and they can take oral fluids without nausea or vomiting. It should also be noted that no evidence was identified in the search which compared in particular different routes of administration or different oral fluids for rehydration. Therefore, specific recommendations for oral fluids were not made.

When reviewing the evidence for type of fluids for rehydration, the committee noted that the evidence did not favour any of the interventions. While there were some significant results, evidence for the critical outcomes (cerebral oedema and mortality) did not favour an IV fluid for rehydration. A similar trend was also observed with evidence for rate, and volume of rehydration.

The committee noted that both fluid protocols followed in the Kupperman study were safe to use as the study did not identify a significant difference in mortality or clinically apparent brain injury. This study was considered high in quality and also had a large sample size (*n* 1361). While the pathogenesis of cerebral oedema is not completely understood, the study highlighted that cerebral oedema is a feature of clinically apparent brain injury and often develops hours or days after diagnosis of brain injury. This finding suggests that cerebral oedema may be a consequence rather than a cause of brain injury. The committee further noted that the trial highlighted that restrictions to fluid administration as advised in the 2015 guideline were not necessarily required.

In line with the evidence identified from the PECARN Trial and applying their clinical expertise, the committee recommended that for children and young people who are hypovolaemic but not in shock, an initial bolus of 10ml/kg of 0.9% sodium chloride should be given over 30 minutes. A second bolus may be considered to improve tissue perfusion. Separate recommendations were also developed for children and young people who present with shock. The committee further recommended that before giving more than one IV fluid

bolus of 10 ml/kg 0.9% sodium chloride, it should be discussed with the responsible senior paediatrician.

The committee also highlighted that separate recommendations were necessary for children and young people with signs of shock. Recommendations developed in 2015 stated that IV bolus should not be given to children and young people with mild or moderate DKA and should not be routinely given to children and young people with severe DKA. The rationale provided for these recommendations further stated that fluid bolus should be avoided unless there are signs of shock associated with poor urine output or hypotension.

The committee noted that while shock is a rare occurrence in children and young people with DKA, it can occur, and such patients require more fluid boluses to improve tissue perfusion. Furthermore, the committee highlighted that restricting initial fluid boluses can result in less fluids being administered over the 48-hour period. The committee stated that this may be problematic as recent hypothesis and data suggests that brain injury may result from cerebral hypoperfusion and the effects of reperfusion and neuro-inflammation that occurs during episodes of DKA. The committee highlighted that the 2015 recommendations could have been made with the risk of cerebral oedema in mind as the previous hypothesis stated that rapid administration of IV fluids reduces serum osmolality which results in brain swelling. Based on their clinical judgment and the RCT evidence identified in the review, particularly the PECARN Trial, the committee recommended that in children and young people with DKA who have signs of shock, an initial intravenous bolus of 20 ml/kg 0.9% sodium chloride should be given as soon as possible.

The committee further highlighted that assessment of dehydration is generally poor in children and young people with DKA and the current recommendations on calculating total fluid requirement can result in less fluid being given over the 48-hour period. The committee also highlighted that this recommendation is not in line with current practice. Based on RCT evidence identified in this review, particularly the PECARN trial, the committee retained recommendations on calculating the fluid deficit and stated that in children and young people with mild to moderate DKA, 5% dehydration should be assumed. This means that a child weighing 10kg who is 5% dehydrated would have a water deficit of 500mls. Furthermore, 10% dehydration should be assumed in children and young people with severe DKA.

The recommendation for calculating fluid maintenance requirement was amended to include the Holliday-Segar formula. The committee noted that this formula has been shown to be safe with no adverse events and is commonly used in practice. The International Society for Paediatric and Adolescent Diabetes (ISPAD) guideline and the British Society of Paediatric Endocrinology and Diabetes (BSPED) guideline also recommend the use of this formula when calculating maintenance requirement.

The committee noted that the new recommendations will provide a more balanced approach for calculating the total fluid requirement. However, the committee did highlight that caution must be taken when calculating the fluid requirement for children and young people who are obese. Based on their clinical understanding, the committee agreed that a maximum weight of 75kg should be used in calculating fluid requirement for children and young people who are obese as this is approaching fluid requirements of adults with DKA. This will avoid excessive fluid administration and minimise risks in children and young people who are obese.

No evidence was identified for the use of potassium in the management of DKA. However, the committee highlighted that children and young people with DKA can develop hypokalaemia which occurs when there is a significant depletion of potassium in the body. Based on their clinical expertise and their understanding of the evidence on the

pathophysiology of DKA the committee retained the existing recommendation but expanded it to state that 40 mmol/litre potassium chloride should be added in all fluids (except the initial intravenous boluses) unless the child or young person with DKA has acute kidney injury or their potassium level is above the normal range.

The committee further highlighted that the administration of insulin and correction of acidosis, drives potassium into the cells and can lead to a fall in potassium levels. This is a major concern as this can cause cardiac arrhythmias and mortality. This means that treatment should not be delayed in children and young people with potassium levels above normal range. Based on their clinical understanding, the committee recommended that in this population, potassium should only be added if the potassium level is less than 5.5 mmol/litre or they have passed urine, which gives the assurances that the child or young person does not have renal failure.

Hypoglycaemia is another complication that can occur in children and young people with DKA. No evidence was identified in the search for the addition of glucose to IV fluids. Therefore, the committee retained the current recommendations which state that 0.9% sodium chloride should be used without added glucose for both rehydration and maintenance fluid until the plasma glucose concentration is below 14 mmol/ litre. When the glucose concentration falls below 14 mmol/litre, fluids should be changed to 0.9% sodium chloride with 5% glucose and 40mmol/litre potassium chloride.

Limited evidence was identified which examined the effectiveness of adding sodium bicarbonate compared to no sodium bicarbonate. However, the evidence did not favour the use of sodium bicarbonate as an additive to IV fluids. Based on this evidence and their clinical understanding the committee agreed that sodium bicarbonate should not be routinely used. The committee also further highlighted a small number of children and young people with DKA can exhibit compromised cardiac contractility caused by life-threatening hyperkalaemia or severe acidosis. Such seriously ill children and young people can benefit from intravenous sodium bicarbonate. Based on this understanding, the committee expanded on the current recommendation to state that intravenous sodium bicarbonate should not be given to children and young people with DKA unless their cardiac contractility has been compromised by life-threatening hyperkalaemia or severe acidosis. The committee also agreed that before starting treatment, the decision should be discussed with the paediatric intensivist.

1.1.11.4 Cost effectiveness and resource use

No economic evidence was identified for this review question. The committee noted that new recommendations are in line with current practice and therefore should result in negligible cost differences. As the costs and consequences of adverse effects are severe, cost-effectiveness is driven by treatment effectiveness.

1.1.11.5 Other factors the committee took into account

The committee removed a recommendation which states that clinicians may consider inserting a urinary catheter if it is not possible to accurately measure urine output for a child or young person with DKA. While the committee agreed it was important to monitor patients, urinary catheterisation is not a commonly used in practice but may be adopted in an intensive care scenario when managing a seriously ill child or young person with DKA. As this is general guidance, the committee did not think a recommendation on urinary catheterisation was within the remit of this guideline.

The committee also highlighted that no prospective audits have been established to monitor change in practice after the 2015 DKA recommendations were produced. The committee agreed that it was important to assess the implementation of these updated recommendations in practice. As there is not an existing audit, the committee could not make any research recommendations but agreed that an audit of practice would be valuable.

Finally, the committee identified the following equality issues:

- Age – children under the age of five have a greater risk of DKA
- Race – Black and minority ethnic children present to hospital with DKA more frequently
- Sex - girls and young women are more likely to develop DKA
- Socio-economic factors - Children and young people in the most deprived areas of the UK are more likely to be hospitalised for DKA

The committee considered these equality issues but were of the opinion that these did not directly impact on fluid therapy for the management of DKA in children and young people. These equality issues would not influence the optimal route of fluid administration, type of fluid (including additives) or the rate and volume for rehydration in children and young people with DKA.

1.1.12 Recommendations supported by this evidence review

This evidence review supports recommendations 1.4.21 – 1.4.29, 1.4.34, 1.4.35 and 1.4.37.

1.4.21 Treat DKA with intravenous fluids and intravenous insulin if the child or young person is not alert, is nauseated or vomiting, or is clinically dehydrated. [2020]

1.4.22 Do not give oral fluids to a child or young person who is receiving intravenous fluids for DKA unless ketosis is resolving, they are alert, and they are not nauseated or vomiting. [2020]

1.4.23 For children and young people who are hypovolaemic but not in shock:

- give an initial intravenous bolus of 10 ml/kg 0.9% sodium chloride over 30 minutes
- only consider giving a second intravenous bolus if needed to improve tissue perfusion
- discuss with the responsible senior paediatrician before giving more than one intravenous bolus of 10 ml/kg 0.9% sodium chloride to a child or young person with DKA
- when calculating the total fluid requirement, exclude these initial bolus volumes from the total. [2020]

1.4.24 For children and young people who have signs of shock (weak thread pulse, tachycardia, prolonged capillary refill, tachypnoea or hypotension), give an initial intravenous bolus of 20 ml/kg 0.9% sodium chloride as soon as possible. Be aware that shock is rare in children and young people with DKA. [2020]

1.4.25 Calculate the total fluid requirement for the first 48 hours in children and young people with DKA by adding the estimated fluid deficit to the fluid maintenance requirement:

- For the fluid deficit:
  - in mild to moderate DKA (blood pH 7.1 or above), assume 5% dehydration (so a 10 kg child needs 500 ml)
  - in severe DKA (blood pH below 7.1), assume 10% dehydration
  - aim to replace the deficit evenly over the first 48 hours.
- For the fluid maintenance requirement, use the Holliday-Segar formula:
  - give 100 ml/kg for the first 10 kg of weight
  - give 50 ml/kg for the second 10 kg of weight
  - give 20 ml/kg for every kg after this
  - use a maximum weight of 75 kg in the calculation.

When calculating the total fluid requirement, exclude any initial bolus volumes given. [2020]

1.4.26 Use 0.9% sodium chloride without added glucose for both rehydration and maintenance fluid in children and young people with DKA, until the plasma glucose concentration is below 14 mmol/litre. [2020]

1.4.27 Include 40 mmol/litre potassium chloride in all fluids (except the initial intravenous boluses) given to children and young people with DKA, unless they have acute kidney injury or their potassium level is above the normal range. [2020]

1.4.28 For children and young people with potassium levels above the normal range, only add 40 mmol/litre potassium chloride to their intravenous fluids if:

- their potassium is less than 5.5 mmol/litre or
- they have passed urine [2020]

1.4.29 Do not give intravenous sodium bicarbonate to children and young people with DKA unless:

- they have compromised cardiac contractility, caused by life-threatening hyperkalaemia or severe acidosis and
- you have discussed with the paediatric intensivist. [2020]

1.4.34 When the plasma glucose concentration falls below 14 mmol/litre in children and young people with DKA, change fluids to 0.9% sodium chloride with 5% glucose and 40 mmol/litre potassium chloride. [2020]

1.4.35 If a child or young person's plasma glucose falls below 6 mmol/litre during DKA treatment:

- increase the glucose concentration of the intravenous fluid infusion and
- if they have persisting ketosis, continue to give insulin at a dosage of least 0.05 units/kg/hour. [2020]

1.4.37 Think about stopping intravenous fluid therapy for DKA in a child or young person if ketosis is resolving, their pH has reached 7.3, they are alert, and they can take oral fluids without nausea or vomiting. [2020]

1.1.13 References – included studies

1.1.13.1 Effectiveness

RCTs

Bakes, Katherine, Haukoos, Jason S, Deakyne, Sara J et al. (2016) Effect of Volume of Fluid Resuscitation on Metabolic Normalization in Children Presenting in Diabetic Ketoacidosis: A Randomized Controlled Trial. The Journal of emergency medicine 50(4): 551-9

Glaser NS, Wootton-Gorges SL, Buonocore MH et al. (2013) Subclinical cerebral edema in children with diabetic ketoacidosis randomized to 2 different rehydration protocols. Pediatrics 131(1): e73

Kuppermann, Nathan, Ghetti, Simona, Schunk, Jeff E et al. (2018) Clinical Trial of Fluid Infusion Rates for Pediatric Diabetic Ketoacidosis. The New England journal of medicine 378(24): 2275-2287

Shafi, Obeid and Kumar, Virendra (2018) Initial Fluid Therapy in Pediatric Diabetic Ketoacidosis: A comparison of Hypertonic Saline Solution and Normal Saline Solution. Pediatric endocrinology, diabetes, and metabolism 24(2): 56-64

Williams, V., Jayashree, M., Nallasamy, K. et al. (2020) 0.9% saline versus Plasma-Lyte as initial fluid in children with diabetic ketoacidosis (SPinK trial): A double-blind randomized controlled trial. Critical Care 24(1): 1

Yung, Michael; Letton, Georgia; Keeley, Steve (2017) Controlled trial of Hartmann's solution versus 0.9% saline for diabetic ketoacidosis. Journal of paediatrics and child health 53(1): 12-17

Observational studies

Basnet, Sangita, Venepalli, Preethi K, Andoh, Jennifer et al. (2014) Effect of normal saline and half normal saline on serum electrolytes during recovery phase of diabetic ketoacidosis. Journal of intensive care medicine 29(1): 38-42

Bergmann, Kelly R, Abuzzahab, M Jennifer, Nowak, Jeffrey et al. (2018) Resuscitation With Ringer's Lactate Compared With Normal Saline for Pediatric Diabetic Ketoacidosis. Pediatric emergency care

Felner EI and White PC (2001) Improving management of diabetic ketoacidosis in children. Pediatrics 108(3): 735-740

Green SM, Rothrock SG, Ho JD et al. (1998) Failure of adjunctive bicarbonate to improve outcome in severe pediatric diabetic ketoacidosis. Annals of emergency medicine 31(1): 41-48

Mar TJ, Traisman HS, Traisman ES et al. (1981) Juvenile ketoacidosis. The use of sodium bicarbonate in the treatment of diabetic children. The Journal of the Kansas Medical Society 82(6): 282-284

Savaş-Erdeve Ş, Berberoğlu M, Oygar P et al. (2011) Efficiency of fluid treatments with different sodium concentration in children with type 1 diabetic ketoacidosis. Journal of clinical research in pediatric endocrinology 3(3): 149-153

1.1.13.2 Economic

None

1.1.13.3 Other

None

1 Appendices

2 Appendix A – Review protocols

3 Review protocol for fluid therapy for the management of DKA

ID	Field	Content
0.	PROSPERO registration number	N/ A
1.	Review title	Route of administration, type of fluid and rate and volume of rehydration for the management of diabetic ketoacidosis (DKA)
2.	Review question	In children and young people with diabetic ketoacidosis: • What is the appropriate route of fluid administration for rehydration? • What fluids (including additives) should be used for rehydration? • At what rate, including volume of fluid should children and young people be rehydrated?

3.	Objective	To determine the optimal route of administration, type of fluid (including additives) and rate and volume for rehydration in children and young people with DKA.
4.	Searches	The following databases will be searched: Clinical searches: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • DARE • MEDLINE • MEDLINE In Process • MEDLINE ePubs • Emcare Economic searches: • Econlit • Embase • HTA • MEDLINE • MEDLINE In Process

		• MEDLINE ePubs • NHS EED • Emcare Searches will be restricted by: • English language • Study designs of RCTs, SRs and observational studies will be applied • Animal studies will be excluded from the search results • Conference abstracts will be excluded from the search results • The search will be date limited to find studies from 1st June 2014 to present Other searches: • The MHRA website will be searched for reports of adverse events The searches will be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion (depending on publication date).

		The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Diabetic ketoacidosis in children and young people with type 1 and type 2 diabetes.
6.	Population	Inclusion: Children and young people with type 1 or type 2 diabetes with diabetic ketoacidosis (although the diabetes may not yet have been recognised, for example, if the child or young person is presenting for the first time with DKA) Diabetic ketoacidosis: A serious complication of diabetes. Diagnosis in children and young people who have: • Acidosis and a bicarbonate of <15 mmol/L **or** pH <7.3 and • Ketones > 3.0 mmol per litre Severity of DKA is categorised by the degree of acidosis: • **Mild DKA**: venous pH <7.3 or serum bicarbonate <15 mmol/L • **Moderate DKA**: venous pH <7.2 or serum bicarbonate <10 mml/L • **Severe DKA**: venous pH <7.1 or serum bicarbonate <5 mmol/L Definition based on the International Society for Paediatric and Adolescent Diabetes (ISPAD) 2018 consensus guideline on diabetic ketoacidosis and hyperglycaemic hyperosmolar state.

		Studies using different definitions of diabetic ketoacidosis will be included and assessed appropriately through GRADE by downgrading for indirectness. **Note:** Children and young people are defined as those younger than 18 years of age. In practice, children and young people can also be defined as aged 18 years and up to the 19th birthday when considering paediatric best practice tariffs. Studies including children and young people aged younger than 18 years and those including young people aged 18 years and up to their 19th birthday will be considered for inclusion. Exclusion: Children and young people with other forms of diabetes mellitus (for example, monogenic diabetes and cystic fibrosis-related diabetes) Studies which include a mixed population (children and young people with type 1 or type 2 diabetes) but do not report the data separately will also be included
7.	Intervention	**Route of administration:** • Oral • Intravenous

		Type of fluids:
		• Any isotonic fluid that can be taken orally
		
		• Fluids administered intravenously:
		  ○ Saline (sodium chloride) solution at different concentrations (e.g. 0.45% or 0.9%)
		  ○ Hartmann's solution
		  ○ Ringer's lactate solution
		• IV fluid with additives:
		  ○ Glucose
		  ○ Potassium
		  ○ Bicarbonate
		  ○ Phosphate
		
		Volume and rate of rehydration:
		• Oral:
		  ○ Different volumes e.g. high volume or low volume (as defined by author)
		• IV:
		  ○ Different rates e.g. rapid rate, fast rate or slow rate (as defined by author)
		  ○ Different volumes e.g. high volume or low volume (as defined by author)

8.	Comparator	**Route of administration:** • Oral vs IV

		Type of fluids:
		• Different oral fluids compared to each other*
		• Different intravenous fluids compared to each other*
		  ○ Different additives compared to each other**
		  ○ Additives compared to no additives. **
		* Rate and volume should be the same in both arms of the study.
		** Fluid regimen should be the same in both arms of the study.
		Volume and rate of rehydration:
		Oral fluids:
		• Different volumes compared to each other (low volume vs. high volume)***
		IV fluids:
		• Different rates compared to each other (e.g. slow rate vs. rapid rate) ***
		• Different volumes compared to each other (low volume vs. high volume) ***
		*** Type of fluid and route of administration should be the same in both arms of the study.

9.	Types of study to be included	• Systematic reviews and RCTs • Comparative prospective observational studies ○ If no comparative prospective observational studies are identified, comparative retrospective observational studies will be included.
10.	Other exclusion criteria	• Non-English language studies

		• Conference abstracts
11.	Context	This review is part of an update of the NICE guideline on diabetes (type 1 and type 2) in children and young people: diagnosis and management. This guideline covers children and young people (younger than 18 years) with type 1 and type 2 diabetes. This guideline will also cover all settings in which NHS care is received or commissioned.
12.	Primary outcomes (critical outcomes)	• Mortality • Incidence of cerebral oedema (this could cause morbidity or mortality), to include participants with symptoms or signs suggestive of cerebral oedema (for example, development of unconsciousness) provided these are reported as being related to cerebral oedema Note: Core outcome sets were explored however none were identified for this population. Important follow up points: • During treatment (first hour, 24 hours, 48 hours) • After recovery from DKA (up to a week, 3 months or 6 months post discharge or recover) For further information on how data will be analysed see Section 16.
13.	Secondary outcomes (important outcomes)	• Time to resolution of dehydration • Rate of change of blood glucose concentration or resolution of hyperglycaemia • Resolution of acidosis/ resolution of ketosis • Serum chloride concentration • Serum sodium concentration • Healthcare utilisation (for example, duration of admission, requirement for ventilation [as a proxy for severity of DKA or presence of cerebral oedema]) • Acute cases of renal failure

		• Neurologic status - decline in neurological status measured using validated scores such as the Glasgow Coma Scale score (e.g. magnitude of decline or the duration of time in which GCS was less than 14) • IQ (assessed using validated scales such as the Wechsler Preschool and Primary School Scale of Intelligence short form) Note: Core outcome sets were explored however none were identified for this population.
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. This review will make use of the priority screening functionality within the EPPI-reviewer software. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). Study investigators may be contacted for missing data where time and resources allow.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. Randomised control trials (individuals or cluster) will be assessed using the Cochrane risk of bias tool 2.0.

		Assessment of observational studies will be dependent on study design. Cohort studies will be assessed using the Cochrane ROBINS-1 tool.

16.	Strategy for data synthesis	For details please see section 6 of Developing NICE guidelines: the manual
		
		Both RCTs and comparative observational studies will be included in the review. When conducting GRADE, RCT evidence will start as high quality evidence while comparative observational evidence will start as moderate quality evidence.
		
		Meta-analysis will be conducted where appropriate.
		
		Evidence will be stratified ~~grouped~~ in the following categories:
		
		• Type 1 diabetes
		
		• Type 2 diabetes
		
		Furthermore, outcomes in these categories will be stratified into the following time-points:
		
		• During treatment:
		  ○ first hour
		  ○ 24 hours
		  ○ 48 hours
		• After recovery from DKA and patient discharge:
		  ○ Up to a week post discharge or recovery from DKA
		  ○ 3 months post discharge or recovery from DKA (or the one nearest to 3 months if multiple time-points are given)

		○ 6 months post discharge or recovery from DKA (or the one nearest to 6 months if multiple time-points are given) Studies which include a mixed population (children and young people with type 1 or type 2 diabetes) but do not report the data separately will also be included and will be assessed appropriately through GRADE by downgrading for indirectness. These studies will also be analysed separately to studies including children and young people with type 1 or type 2 diabetes. Additionally, a definition of ketoacidosis has been provided but studies using different definitions will be included and assessed appropriately through GRADE by downgrading for indirectness. Specific definitions have not been provided for different rates (e.g. rapid, fast or slow rate) or volumes (e.g. high or low volume). Definitions provided by the authors will be included and pooled together in the meta-analysis.

17.	Analysis of sub-groups	For all three questions results will be stratified by the following subgroups where possible:
		• Age:
		  ○ Children under 5s
		  ○ School age children (5-12 years)
		  ○ Adolescents (>12 years)
		• Recognised diabetes (defined as a child known to have diabetes mellitus)
		• First presentation of diabetes (e.g. if the child or young person is presenting for the first time with DKA)
		• Severity of DKA(based on ISPAD definition (see Section 6))
		
		For question examining the rate and volume of fluid administration:
		• results will be stratified by type of fluid.
		
		For question examining type of fluid:
		• results will be stratified by rate and volume of fluid
		
		If heterogeneity is present, a random effects (RE) model will be adapted.

18.	Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic

		☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)		
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	6/12/19		
22.	Anticipated completion date	16/12/20		
23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches	☐	☐
		Piloting of the study	☐	☐

		selection process		
		Formal screening of search results against eligibility criteria	☐	☐
		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Named contact	**5a. Named contact** Guideline Updates Team		

		5b Named contact e-mail Diabetesupdate@nice.org.uk **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE)
25.	Review team members	From the Guideline Updates Team: • Dr Caroline Mulvihill • Ms Shreya Shukla • Mr Gabriel Rogers • Mr Thomas Jones • Ms Sarah Glover
26.	Funding sources/sponsor	This systematic review is being completed by the Centre for Guidelines which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part

		of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10158
29.	Other registration details	None
30.	Reference/URL for published protocol	None
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	Diabetic ketoacidosis, rehydration, fluid therapy, volume, rate, cerebral oedema, children, young people
33.	Details of existing review of same topic by same authors	None

34.	Current review status	☒ Ongoing ☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35..	Additional information	
36.	Details of final publication	www.nice.org.uk

Appendix B - Methods

Priority screening

The reviews undertaken for this guideline all made use of the priority screening functionality with the EPPI-reviewer systematic reviewing software. This uses a machine learning algorithm (specifically, an SGD classifier) to take information on features (1, 2 and 3 word blocks) in the titles and abstract of papers marked as being 'includes' or 'excludes' during the title and abstract screening process, and re-orders the remaining records from most likely to least likely to be an include, based on that algorithm. This re-ordering of the remaining records occurs every time 25 additional records have been screened. Due to the number of records identified for this review, a stopping criterion was not used when conducting screening. Therefore, all records were screened.

As an additional check to ensure this approach did not miss relevant studies, the included studies lists of included systematic reviews were searched to identify any papers not identified through the primary search. If additional studies were identified that were erroneously excluded during the priority screening process, the full database was subsequently screened.

Evidence of effectiveness of interventions

Both RCTs and cohort studies were included in this review. RCTs were considered high quality evidence. During the development of the review protocol, it was agreed that comparative observational studies would start as moderate quality evidence. However, during quality assessment ROBINS-I tool was utilised which uses one unified scale of risk of bias across study types. Therefore, observational studies were also considered high quality.

Quality assessment

Individual RCTs were quality assessed using the Cochrane Risk of Bias Tool 2.0. Cohort studies were quality assessed using the ROBINS-I tool. Each individual study was classified into one of the following groups:

- Low risk of bias – The true effect size for the study is likely to be close to the estimated effect size.
- Moderate risk of bias – There is a possibility the true effect size for the study is substantially different to the estimated effect size.
- High risk of bias – It is likely the true effect size for the study is substantially different to the estimated effect size.
- Critical risk of bias (ROBINS-I only) - It is very likely the true effect size for the study is substantially different to the estimated effect size.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, intervention, comparator and/or outcomes in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, intervention, comparator and/or outcomes.

- Partially indirect – Important deviations from the protocol in one of the following areas: population, intervention, comparator and/or outcomes.
- Indirect – Important deviations from the protocol in at least two of the following areas: population, intervention, comparator and/or outcomes.

Methods for combining intervention evidence

Meta-analyses of interventional data were conducted with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011).

Where different studies presented continuous data measuring the same outcome but using different numerical scales (e.g. a 0-10 and a 0-100 visual analogue scale), these outcomes were all converted to the same scale before meta-analysis was conducted on the mean differences. Where outcomes measured the same underlying construct but used different instruments/metrics, data were analysed using standardised mean differences (Hedges' g).

A pooled relative risk was calculated for dichotomous outcomes (using the Mantel–Haenszel method) reporting numbers of people having an event, and a pooled incidence rate ratio was calculated for dichotomous outcomes reporting total numbers of events. Both relative and absolute risks were presented, with absolute risks calculated by applying the relative risk to the risk in the comparator arm of the meta-analysis (calculated as the total number events in the comparator arms of studies in the meta-analysis divided by the total number of participants in the comparator arms of studies in the meta-analysis).

Fixed- and random-effects models (der Simonian and Laird) were fitted for all syntheses, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models were the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model were clearly not met, even after appropriate pre-specified subgroup analyses were conducted, random-effects results are presented. Fixed-effects models were deemed to be inappropriate if one or both of the following conditions was met:

- Significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. This decision was made and recorded before any data analysis was undertaken.
- The presence of significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$.

However, in cases where the results from individual pre-specified subgroup analyses are less heterogeneous (with $I^2 < 50\%$) the results from these subgroups will be reported using fixed effects models. This may lead to situations where pooled results are reported from random-effects models and subgroup results are reported from fixed-effects models.

In situations where subgroup analyses were conducted, pooled results and results for the individual subgroups are reported when there was evidence of between group heterogeneity, defined as a statistically significant test for subgroup interactions (at the 95% confidence level). Where no such evidence as identified, only pooled results are presented.

In any meta-analyses where some (but not all) of the data came from studies at critical or high risk of bias, a sensitivity analysis was conducted, excluding those studies from the analysis. Results from both the full and restricted meta-analyses are reported. Similarly, in any meta-analyses where some (but not all) of the data came from indirect studies, a sensitivity analysis was conducted, excluding those studies from the analysis.

Meta-analyses were performed in Cochrane Review Manager V5.3, with the exception of incidence rate ratio analyses which were carried out in R version 3.3.4.

Minimal clinically important differences (MIDs)

The Core Outcome Measures in Effectiveness Trials (COMET) database was searched to identify published minimal clinically important difference thresholds relevant to this guideline. Identified MIDs were assessed to ensure they had been developed and validated in a methodologically rigorous way, and were applicable to the populations, interventions and outcomes specified in this guideline.

In addition, the Guideline Committee were asked to prospectively specify any outcomes where they felt a consensus MID could be defined from their experience. In particular, any questions looking to evaluate non-inferiority (that one treatment is not meaningfully worse than another) required an MID to be defined to act as a non-inferiority margin.

No MIDs were identified through this process. Therefore, for continuous outcomes expressed as a mean difference where no other MID was available, an MID of 0.5 of the median standard deviations of the comparison group arms was used (Norman et al. 2003). For continuous outcomes expressed as a standardised mean difference where no other MID was available, an MID of 0.5 was used. For relative risks and hazard ratios, where no other MID was available, the line of no effect was used.

When decisions were made in situations where MIDs were not available, the 'Evidence to Recommendations' section of that review makes explicit the committee's view of the expected clinical importance and relevance of the findings. In particular, this includes consideration of whether the whole effect of a treatment (which may be felt across multiple independent outcome domains) would be likely to be clinically meaningful, rather than simply whether each individual sub outcome might be meaningful in isolation.

GRADE for pairwise meta-analyses of interventional evidence

GRADE was used to assess the quality of evidence for the selected outcomes as specified in 'Developing NICE guidelines: the manual (2014)'. Data from randomised controlled trials, non-randomised controlled trials and comparative observational studies were initially rated as high quality.. The quality of the evidence for each outcome was downgraded or not from this initial point, based on the criteria given in Table 1.

Table 1: Rationale for downgrading quality of evidence for intervention studies

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels.

GRADE criteria	Reasons for downgrading quality
	Extremely serious: If greater than 33.3% of the weight in a meta-analysis came from studies at critical risk of bias, the outcome was downgraded three levels Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies at high and low risk of bias.
Indirectness	Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between direct and indirect studies.
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I^2 statistic. N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study. Not serious: If the I^2 was less than 33.3%, the outcome was not downgraded. Serious: If the I^2 was between 33.3% and 66.7%, the outcome was downgraded one level. Very serious: If the I^2 was greater than 66.7%, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies with the smallest and largest effect sizes.
Imprecision	If an MID other than the line of no effect was defined for the outcome, the outcome was downgraded once if the 95% confidence interval for the effect size crossed one line of the MID, and twice if it crosses both lines of the MID. If the line of no effect was defined as an MID for the outcome, it was downgraded once if the 95% confidence interval for the effect size crossed the line of no effect (i.e. the outcome was not statistically significant), and twice if the sample size of the study was sufficiently small that it is not plausible any realistic effect size could have been detected. If relative risk could not be estimated (due to zero events in both arms), outcome was downgraded for very serious imprecision as effect size could not be calculated.

GRADE criteria	Reasons for downgrading quality
	Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios.

Summary of evidence is presented in section 1.1.6. This summarises the effect size, quality of evidence and interpretation of the evidence in relation to the significance of the data.

Evidence was also identified for which GRADE could not be applied as the evidence was presented in the form of median and interquartile range. This evidence is presented in Appendix G. This evidence has been summarised narratively in section 1.1.10.

Appendix C – Literature search strategies

Clinical

Database: MEDLINE
Strategy used: Database: Ovid MEDLINE(R) <1946 to February 11, 2020> Search Strategy: --- 1 Diabetic Ketoacidosis/ (6312) 2 (DK or DKA).tw. (3081) 3 (DM adj4 (keto* or acidi* or gastropare*)).tw. (71) 4 or/1-3 (8271) 5 exp Diabetes Mellitus/ (417002) 6 diabet*.tw. (532080) 7 (DM adj4 ("type 1" or type1 or "type I" or "type one" or T1 or T-1 or TI or T-I)).tw. (1609) 8 lada.tw. (522) 9 (dm1 or iddm or t1d* or dka).tw. (18609) 10 (dm2 or t2d* or mody or niddm).tw. (30739) 11 (DM adj4 ("type 2" or type2 or "type ii" or "type two" or T2 or T-2 or TII or T-II)).tw. (4115) 12 (DM adj4 (autoimmun* or auto immun* or brittle or labile or insulin depend* or insulin deficien*)).tw. (305) 13 (DM adj4 onset* adj4 (maturit* or adult* or slow*)).tw. (62) 14 (DM adj4 depend* adj4 (non-insulin* or non insulin* or noninsulin*)).tw. (90) 15 (DM adj4 (earl* or sudden onset or juvenile or child*)).tw. (833) 16 or/5-15 (596510) 17 Ketosis/ (2147) 18 (keto* or acidos* or acidoketos* or ketoacidaemi* or ketoacidemi* or hyperketo* or hyper-keto* or ketotic or ketonuri* or keton?emi* or acetonemi* or acetonuri*).tw. (120208)

19 17 or 18 (120408)

20 16 and 19 (12328)

21 4 or 20 (15588)

22 exp Fluid Therapy/ (19860)

23 Rehydration Solutions/ (1444)

24 Water-Electrolyte Balance/ (28875)

25 Water-Electrolyte Imbalance/ (5182)

26 (fluid* or solution* or electrolyte* or hydrat* or rehydrat* or re-hydrat* or "re hydrat*" or resuscitat*).tw. (1017177)

27 Drug Administration Routes/ (5625)

28 (drug adj4 admin* adj4 route*).tw. (1229)

29 (drug adj4 deliver* adj4 system*).tw. (20322)

30 Administration, Oral/ (140742)

31 Administration, Intravenous/ (8655)

32 (oral* or intravenous or IV).tw. (1108706)

33 ((vein or venous) adj4 (infus* or inject* or drip or transfus*)).tw. (9714)

34 Infusions, Intravenous/ (54472)

35 Infusions, Intraosseous/ (713)

36 ((intra-osseous or intraosseous or IO or intra-bone or intrabone or "intra bone" or system* or pump* or subcutan* or drip) adj4 (infus* or inject* or admin* or appl*)).tw. (140740)

37 infusor*.tw. (400)

38 (perfusion adj4 pump*).tw. (614)

39 exp Infusions, Subcutaneous/ (1166)

40 hypodermoclysis.tw. (120)

41 Infusion Pump/ (5300)

42 Intubation, Gastrointestinal/ (9580)

43 (intubat* adj4 (gastrointestin* or gastro-intestin* or "gastro intestin*" or nasogastric*)).tw. (551)

44 (fluid bolus or two bag or ORT).tw. (1467)

45 Time Factors/ (1174507)

46	(time adj4 factor*).tw. (18669)
47	Drug Administration Schedule/ (99082)
48	(drug adj4 admin* adj4 schedul*).tw. (418)
49	(drug adj4 deliver* adj4 schedul*).tw. (92)
50	Sodium/ (105097)
51	(sodium* or salt*).tw. (428840)
52	(acetic adj4 acid).tw. (32894)
53	exp Chlorides/ (133636)
54	(chloride* or chlorhydrate* or hydrochloride* or monochloride*).tw. (161267)
55	Glucose/ or Glucose Solution, Hypertonic/ (154527)
56	(glucose or d-glucose or dextrose or l-glucose).tw. (414560)
57	Saline Solution, Hypertonic/ (5551)
58	Saline Solution/ or Ringer's Lactate/ (1720)
59	(saline* or Na-Cl* or Na-Cl* or Nacl* or NaCl* or hartmann* or ringer*).tw. (227442)
60	exp Bicarbonates/ (24576)
61	(bicarbonate* or dicarbonate* or baros* or hydrocarbonate*).tw. (27786)
62	(hydrogen adj4 carbonate*).tw. (365)
63	(carbonic adj4 acid adj4 ion*).tw. (25)
64	Potassium/ or Potassium Acetate/ (100804)
65	(potassium or KCL or K39 or Kalium).tw. (137963)
66	Phosphates/ (62400)
67	(phosphate* or orthophosphate*).tw. (231304)
68	or/22-67 (4489626)
69	21 and 68 (7355)
70	animals/ not humans/ (4639408)
71	69 not 70 (6243)
72	limit 71 to english language (5266)
73	limit 72 to ed=20140601-20200212 (1261)

74 randomized controlled trial.pt. (500124)

75 randomi?ed.mp. (777830)

76 placebo.mp. (191641)

77 or/74-76 (828897)

78 (MEDLINE or pubmed).tw. (154671)

79 systematic review.tw. (112785)

80 systematic review.pt. (121052)

81 meta-analysis.pt. (110859)

82 intervention$.ti. (119270)

83 or/78-82 (362134)

84 77 or 83 (1087093)

85 Observational Studies as Topic/ (4691)

86 Observational Study/ (74656)

87 Epidemiologic Studies/ (8208)

88 exp Case-Control Studies/ (1055845)

89 exp Cohort Studies/ (1956602)

90 Cross-Sectional Studies/ (318160)

91 Controlled Before-After Studies/ (481)

92 Historically Controlled Study/ (171)

93 Interrupted Time Series Analysis/ (779)

94 Comparative Study.pt. (1854161)

95 case control$.tw. (109277)

96 case series.tw. (56935)

97 (cohort adj (study or studies)).tw. (160838)

98 cohort analy$.tw. (6389)

99 (follow up adj (study or studies)).tw. (44470)

100 (observational adj (study or studies)).tw. (81969)

101 longitudinal.tw. (197436)

102 prospective.tw. (482132)

103 retrospective.tw. (426166)

104 cross sectional.tw. (272513)

105 or/85-104 (4279920)

106 73 and 84 (229)

107 73 and 105 (407)

108 106 or 107 (558)

1

Database: MEDLINE IN PROCESS

Strategy used:

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to February 11, 2020>

Search Strategy:

---

1 Diabetic Ketoacidosis/ (0)

2 (DK or DKA).tw. (596)

3 (DM adj4 (keto* or acidi* or gastropare*)).tw. (11)

4 or/1-3 (603)

5 exp Diabetes Mellitus/ (0)

6 diabet*.tw. (68328)

7 (DM adj4 ("type 1" or type1 or "type I" or "type one" or T1 or T-1 or TI or T-I)).tw. (290)

8 lada.tw. (74)

9 (dm1 or iddm or t1d* or dka).tw. (2571)

10 (dm2 or t2d* or mody or niddm).tw. (6801)

11 (DM adj4 ("type 2" or type2 or "type ii" or "type two" or T2 or T-2 or TII or T-II)).tw. (910)

12 (DM adj4 (autoimmun* or auto immun* or brittle or labile or insulin depend* or insulin deficien*)).tw. (50)

13 (DM adj4 onset* adj4 (maturit* or adult* or slow*)).tw. (6)

14 (DM adj4 depend* adj4 (non-insulin* or non insulin* or noninsulin*)).tw. (10)

15 (DM adj4 (earl* or sudden onset or juvenile or child*)).tw. (125)

16 or/5-15 (68888)

17 Ketosis/ (0)

18 (keto* or acidos* or acidoketos* or ketoacidaemi* or ketoacidemi* or hyperketo* or hyper-keto* or ketotic or ketonuri* or keton?emi* or acetonemi* or acetonuri*).tw. (18379)

19 17 or 18 (18379)

20 16 and 19 (1388)

21 4 or 20 (1671)

22 exp Fluid Therapy/ (0)

23 Rehydration Solutions/ (0)

24 Water-Electrolyte Balance/ (0)

25 Water-Electrolyte Imbalance/ (0)

26 (fluid* or solution* or electrolyte* or hydrat* or rehydrat* or re-hydrat* or "re hydrat*" or resuscitat*).tw. (231292)

27 Drug Administration Routes/ (0)

28 (drug adj4 admin* adj4 route*).tw. (137)

29 (drug adj4 deliver* adj4 system*).tw. (3442)

30 Administration, Oral/ (0)

31 Administration, Intravenous/ (0)

32 (oral* or intravenous or IV).tw. (113694)

33 ((vein or venous) adj4 (infus* or inject* or drip or transfus*)).tw. (739)

34 Infusions, Intravenous/ (0)

35 Infusions, Intraosseous/ (0)

36 ((intra-osseous or intraosseous or IO or intra-bone or intrabone or "intra bone" or system* or pump* or subcutan* or drip) adj4 (infus* or inject* or admin* or appl*)).tw. (20261)

37 infusor*.tw. (33)

38 (perfusion adj4 pump*).tw. (24)

39 exp Infusions, Subcutaneous/ (0)

40 hypodermoclysis.tw. (10)

41 Infusion Pump/ (0)

42 Intubation, Gastrointestinal/ (0)

43 (intubat* adj4 (gastrointestin* or gastro-intestin* or "gastro intestin*" or nasogastric*)).tw. (51)

44 (fluid bolus or two bag or ORT).tw. (208)

45 Time Factors/ (0)

46 (time adj4 factor*).tw. (2860)

47 Drug Administration Schedule/ (0)

48 (drug adj4 admin* adj4 schedul*).tw. (24)

49 (drug adj4 deliver* adj4 schedul*).tw. (7)

50 Sodium/ (0)

51 (sodium* or salt*).tw. (70278)

52 (acetic adj4 acid).tw. (6320)

53 exp Chlorides/ (0)

54 (chloride* or chlorhydrate* or hydrochloride* or monochloride*).tw. (26669)

55 Glucose/ or Glucose Solution, Hypertonic/ (0)

56 (glucose or d-glucose or dextrose or l-glucose).tw. (47503)

57 Saline Solution, Hypertonic/ (0)

58 Saline Solution/ or Ringer's Lactate/ (0)

59 (saline* or Na-Cl* or Na-Cl* or Nacl* or NaCl* or hartmann* or ringer*).tw. (24871)

60 exp Bicarbonates/ (0)

61 (bicarbonate* or dicarbonate* or baros* or hydrocarbonate*).tw. (2585)

62 (hydrogen adj4 carbonate*).tw. (112)

63 (carbonic adj4 acid adj4 ion*).tw. (19)

64 Potassium/ or Potassium Acetate/ (0)

65 (potassium or KCL or K39 or Kalium).tw. (16759)

66 Phosphates/ (0)

67 (phosphate* or orthophosphate*).tw. (24246)

68 or/22-67 (495519)

69 21 and 68 (773)

70 animals/ not humans/ (0)

71 69 not 70 (773)

72 limit 71 to english language (759)

73 limit 72 to dt=20140601-20200212 (605)

74 randomized controlled trial.pt. (276)

75 randomi?ed.mp. (70394)

76 placebo.mp. (17332)

77 or/74-76 (76533)

78 (MEDLINE or pubmed).tw. (33132)

79 systematic review.tw. (27200)

80 systematic review.pt. (651)

81 meta-analysis.pt. (43)

82 intervention$.ti. (20043)

83 or/78-82 (63674)

84 77 or 83 (126019)

85 Observational Studies as Topic/ (0)

86 Observational Study/ (89)

87 Epidemiologic Studies/ (0)

88 exp Case-Control Studies/ (1)

89 exp Cohort Studies/ (1)

90 Cross-Sectional Studies/ (0)

91 Controlled Before-After Studies/ (0)

92 Historically Controlled Study/ (0)

93 Interrupted Time Series Analysis/ (0)

94 Comparative Study.pt. (45)

95 case control$.tw. (13542)

96 case series.tw. (11937)

97 (cohort adj (study or studies)).tw. (27279)

98 cohort analy$.tw. (1008)

99 (follow up adj (study or studies)).tw. (3345)

100 (observational adj (study or studies)).tw. (16114)

101 longitudinal.tw. (32556)

102 prospective.tw. (59705)

103 retrospective.tw. (67413)

104 cross sectional.tw. (55523)

105 or/85-104 (232760)

106 73 and 84 (63)

107 73 and 105 (86)

108 106 or 107 (139)

1

Database: MEDLINE EPUBS

Strategy used:

Database: Ovid MEDLINE(R) Epub Ahead of Print <February 11, 2020>

Search Strategy:

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1 Diabetic Ketoacidosis/ (0)

2 (DK or DKA).tw. (80)

3 (DM adj4 (keto* or acidi* or gastropare*)).tw. (2)

4 or/1-3 (81)

5 exp Diabetes Mellitus/ (0)

6 diabet*.tw. (9782)

7 (DM adj4 ("type 1" or type1 or "type I" or "type one" or T1 or T-1 or TI or T-I)).tw. (32)

8 lada.tw. (9)

9 (dm1 or iddm or t1d* or dka).tw. (447)

10 (dm2 or t2d* or mody or niddm).tw. (993)

11 (DM adj4 ("type 2" or type2 or "type ii" or "type two" or T2 or T-2 or TII or T-II)).tw. (101)

12 (DM adj4 (autoimmun* or auto immun* or brittle or labile or insulin depend* or insulin deficien*)).tw. (5)

13 (DM adj4 onset* adj4 (maturit* or adult* or slow*)).tw. (0)

14 (DM adj4 depend* adj4 (non-insulin* or non insulin* or noninsulin*)).tw. (2)

15 (DM adj4 (earl* or sudden onset or juvenile or child*)).tw. (15)

16 or/5-15 (9858)

17 Ketosis/ (0)

18 (keto* or acidos* or acidoketos* or ketoacidaemi* or ketoacidemi* or hyperketo* or hyper-keto* or ketotic or ketonuri* or keton?emi* or acetonemi* or acetonuri*).tw. (1342)

19 17 or 18 (1342)

20 16 and 19 (195)

21 4 or 20 (223)

22 exp Fluid Therapy/ (0)

23 Rehydration Solutions/ (0)

24 Water-Electrolyte Balance/ (0)

25 Water-Electrolyte Imbalance/ (0)

26 (fluid* or solution* or electrolyte* or hydrat* or rehydrat* or re-hydrat* or "re hydrat*" or resuscitat*).tw. (18082)

27 Drug Administration Routes/ (0)

28 (drug adj4 admin* adj4 route*).tw. (25)

29 (drug adj4 deliver* adj4 system*).tw. (456)

30 Administration, Oral/ (0)

31 Administration, Intravenous/ (0)

32 (oral* or intravenous or IV).tw. (15152)

33 ((vein or venous) adj4 (infus* or inject* or drip or transfus*)).tw. (95)

34 Infusions, Intravenous/ (0)

35 Infusions, Intraosseous/ (0)

36 ((intra-osseous or intraosseous or IO or intra-bone or intrabone or "intra bone" or system* or pump* or subcutan* or drip) adj4 (infus* or inject* or admin* or appl*)).tw. (2143)

37 infusor*.tw. (1)

38 (perfusion adj4 pump*).tw. (6)

39 exp Infusions, Subcutaneous/ (0)

40 hypodermoclysis.tw. (2)

41 Infusion Pump/ (0)

42 Intubation, Gastrointestinal/ (0)

43 (intubat* adj4 (gastrointestin* or gastro-intestin* or "gastro intestin*" or nasogastric*)).tw. (7)

44 (fluid bolus or two bag or ORT).tw. (36)

45 Time Factors/ (0)

46 (time adj4 factor*).tw. (433)

47 Drug Administration Schedule/ (0)

48 (drug adj4 admin* adj4 schedul*).tw. (4)

49 (drug adj4 deliver* adj4 schedul*).tw. (1)

50 Sodium/ (0)

51 (sodium* or salt*).tw. (4951)

52 (acetic adj4 acid).tw. (387)

53 exp Chlorides/ (0)

54 (chloride* or chlorhydrate* or hydrochloride* or monochloride*).tw. (1668)

55 Glucose/ or Glucose Solution, Hypertonic/ (0)

56 (glucose or d-glucose or dextrose or l-glucose).tw. (5564)

57 Saline Solution, Hypertonic/ (0)

58 Saline Solution/ or Ringer's Lactate/ (0)

59 (saline* or Na-Cl* or Na-Cl* or Nacl* or NacI* or hartmann* or ringer*).tw. (2533)

60 exp Bicarbonates/ (0)

61 (bicarbonate* or dicarbonate* or baros* or hydrocarbonate*).tw. (253)

62 (hydrogen adj4 carbonate*).tw. (7)

63 (carbonic adj4 acid adj4 ion*).tw. (0)

64 Potassium/ or Potassium Acetate/ (0)

65 (potassium or KCL or K39 or Kalium).tw. (1283)

66 Phosphates/ (0)

67 (phosphate* or orthophosphate*).tw. (2217)

68 or/22-67 (46913)

69 21 and 68 (132)

70 animals/ not humans/ (0)

71 69 not 70 (132)

72 limit 71 to english language (130)

73 randomized controlled trial.pt. (1)

74 randomi?ed.mp. (12912)

75 placebo.mp. (2942)

76 or/73-75 (13891)

77 (MEDLINE or pubmed).tw. (6745)

78 systematic review.tw. (6529)

79 systematic review.pt. (28)

80 meta-analysis.pt. (26)

81 intervention$.ti. (3928)

82 or/77-81 (13255)

83 76 or 82 (23946)

84 Observational Studies as Topic/ (0)

85 Observational Study/ (4)

86 Epidemiologic Studies/ (0)

87 exp Case-Control Studies/ (0)

88 exp Cohort Studies/ (0)

89 Cross-Sectional Studies/ (0)

90 Controlled Before-After Studies/ (0)

91 Historically Controlled Study/ (0)

92 Interrupted Time Series Analysis/ (0)

93 Comparative Study.pt. (0)

94 case control$.tw. (2404)

95 case series.tw. (1952)

96 (cohort adj (study or studies)).tw. (7019)

97 cohort analy$.tw. (285)

98 (follow up adj (study or studies)).tw. (559)

99 (observational adj (study or studies)).tw. (3337)

100 longitudinal.tw. (6733)

101 prospective.tw. (10883)

102 retrospective.tw. (14277)

103 cross sectional.tw. (8411)

104 or/84-103 (43126)

105 72 and 83 (12)

106 72 and 104 (20)

107 105 or 106 (32)

1

Database: EMBASE

Strategy used:

Database: Embase <1974 to 2020 February 11>

Search Strategy:

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1 Diabetic Ketoacidosis/ (11739)

2 (DK or DKA).tw. (6916)

3 (DM adj4 (keto* or acidi* or gastropare*)).tw. (180)

4 or/1-3 (15679)

5 exp Diabetes Mellitus/ (925948)

6 diabet*.tw. (903373)

7 (DM adj4 ("type 1" or type1 or "type I" or "type one" or T1 or T-1 or TI or T-I)).tw. (3819)

8 lada.tw. (961)

9 (dm1 or iddm or t1d* or dka).tw. (37934)

10 (dm2 or t2d* or mody or niddm).tw. (67126)

11 (DM adj4 ("type 2" or type2 or "type ii" or "type two" or T2 or T-2 or TII or T-II)).tw. (10048)

12 (DM adj4 (autoimmun* or auto immun* or brittle or labile or insulin depend* or insulin deficien*)).tw. (678)

13 (DM adj4 onset* adj4 (maturit* or adult* or slow*)).tw. (105)

14 (DM adj4 depend* adj4 (non-insulin* or non insulin* or noninsulin*)).tw. (160)

15 (DM adj4 (earl* or sudden onset or juvenile or child*)).tw. (1796)

16 or/5-15 (1098935)

17 Ketoacidosis/ (6677)

18 (keto* or acidos* or acidoketos* or ketoacidaemi* or ketoacidemi* or hyperketo* or hyper-keto* or ketotic or ketonuri* or keton?emi* or acetonemi* or acetonuri*).tw. (175609)

19 17 or 18 (177221)

20 16 and 19 (21689)

21 4 or 20 (28663)

22 exp Fluid Therapy/ or exp Infusion fluid/ (116807)

23 oral rehydration solution/ (2907)

24 exp electrolyte balance/ or exp electrolyte/ (255696)

25 (fluid* or solution* or electrolyte* or hydrat* or rehydrat* or re-hydrat* or "re hydrat*" or resuscitat*).tw. (1492203)

26 exp Drug Administration Route/ (1113204)

27 (drug adj4 admin* adj4 route*).tw. (2045)

28 (drug adj4 deliver* adj4 system*).tw. (34291)

29 Oral Drug Administration/ (386075)

30 exp Intravenous Drug Administration/ (355715)

31 (oral* or intravenous or IV).tw. (1679900)

32 ((vein or venous) adj4 (infus* or inject* or drip or transfus*)).tw. (16820)

33 exp Intraosseous Drug Administration/ (714)

34 ((intra-osseous or intraosseous or IO or intra-bone or intrabone or "intra bone" or system* or pump* or subcutan* or drip) adj4 (infus* or inject* or admin* or appl*)).tw. (211062)

35 infusor*.tw. (410)

36 (perfusion adj4 pump*).tw. (799)

37 Subcutaneous Drug Administration/ or Hypodermoclysis/ (92822)

38 hypodermoclys*.tw. (139)

39 exp Infusion Pump/ (8775)

40 exp Digestive Tract Intubation/ (5879)

41 (intubat* adj4 (gastrointestin* or gastro-intestin* or "gastro intestin*" or nasogastric*)).tw. (702)

42 (fluid bolus or two bag or ORT).tw. (2729)

43 Time Factor/ (32342)

44 (time adj4 factor*).tw. (30273)

45 exp Drug Administration/ (1186551)

46 (drug adj4 admin* adj4 schedul*).tw. (548)

47 (drug adj4 deliver* adj4 schedul*).tw. (115)

48 Acetic Acid/ or exp Inorganic Salt/ (840163)

49 (sodium* or salt*).tw. (582203)

50 (acetic adj4 acid).tw. (48842)

51 Chloride/ (40831)

52 (chloride* or chlorhydrate* or hydrochloride* or monochloride*).tw. (227860)

53 Glucose/ (392979)

54 (glucose or d-glucose or dextrose or l-glucose).tw. (607257)

55 (saline* or Na-Cl* or Na-Cl* or Nacl* or NacI* or hartmann* or ringer*).tw. (325697)

56 (bicarbonate* or dicarbonate* or baros* or hydrocarbonate*).tw. (38749)

57 (hydrogen adj4 carbonate*).tw. (609)

58 (carbonic adj4 acid adj4 ion*).tw. (29)

59	(potassium or KCL or K39 or Kalium).tw. (178435)
60	(phosphate* or orthophosphate*).tw. (286237)
61	or/22-60 (5962035)
62	21 and 61 (16102)
63	nonhuman/ not human/ (4552889)
64	62 not 63 (14879)
65	limit 64 to english language (13389)
66	limit 65 to dc=20140601-20200212 (5832)
67	limit 66 to (conference abstract or conference paper or "conference review") (2751)
68	66 not 67 (3081)
69	random:.tw. (1500401)
70	placebo:.mp. (447102)
71	double-blind:.tw. (206036)
72	or/69-71 (1752190)
73	(MEDLINE or pubmed).tw. (245300)
74	exp systematic review/ or systematic review.tw. (281036)
75	meta-analysis/ (180459)
76	intervention$.ti. (192052)
77	or/73-76 (626095)
78	72 or 77 (2181702)
79	68 and 78 (570)
80	Clinical study/ (154553)
81	Case control study/ (151819)
82	Family study/ (25960)
83	Longitudinal study/ (135655)
84	Retrospective study/ (877524)
85	comparative study/ (835999)
86	Prospective study/ (579711)

87	Randomized controlled trials/ (173699)
88	86 not 87 (573647)
89	Cohort analysis/ (548531)
90	cohort analy$.tw. (12332)
91	(Cohort adj (study or studies)).tw. (284834)
92	(Case control$ adj (study or studies)).tw. (133108)
93	(follow up adj (study or studies)).tw. (62104)
94	(observational adj (study or studies)).tw. (159542)
95	(epidemiologic$ adj (study or studies)).tw. (104201)
96	(cross sectional adj (study or studies)).tw. (207345)
97	case series.tw. (98892)
98	prospective.tw. (832624)
99	retrospective.tw. (844844)
100	or/80-85,88-99 (3885037)
101	68 and 100 (681)
102	79 or 101 (1117)

1

Database: COCHRANE

Strategy used:

Search Name: GU diabetes _ DKA

Date Run: 12/02/2020 16:00:46

Comment:

ID	Search	Hits
#1	MeSH descriptor: [Diabetic Ketoacidosis] this term only	128
#2	((DK or DKA)):ti,ab,kw	707

#3 ((DM near/4 (keto* or acidi* or gastropare*))):ti,ab,kw 12

#4 #1 or #2 or #3 782

#5 MeSH descriptor: [Diabetes Mellitus] explode all trees 30230

#6 (diabet*):ti,ab,kw 91042

#7 ((DM near/4 ("type 1" or type1 or "type I" or "type one" or T1 or T-1 or TI or T-I))):ti,ab,kw 264

#8 (lada):ti,ab,kw 66

#9 ((dm1 or iddm or t1d* or dka)):ti,ab,kw 3188

#10 ((dm2 or t2d* or mody or niddm)):ti,ab,kw 10004

#11 ((DM near/4 ("type 2" or type2 or "type ii" or "type two" or T2 or T-2 or TII or T-II))):ti,ab,kw 1196

#12 ((DM near/4 (autoimmun* or auto immun* or brittle or labile or insulin depend* or insulin deficien*))):ti,ab,kw 576

#13 ((DM near/4 onset* near/4 (maturit* or adult* or slow*))):ti,ab,kw 0

#14 ((DM near/4 depend* near/4 (non-insulin* or non insulin* or noninsulin*))):ti,ab,kw 220

#15 ((DM near/4 (earl* or sudden onset or juvenile or child*))):ti,ab,kw 256

#16 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 92319

#17 MeSH descriptor: [Ketosis] this term only 66

#18 ((keto* or acidos* or acidoketos* or ketoacidaemi* or ketoacidemi* or hyperketo* or hyper-keto* or ketotic or ketonuri* or keton?emi* or acetonemi* or acetonuri*)):ti,ab,kw 11612

#19 #17 or #18 11612

#20 #16 and #19 1506

#21 #4 or #20 2028

#22 MeSH descriptor: [Fluid Therapy] explode all trees 1634

#23 MeSH descriptor: [Rehydration Solutions] this term only 291

#24 MeSH descriptor: [Water-Electrolyte Balance] this term only 714

#25 MeSH descriptor: [Water-Electrolyte Imbalance] this term only 115

#26 ((fluid* or solution* or electrolyte* or hydrat* or rehydrat* or re-hydrat* or "re hydrat*" or resuscitat*)):ti,ab,kw 88321

#27 MeSH descriptor: [Drug Administration Routes] this term only 353

#28 ((drug near/4 admin* near/4 route*)):ti,ab,kw 914

#29 ((drug near/4 deliver* near/4 system*)):ti,ab,kw2811

#30 MeSH descriptor: [Administration, Oral] this term only 22695

#31 MeSH descriptor: [Administration, Intravenous] this term only 1048

#32 ((oral* or intravenous or IV)):ti,ab,kw 284979

#33 (((vein or venous) near/4 (infus* or inject* or drip or transfus*))):ti,ab,kw 1443

#34 MeSH descriptor: [Infusions, Intravenous] this term only10117

#35 MeSH descriptor: [Infusions, Intraosseous] this term only 41

#36 (((intra-osseous or intraosseous or IO or intra-bone or intrabone or "intra bone" or system* or pump* or subcutan* or drip) near/4 (infus* or inject* or admin* or appl*))):ti,ab,kw 28245

#37 (infusor*):ti,ab,kw 72

#38 ((perfusion near/4 pump*)):ti,ab,kw 66

#39 MeSH descriptor: [Infusions, Subcutaneous] explode all trees 146

#40 (hypodermoclysis):ti,ab,kw 32

#41 MeSH descriptor: [Infusion Pumps] this term only 471

#42 MeSH descriptor: [Intubation, Gastrointestinal] this term only 666

#43 ((intubat* near/4 (gastrointestin* or gastro-intestin* or "gastro intestin*" or nasogastric*))):ti,ab,kw 789

#44 ((fluid bolus or two bag or ORT)):ti,ab,kw 2026

#45 MeSH descriptor: [Time Factors] this term only 63813

#46 ((time near/4 factor*)):ti,ab,kw 66337

#47 MeSH descriptor: [Drug Administration Schedule] this term only 23341

#48 ((drug near/4 admin* near/4 schedul*)):ti,ab,kw 23416

#49 ((drug near/4 deliver* near/4 schedul*)):ti,ab,kw 18

#50 MeSH descriptor: [Sodium] this term only 2062

#51 ((sodium* or salt*)):ti,ab,kw 42871

#52 ((acetic near/4 acid)):ti,ab,kw 1089

#53 MeSH descriptor: [Chlorides] explode all trees 2940

#54 ((chloride* or chlorhydrate* or hydrochloride* or monochloride*)):ti,ab,kw 27404

#55	MeSH descriptor: [Glucose] this term only	3274
#56	MeSH descriptor: [Glucose Solution, Hypertonic] this term only	92
#57	((glucose or d-glucose or dextrose or l-glucose)):ti,ab,kw	62627
#58	MeSH descriptor: [Saline Solution, Hypertonic] this term only	499
#59	MeSH descriptor: [Saline Solution] this term only	51
#60	MeSH descriptor: [Ringer's Lactate] this term only	247
#61	((saline* or Na-Cl* or Na-Cl* or Nacl* or NaCl* or hartmann* or ringer*)):ti,ab,kw	37616
#62	MeSH descriptor: [Bicarbonates] explode all trees	1252
#63	((bicarbonate* or dicarbonate* or baros* or hydrocarbonate*)):ti,ab,kw	4042
#64	((hydrogen near/4 carbonate*)):ti,ab,kw	31
#65	((carbonic near/4 acid near/4 ion*)):ti,ab,kw	2
#66	MeSH descriptor: [Potassium] this term only	2179
#67	MeSH descriptor: [Potassium Acetate] this term only	1
#68	((potassium or KCL or K39 or Kalium)):ti,ab,kw	11942
#69	MeSH descriptor: [Phosphates] this term only	1274
#70	((phosphate* or orthophosphate*)):ti,ab,kw	12266
#71	{or #22-#70}	511770
#72	#23 and #71 with Cochrane Library publication date Between Jun 2014 and Feb 2020	47

1

Database: CRD

Strategy used:

Line	Search	Hits	
1	(MeSH DESCRIPTOR Diabetic Ketoacidosis)	12	Delete
2	(((DK or DKA)))	520	Delete
3	((DM) AND ((keto* or acidi* or gastropare*)))	3	Delete
4	(#1 OR #2 OR #3)	532	Delete

5	(MeSH DESCRIPTOR Diabetes Mellitus EXPLODE ALL TREES)	2444	Delete
6	(diabet*)	4478	Delete
7	((DM) AND ("type 1" or type1 or "type I" or "type one" or T1 or T-1 or TI or T-I))	29	Delete
8	(lada)	1	Delete
9	(dm1 or iddm or t1d* or dka)	53	Delete
10	(dm2 or t2d* or mody or niddm)	83	Delete
11	((DM) AND (("type 2" or type2 or "type ii" or "type two" or T2 or T-2 or TII or T-II)))	53	Delete
12	((DM) AND ((autoimmun* or auto immun* or brittle or labile or insulin depend* or insulin deficien*)))	8	Delete
13	((DM) AND (onset*) AND ((maturit* or adult* or slow*)))	14	Delete
14	((DM) AND (depend*) AND ((non-insulin* or non insulin* or noninsulin*)))	4	Delete
15	((DM) AND ((earl* or sudden onset or juvenile or child*)))	118	Delete
16	(#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15)	4631	Delete
17	(MeSH DESCRIPTOR Ketosis)	3	Delete
18	(((keto* or acidos* or acidoketos* or ketoacidaemi* or ketoacidemi* or hyperketo* or hyper-keto* or ketotic or ketonuri* or keton?emi* or acetonemi* or acetonuri*)))	324	Delete
19	(#17 OR #18)	324	Delete
20	(#16 AND #19)	70	Delete
21	(#4 OR #20)	587	Delete
22	(MeSH DESCRIPTOR Fluid Therapy EXPLODE ALL TREES)	131	Delete
23	(MeSH DESCRIPTOR Rehydration Solutions)	19	Delete
24	(MeSH DESCRIPTOR Water-Electrolyte Balance)	5	Delete
25	(MeSH DESCRIPTOR Water-Electrolyte Imbalance)	1	Delete
26	(((fluid* or solution* or electrolyte* or hydrat* or rehydrat* or re-hydrat* or "re hydrat*" or resuscitat*)))	2135	Delete
27	(MeSH DESCRIPTOR Drug Administration Routes)	35	Delete
28	(((drug and admin* and route*)))	311	Delete

29	(((drug and deliver* and system*)))	1108	Delete
30	(MeSH DESCRIPTOR Administration, Oral)	726	Delete
31	(MeSH DESCRIPTOR Administration, Intravenous)	52	Delete
32	(((oral* or intravenous or IV)))	7863	Delete
33	(((vein or venous)) AND ((infus* or inject* or drip or transfus*)))	309	Delete
34	(MeSH DESCRIPTOR Infusions, Intravenous)	351	Delete
35	(MeSH DESCRIPTOR Infusions, Intraosseous)	3	Delete
36	(((intra-osseous or intraosseous or IO or intra-bone or intrabone or "intra bone" or system* or pump* or subcutan* or drip)) AND ((infus* or inject* or admin* or appl*)))	18089	Delete
37	(infusor*)	4	Delete
38	(perfusion and pump*)	14	Delete
39	(MeSH DESCRIPTOR Infusions, Subcutaneous EXPLODE ALL TREES)	21	Delete
40	(hypodermoclysis)	2	Delete
41	(MeSH DESCRIPTOR Infusion Pumps)	43	Delete
42	(MeSH DESCRIPTOR Intubation, Gastrointestinal)	57	Delete
43	((intubat*) AND (gastrointestin* or gastro-intestin* or "gastro intestin*" or nasogastric*))	77	Delete
44	(fluid bolus or two bag or ORT)	14	Delete
45	(MeSH DESCRIPTOR Time Factors)	3076	Delete
46	(time and factor*)	7112	Delete
47	(MeSH DESCRIPTOR Drug Administration Schedule)	815	Delete
48	(drug and admin* and schedul*)	1218	Delete
49	(drug and deliver* and schedul*)	134	Delete
50	(MeSH DESCRIPTOR Sodium)	13	Delete
51	(sodium* or salt*)	894	Delete
52	(acetic and acid)	42	Delete
53	(MeSH DESCRIPTOR Chlorides EXPLODE ALL TREES)	69	Delete

54	(((chloride* or chlorhydrate* or hydrochloride* or monochloride*)))	602	Delete
55	(MeSH DESCRIPTOR Glucose)	56	Delete
56	(MeSH DESCRIPTOR Glucose Solution, Hypertonic)	2	Delete
57	(((glucose or d-glucose or dextrose or l-glucose)))	1283	Delete
58	(MeSH DESCRIPTOR Saline Solution, Hypertonic)	24	Delete
59	(((saline* or Na-Cl* or Na-Cl* or Nacl* or NacI* or hartmann* or ringer*)))	621	Delete
60	(MeSH DESCRIPTOR Bicarbonates EXPLODE ALL TREES)	22	Delete
61	(((bicarbonate* or dicarbonate* or baros* or hydrocarbonate*)))	73	Delete
62	(((hydrogen and carbonate*)))	0	Delete
63	(((carbonic and acid and ion*)))	0	Delete
64	(MeSH DESCRIPTOR Potassium)	23	Delete
65	(MeSH DESCRIPTOR Potassium Acetate)	0	Delete
66	(((potassium or KCL or K39 or Kalium)))	205	Delete
67	(MeSH DESCRIPTOR Phosphates)	32	Delete
68	(((phosphate* or orthophosphate*)))	189	Delete
69	(#22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68)	28822	Delete
70	(#21 AND #69)	217	Delete
71	((#70) WHERE LPD FROM 01/06/2014 TO 11/02/2020)	6	Delete

1

Database: Emcare
Strategy used: Database: Ovid Emcare <1995 to 2020 week 06> Search Strategy:

---

1 Diabetic Ketoacidosis/ (3417)

2 (DK or DKA).tw. (1250)

3 (DM adj4 (keto* or acidi* or gastropare*)).tw. (12)

4 or/1-3 (3986)

5 exp Diabetes Mellitus/ (215456)

6 diabet*.tw. (184022)

7 (DM adj4 ("type 1" or type1 or "type I" or "type one" or T1 or T-1 or TI or T-I)).tw. (502)

8 lada.tw. (177)

9 (dm1 or iddm or t1d* or dka).tw. (5731)

10 (dm2 or t2d* or mody or niddm).tw. (12425)

11 (DM adj4 ("type 2" or type2 or "type ii" or "type two" or T2 or T-2 or TII or T-II)).tw. (1652)

12 (DM adj4 (autoimmun* or auto immun* or brittle or labile or insulin depend* or insulin deficien*)).tw. (78)

13 (DM adj4 onset* adj4 (maturit* or adult* or slow*)).tw. (10)

14 (DM adj4 depend* adj4 (non-insulin* or non insulin* or noninsulin*)).tw. (29)

15 (DM adj4 (earl* or sudden onset or juvenile or child*)).tw. (307)

16 or/5-15 (240388)

17 Ketoacidosis/ (1266)

18 (keto* or acidos* or acidoketos* or ketoacidaemi* or ketoacidemi* or hyperketo* or hyper-keto* or ketotic or ketonuri* or keton?emi* or acetonemi* or acetonuri*).tw. (16402)

19 17 or 18 (16875)

20 16 and 19 (3897)

21 4 or 20 (5854)

22 exp Fluid Therapy/ or exp Infusion fluid/ (37230)

23 oral rehydration solution/ (954)

24 exp electrolyte balance/ or exp electrolyte/ (46925)

25 (fluid* or solution* or electrolyte* or hydrat* or rehydrat* or re-hydrat* or "re hydrat*" or resuscitat*).tw. (221493)

26 exp Drug Administration Route/ (86865)

27 (drug adj4 admin* adj4 route*).tw. (328)

28 (drug adj4 deliver* adj4 system*).tw. (3222)

29 Oral Drug Administration/ (21771)

30 exp Intravenous Drug Administration/ (27102)

31 (oral* or intravenous or IV).tw. (290648)

32 ((vein or venous) adj4 (infus* or inject* or drip or transfus*)).tw. (2146)

33 exp Intraosseous Drug Administration/ (254)

34 ((intra-osseous or intraosseous or IO or intra-bone or intrabone or "intra bone" or system* or pump* or subcutan* or drip) adj4 (infus* or inject* or admin* or appl*)).tw. (32164)

35 infusor*.tw. (62)

36 (perfusion adj4 pump*).tw. (123)

37 Subcutaneous Drug Administration/ or Hypodermoclysis/ (5703)

38 hypodermoclys*.tw. (69)

39 exp Infusion Pump/ (2611)

40 exp Digestive Tract Intubation/ (1699)

41 (intubat* adj4 (gastrointestin* or gastro-intestin* or "gastro intestin*" or nasogastric*)).tw. (155)

42 (fluid bolus or two bag or ORT).tw. (676)

43 Time Factor/ (1165)

44 (time adj4 factor*).tw. (7041)

45 exp Drug Administration/ (97925)

46 (drug adj4 admin* adj4 schedul*).tw. (94)

47 (drug adj4 deliver* adj4 schedul*).tw. (11)

48 Acetic Acid/ or exp Inorganic Salt/ (124456)

49 (sodium* or salt*).tw. (52046)

50 (acetic adj4 acid).tw. (3522)

51 Chloride/ (3547)

52 (chloride* or chlorhydrate* or hydrochloride* or monochloride*).tw. (16131)

53 Glucose/ (81096)

54	(glucose or d-glucose or dextrose or l-glucose).tw. (88868)
55	(saline* or Na-Cl* or Na-Cl* or Nacl* or NacI* or hartmann* or ringer*).tw. (43420)
56	(bicarbonate* or dicarbonate* or baros* or hydrocarbonate*).tw. (3899)
57	(hydrogen adj4 carbonate*).tw. (39)
58	(carbonic adj4 acid adj4 ion*).tw. (1)
59	(potassium or KCL or K39 or Kalium).tw. (14715)
60	(phosphate* or orthophosphate*).tw. (24140)
61	or/22-60 (828600)
62	21 and 61 (3250)
63	nonhuman/ not human/ (392209)
64	62 not 63 (3135)
65	limit 64 to english language (2973)
66	limit 65 to dc=20140601-20200212 (1301)
67	limit 66 to (conference abstract or conference paper or "conference review") (31)
68	66 not 67 (1270)
69	random:.tw. (422338)
70	placebo:.mp. (110102)
71	double-blind:.tw. (47817)
72	or/69-71 (478544)
73	(MEDLINE or pubmed).tw. (88546)
74	exp systematic review/ or systematic review.tw. (110922)
75	meta-analysis/ (55911)
76	intervention$.ti. (81102)
77	or/73-76 (235827)
78	72 or 77 (642558)
79	68 and 78 (265)
80	Clinical study/ (45399)
81	Case control study/ (33617)

82 Family study/ (8749)
83 Longitudinal study/ (53637)
84 Retrospective study/ (198020)
85 comparative study/ (116407)
86 Prospective study/ (160163)
87 Randomized controlled trials/ (63538)
88 86 not 87 (158171)
89 Cohort analysis/ (163284)
90 cohort analy$.tw. (3267)
91 (Cohort adj (study or studies)).tw. (91295)
92 (Case control$ adj (study or studies)).tw. (32205)
93 (follow up adj (study or studies)).tw. (14930)
94 (observational adj (study or studies)).tw. (47431)
95 (epidemiologic$ adj (study or studies)).tw. (24505)
96 (cross sectional adj (study or studies)).tw. (75459)
97 case series.tw. (25526)
98 prospective.tw. (213336)
99 retrospective.tw. (181786)
100 or/80-85,88-99 (895064)
101 68 and 100 (270)
102 79 or 101 (478)

1

MHRA
Search terms: Saline "Hartmann's"

"Ringer's Lactate"
"Sodium Chloride"
Salt
"Glucose solution"
Dextrose
NaCL or Na-cl
Bicarbonate
Dicarbonate
Baros
Hydrocarbonate
"Hydrogen carbonate"
"carbonic acid"
Potassium
KCL
K39
Kalium
Phosphate
Orthophosphate

Health Economics

Database: MEDLINE
Strategy used: Database: Ovid MEDLINE(R) <1946 to February 12, 2020> Search Strategy: --- 1 Diabetic Ketoacidosis/ (6312)

2 (DK or DKA).tw. (3082)

3 (DM adj4 (keto* or acidi* or gastropare*)).tw. (71)

4 or/1-3 (8272)

5 exp Diabetes Mellitus/ (417196)

6 diabet*.tw. (532357)

7 (DM adj4 ("type 1" or type1 or "type I" or "type one" or T1 or T-1 or TI or T-I)).tw. (1610)

8 lada.tw. (523)

9 (dm1 or iddm or t1d* or dka).tw. (18614)

10 (dm2 or t2d* or mody or niddm).tw. (30765)

11 (DM adj4 ("type 2" or type2 or "type ii" or "type two" or T2 or T-2 or TII or T-II)).tw. (4120)

12 (DM adj4 (autoimmun* or auto immun* or brittle or labile or insulin depend* or insulin deficien*)).tw. (305)

13 (DM adj4 onset* adj4 (maturit* or adult* or slow*)).tw. (62)

14 (DM adj4 depend* adj4 (non-insulin* or non insulin* or noninsulin*)).tw. (90)

15 (DM adj4 (earl* or sudden onset or juvenile or child*)).tw. (833)

16 or/5-15 (596801)

17 Ketosis/ (2148)

18 (keto* or acidos* or acidoketos* or ketoacidaemi* or ketoacidemi* or hyperketo* or hyper-keto* or ketotic or ketonuri* or keton?emi* or acetonemi* or acetonuri*).tw. (120232)

19 17 or 18 (120432)

20 16 and 19 (12332)

21 4 or 20 (15593)

22 exp Fluid Therapy/ (19871)

23 Rehydration Solutions/ (1444)

24 Water-Electrolyte Balance/ (28879)

25 Water-Electrolyte Imbalance/ (5183)

26 (fluid* or solution* or electrolyte* or hydrat* or rehydrat* or re-hydrat* or "re hydrat*" or resuscitat*).tw. (1017456)

27 Drug Administration Routes/ (5627)

28 (drug adj4 admin* adj4 route*).tw. (1229)

29 (drug adj4 deliver* adj4 system*).tw. (20333)

30 Administration, Oral/ (140774)

31 Administration, Intravenous/ (8664)

32 (oral* or intravenous or IV).tw. (1109028)

33 ((vein or venous) adj4 (infus* or inject* or drip or transfus*)).tw. (9716)

34 Infusions, Intravenous/ (54480)

35 Infusions, Intraosseous/ (713)

36 ((intra-osseous or intraosseous or IO or intra-bone or intrabone or "intra bone" or system* or pump* or subcutan* or drip) adj4 (infus* or inject* or admin* or appl*)).tw. (140778)

37 infusor*.tw. (400)

38 (perfusion adj4 pump*).tw. (614)

39 exp Infusions, Subcutaneous/ (1166)

40 hypodermoclysis.tw. (120)

41 Infusion Pump/ (5300)

42 Intubation, Gastrointestinal/ (9581)

43 (intubat* adj4 (gastrointestin* or gastro-intestin* or "gastro intestin*" or nasogastric*)).tw. (551)

44 (fluid bolus or two bag or ORT).tw. (1467)

45 Time Factors/ (1174766)

46 (time adj4 factor*).tw. (18673)

47 Drug Administration Schedule/ (99108)

48 (drug adj4 admin* adj4 schedul*).tw. (418)

49 (drug adj4 deliver* adj4 schedul*).tw. (92)

50 Sodium/ (105105)

51 (sodium* or salt*).tw. (428926)

52 (acetic adj4 acid).tw. (32901)

53 exp Chlorides/ (133646)

54 (chloride* or chlorhydrate* or hydrochloride* or monochloride*).tw. (161298)

55 Glucose/ or Glucose Solution, Hypertonic/ (154551)

56 (glucose or d-glucose or dextrose or l-glucose).tw. (414689)

57 Saline Solution, Hypertonic/ (5552)

58 Saline Solution/ or Ringer's Lactate/ (1722)

59 (saline* or Na-Cl* or Na-Cl* or Nacl* or NaCl* or hartmann* or ringer*).tw. (227485)

60 exp Bicarbonates/ (24577)

61 (bicarbonate* or dicarbonate* or baros* or hydrocarbonate*).tw. (27789)

62 (hydrogen adj4 carbonate*).tw. (365)

63 (carbonic adj4 acid adj4 ion*).tw. (25)

64 Potassium/ or Potassium Acetate/ (100807)

65 (potassium or KCL or K39 or Kalium).tw. (137981)

66 Phosphates/ (62408)

67 (phosphate* or orthophosphate*).tw. (231352)

68 or/22-67 (4490732)

69 21 and 68 (7357)

70 animals/ not humans/ (4640070)

71 69 not 70 (6245)

72 limit 71 to english language (5268)

73 limit 72 to ed=20140601-20200213 (1263)

74 Economics/ (27130)

75 exp "Costs and Cost Analysis"/ (232579)

76 Economics, Dental/ (1910)

77 exp Economics, Hospital/ (24220)

78 exp Economics, Medical/ (14162)

79 Economics, Nursing/ (3996)

80 Economics, Pharmaceutical/ (2913)

81 Budgets/ (11224)

82 exp Models, Economic/ (14715)

83 Markov Chains/ (13986)

84 Monte Carlo Method/ (27788)

85 Decision Trees/ (10899)

86 econom$.tw. (230976)

87 cba.tw. (9705)

88 cea.tw. (20202)

89 cua.tw. (975)

90 markov$.tw. (17479)

91 (monte adj carlo).tw. (29286)

92 (decision adj3 (tree$ or analys$)).tw. (12893)

93 (cost or costs or costing$ or costly or costed).tw. (447358)

94 (price$ or pricing$).tw. (32599)

95 budget$.tw. (23162)

96 expenditure$.tw. (48111)

97 (value adj3 (money or monetary)).tw. (2036)

98 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (3440)

99 or/74-98 (902730)

100 "Quality of Life"/ (188197)

101 quality of life.tw. (221871)

102 "Value of Life"/ (5683)

103 Quality-Adjusted Life Years/ (11827)

104 quality adjusted life.tw. (10401)

105 (qaly$ or qald$ or qale$ or qtime$).tw. (8539)

106 disability adjusted life.tw. (2568)

107 daly$.tw. (2345)

108 Health Status Indicators/ (23206)

109 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (21931)

110 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (1293)

111 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (4719)

112 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (28)

113 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (377)

114 (euroqol or euro qol or eq5d or eq 5d).tw. (8494)

115 (qol or hql or hqol or hrqol).tw. (42347)

116 (hye or hyes).tw. (60)

117 health$ year$ equivalent$.tw. (38)

118 utilit$.tw. (166224)

119 (hui or hui1 or hui2 or hui3).tw. (1259)

120 disutili$.tw. (371)

121 rosser.tw. (92)

122 quality of wellbeing.tw. (13)

123 quality of well-being.tw. (378)

124 qwb.tw. (189)

125 willingness to pay.tw. (4256)

126 standard gamble$.tw. (774)

127 time trade off.tw. (1013)

128 time tradeoff.tw. (228)

129 tto.tw. (876)

130 or/100-129 (477925)

131 99 or 130 (1314376)

132 73 and 131 (87)

1

Database: MEDLINE IN PROCESS
Strategy used:

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to February 12, 2020>

Search Strategy:

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1 Diabetic Ketoacidosis/ (0)

2 (DK or DKA).tw. (596)

3 (DM adj4 (keto* or acidi* or gastropare*)).tw. (11)

4 or/1-3 (603)

5 exp Diabetes Mellitus/ (0)

6 diabet*.tw. (68468)

7 (DM adj4 ("type 1" or type1 or "type I" or "type one" or T1 or T-1 or TI or T-I)).tw. (290)

8 lada.tw. (74)

9 (dm1 or iddm or t1d* or dka).tw. (2575)

10 (dm2 or t2d* or mody or niddm).tw. (6816)

11 (DM adj4 ("type 2" or type2 or "type ii" or "type two" or T2 or T-2 or TII or T-II)).tw. (910)

12 (DM adj4 (autoimmun* or auto immun* or brittle or labile or insulin depend* or insulin deficien*)).tw. (50)

13 (DM adj4 onset* adj4 (maturit* or adult* or slow*)).tw. (6)

14 (DM adj4 depend* adj4 (non-insulin* or non insulin* or noninsulin*)).tw. (10)

15 (DM adj4 (earl* or sudden onset or juvenile or child*)).tw. (125)

16 or/5-15 (69028)

17 Ketosis/ (0)

18 (keto* or acidos* or acidoketos* or ketoacidaemi* or ketoacidemi* or hyperketo* or hyper-keto* or ketotic or ketonuri* or keton?emi* or acetonemi* or acetonuri*).tw. (18401)

19 17 or 18 (18401)

20 16 and 19 (1389)

21 4 or 20 (1672)

22 exp Fluid Therapy/ (0)

23 Rehydration Solutions/ (0)

24 Water-Electrolyte Balance/ (0)

25 Water-Electrolyte Imbalance/ (0)

26 (fluid* or solution* or electrolyte* or hydrat* or rehydrat* or re-hydrat* or "re hydrat*" or resuscitat*).tw. (231568)

27 Drug Administration Routes/ (0)

28 (drug adj4 admin* adj4 route*).tw. (137)

29 (drug adj4 deliver* adj4 system*).tw. (3456)

30 Administration, Oral/ (0)

31 Administration, Intravenous/ (0)

32 (oral* or intravenous or IV).tw. (113920)

33 ((vein or venous) adj4 (infus* or inject* or drip or transfus*)).tw. (743)

34 Infusions, Intravenous/ (0)

35 Infusions, Intraosseous/ (0)

36 ((intra-osseous or intraosseous or IO or intra-bone or intrabone or "intra bone" or system* or pump* or subcutan* or drip) adj4 (infus* or inject* or admin* or appl*)).tw. (20301)

37 infusor*.tw. (33)

38 (perfusion adj4 pump*).tw. (24)

39 exp Infusions, Subcutaneous/ (0)

40 hypodermoclysis.tw. (10)

41 Infusion Pump/ (0)

42 Intubation, Gastrointestinal/ (0)

43 (intubat* adj4 (gastrointestin* or gastro-intestin* or "gastro intestin*" or nasogastric*)).tw. (51)

44 (fluid bolus or two bag or ORT).tw. (208)

45 Time Factors/ (0)

46 (time adj4 factor*).tw. (2863)

47 Drug Administration Schedule/ (0)

48 (drug adj4 admin* adj4 schedul*).tw. (24)

49 (drug adj4 deliver* adj4 schedul*).tw. (7)

50 Sodium/ (0)

51 (sodium* or salt*).tw. (70384)

52 (acetic adj4 acid).tw. (6327)

53 exp Chlorides/ (0)

54 (chloride* or chlorhydrate* or hydrochloride* or monochloride*).tw. (26712)

55 Glucose/ or Glucose Solution, Hypertonic/ (0)

56 (glucose or d-glucose or dextrose or l-glucose).tw. (47584)

57 Saline Solution, Hypertonic/ (0)

58 Saline Solution/ or Ringer's Lactate/ (0)

59 (saline* or Na-Cl* or Na-Cl* or Nacl* or NacI* or hartmann* or ringer*).tw. (24916)

60 exp Bicarbonates/ (0)

61 (bicarbonate* or dicarbonate* or baros* or hydrocarbonate*).tw. (2590)

62 (hydrogen adj4 carbonate*).tw. (112)

63 (carbonic adj4 acid adj4 ion*).tw. (19)

64 Potassium/ or Potassium Acetate/ (0)

65 (potassium or KCL or K39 or Kalium).tw. (16781)

66 Phosphates/ (0)

67 (phosphate* or orthophosphate*).tw. (24303)

68 or/22-67 (496279)

69 21 and 68 (774)

70 animals/ not humans/ (0)

71 69 not 70 (774)

72 limit 71 to english language (760)

73 limit 72 to dt=20140601-20200213 (606)

74 Economics/ (0)

75 exp "Costs and Cost Analysis"/ (0)

76 Economics, Dental/ (0)

77 exp Economics, Hospital/ (0)

78 exp Economics, Medical/ (0)

79 Economics, Nursing/ (0)

80 Economics, Pharmaceutical/ (0)

81 Budgets/ (0)

82 exp Models, Economic/ (0)

83 Markov Chains/ (0)

84 Monte Carlo Method/ (0)

85 Decision Trees/ (0)

86 econom$.tw. (43397)

87 cba.tw. (411)

88 cea.tw. (1838)

89 cua.tw. (197)

90 markov$.tw. (5488)

91 (monte adj carlo).tw. (16562)

92 (decision adj3 (tree$ or analys$)).tw. (2309)

93 (cost or costs or costing$ or costly or costed).tw. (92917)

94 (price$ or pricing$).tw. (5667)

95 budget$.tw. (4861)

96 expenditure$.tw. (6223)

97 (value adj3 (money or monetary)).tw. (346)

98 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (517)

99 or/74-98 (160962)

100 "Quality of Life"/ (0)

101 quality of life.tw. (37218)

102 "Value of Life"/ (0)

103 Quality-Adjusted Life Years/ (0)

104 quality adjusted life.tw. (1621)

105 (qaly$ or qald$ or qale$ or qtime$).tw. (1387)

106 disability adjusted life.tw. (489)

107 daly$.tw. (451)

108 Health Status Indicators/ (0)

109 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (2583)

110 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (746)

111 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (712)

112 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (5)

113 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (19)

114 (euroqol or euro qol or eq5d or eq 5d).tw. (1605)

115 (qol or hql or hqol or hrqol).tw. (7139)

116 (hye or hyes).tw. (8)

117 health$ year$ equivalent$.tw. (2)

118 utilit$.tw. (30118)

119 (hui or hui1 or hui2 or hui3).tw. (175)

120 disutili$.tw. (71)

121 rosser.tw. (5)

122 quality of wellbeing.tw. (7)

123 quality of well-being.tw. (26)

124 qwb.tw. (11)

125 willingness to pay.tw. (925)

126 standard gamble$.tw. (61)

127 time trade off.tw. (118)

128 time tradeoff.tw. (17)

129 tto.tw. (121)

130 or/100-129 (69607)

131 99 or 130 (221378)

132 73 and 131 (43)

1

Database: MEDLINE EPUBS

Strategy used:

Database: Ovid MEDLINE(R) Epub Ahead of Print <February 12, 2020>

Search Strategy:

---

1 Diabetic Ketoacidosis/ (0)

2 (DK or DKA).tw. (80)

3 (DM adj4 (keto* or acidi* or gastropare*)).tw. (2)

4 or/1-3 (81)

5 exp Diabetes Mellitus/ (0)

6 diabet*.tw. (9756)

7 (DM adj4 ("type 1" or type1 or "type I" or "type one" or T1 or T-1 or TI or T-I)).tw. (33)

8 lada.tw. (10)

9 (dm1 or iddm or t1d* or dka).tw. (445)

10 (dm2 or t2d* or mody or niddm).tw. (992)

11 (DM adj4 ("type 2" or type2 or "type ii" or "type two" or T2 or T-2 or TII or T-II)).tw. (102)

12 (DM adj4 (autoimmun* or auto immun* or brittle or labile or insulin depend* or insulin deficien*)).tw. (5)

13 (DM adj4 onset* adj4 (maturit* or adult* or slow*)).tw. (0)

14 (DM adj4 depend* adj4 (non-insulin* or non insulin* or noninsulin*)).tw. (2)

15 (DM adj4 (earl* or sudden onset or juvenile or child*)).tw. (15)

16 or/5-15 (9833)

17 Ketosis/ (0)

18 (keto* or acidos* or acidoketos* or ketoacidaemi* or ketoacidemi* or hyperketo* or hyper-keto* or ketotic or ketonuri* or keton?emi* or acetonemi* or acetonuri*).tw. (1341)

19 17 or 18 (1341)

20 16 and 19 (194)

21 4 or 20 (222)

22 exp Fluid Therapy/ (0)

23 Rehydration Solutions/ (0)

24 Water-Electrolyte Balance/ (0)

25 Water-Electrolyte Imbalance/ (0)

26 (fluid* or solution* or electrolyte* or hydrat* or rehydrat* or re-hydrat* or "re hydrat*" or resuscitat*).tw. (18023)

27 Drug Administration Routes/ (0)

28 (drug adj4 admin* adj4 route*).tw. (26)

29 (drug adj4 deliver* adj4 system*).tw. (455)

30 Administration, Oral/ (0)

31 Administration, Intravenous/ (0)

32 (oral* or intravenous or IV).tw. (15145)

33 ((vein or venous) adj4 (infus* or inject* or drip or transfus*)).tw. (94)

34 Infusions, Intravenous/ (0)

35 Infusions, Intraosseous/ (0)

36 ((intra-osseous or intraosseous or IO or intra-bone or intrabone or "intra bone" or system* or pump* or subcutan* or drip) adj4 (infus* or inject* or admin* or appl*)).tw. (2130)

37 infusor*.tw. (1)

38 (perfusion adj4 pump*).tw. (6)

39 exp Infusions, Subcutaneous/ (0)

40 hypodermoclysis.tw. (2)

41 Infusion Pump/ (0)

42 Intubation, Gastrointestinal/ (0)

43 (intubat* adj4 (gastrointestin* or gastro-intestin* or "gastro intestin*" or nasogastric*)).tw. (7)

44 (fluid bolus or two bag or ORT).tw. (37)

45 Time Factors/ (0)

46	(time adj4 factor*).tw. (433)
47	Drug Administration Schedule/ (0)
48	(drug adj4 admin* adj4 schedul*).tw. (4)
49	(drug adj4 deliver* adj4 schedul*).tw. (1)
50	Sodium/ (0)
51	(sodium* or salt*).tw. (4936)
52	(acetic adj4 acid).tw. (385)
53	exp Chlorides/ (0)
54	(chloride* or chlorhydrate* or hydrochloride* or monochloride*).tw. (1656)
55	Glucose/ or Glucose Solution, Hypertonic/ (0)
56	(glucose or d-glucose or dextrose or l-glucose).tw. (5562)
57	Saline Solution, Hypertonic/ (0)
58	Saline Solution/ or Ringer's Lactate/ (0)
59	(saline* or Na-Cl* or Na-Cl* or Nacl* or NacI* or hartmann* or ringer*).tw. (2523)
60	exp Bicarbonates/ (0)
61	(bicarbonate* or dicarbonate* or baros* or hydrocarbonate*).tw. (251)
62	(hydrogen adj4 carbonate*).tw. (7)
63	(carbonic adj4 acid adj4 ion*).tw. (0)
64	Potassium/ or Potassium Acetate/ (0)
65	(potassium or KCL or K39 or Kalium).tw. (1282)
66	Phosphates/ (0)
67	(phosphate* or orthophosphate*).tw. (2199)
68	or/22-67 (46812)
69	21 and 68 (131)
70	animals/ not humans/ (0)
71	69 not 70 (131)
72	limit 71 to english language (129)
73	Economics/ (0)

74 exp "Costs and Cost Analysis"/ (0)

75 Economics, Dental/ (0)

76 exp Economics, Hospital/ (0)

77 exp Economics, Medical/ (0)

78 Economics, Nursing/ (0)

79 Economics, Pharmaceutical/ (0)

80 Budgets/ (0)

81 exp Models, Economic/ (0)

82 Markov Chains/ (0)

83 Monte Carlo Method/ (0)

84 Decision Trees/ (0)

85 econom$.tw. (5922)

86 cba.tw. (64)

87 cea.tw. (330)

88 cua.tw. (16)

89 markov$.tw. (725)

90 (monte adj carlo).tw. (1181)

91 (decision adj3 (tree$ or analys$)).tw. (412)

92 (cost or costs or costing$ or costly or costed).tw. (12195)

93 (price$ or pricing$).tw. (871)

94 budget$.tw. (521)

95 expenditure$.tw. (1117)

96 (value adj3 (money or monetary)).tw. (71)

97 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (47)

98 or/73-97 (20059)

99 "Quality of Life"/ (0)

100 quality of life.tw. (6798)

101 "Value of Life"/ (0)

102 Quality-Adjusted Life Years/ (0)

103 quality adjusted life.tw. (401)

104 (qaly$ or qald$ or qale$ or qtime$).tw. (348)

105 disability adjusted life.tw. (108)

106 daly$.tw. (92)

107 Health Status Indicators/ (0)

108 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (454)

109 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (42)

110 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (164)

111 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (0)

112 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (4)

113 (euroqol or euro qol or eq5d or eq 5d).tw. (343)

114 (qol or hql or hqol or hrqol).tw. (1323)

115 (hye or hyes).tw. (1)

116 health$ year$ equivalent$.tw. (0)

117 utilit$.tw. (4612)

118 (hui or hui1 or hui2 or hui3).tw. (24)

119 disutili$.tw. (12)

120 rosser.tw. (0)

121 quality of wellbeing.tw. (1)

122 quality of well-being.tw. (6)

123 qwb.tw. (4)

124 willingness to pay.tw. (161)

125 standard gamble$.tw. (8)

126 time trade off.tw. (18)

127 time tradeoff.tw. (3)

128 tto.tw. (19)

129 or/99-128 (11694)

130 98 or 129 (29991)

131 72 and 130 (8)

1

Database: EMBASE

Strategy used:

Database: Embase <1974 to 2020 February 12>

Search Strategy:

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1 Diabetic Ketoacidosis/ (11739)

2 (DK or DKA).tw. (6916)

3 (DM adj4 (keto* or acidi* or gastropare*)).tw. (180)

4 or/1-3 (15679)

5 exp Diabetes Mellitus/ (925948)

6 diabet*.tw. (903373)

7 (DM adj4 ("type 1" or type1 or "type I" or "type one" or T1 or T-1 or TI or T-I)).tw. (3819)

8 lada.tw. (961)

9 (dm1 or iddm or t1d* or dka).tw. (37934)

10 (dm2 or t2d* or mody or niddm).tw. (67126)

11 (DM adj4 ("type 2" or type2 or "type ii" or "type two" or T2 or T-2 or TII or T-II)).tw. (10048)

12 (DM adj4 (autoimmun* or auto immun* or brittle or labile or insulin depend* or insulin deficien*)).tw. (678)

13 (DM adj4 onset* adj4 (maturit* or adult* or slow*)).tw. (105)

14 (DM adj4 depend* adj4 (non-insulin* or non insulin* or noninsulin*)).tw. (160)

15 (DM adj4 (earl* or sudden onset or juvenile or child*)).tw. (1796)

16 or/5-15 (1098935)

17 Ketoacidosis/ (6677)

18 (keto* or acidos* or acidoketos* or ketoacidaemi* or ketoacidemi* or hyperketo* or hyper-keto* or ketotic or ketonuri* or keton?emi* or acetonemi* or acetonuri*).tw. (175609)

19 17 or 18 (177221)

20 16 and 19 (21689)

21 4 or 20 (28663)

22 exp Fluid Therapy/ or exp Infusion fluid/ (116807)

23 oral rehydration solution/ (2907)

24 exp electrolyte balance/ or exp electrolyte/ (255696)

25 (fluid* or solution* or electrolyte* or hydrat* or rehydrat* or re-hydrat* or "re hydrat*" or resuscitat*).tw. (1492203)

26 exp Drug Administration Route/ (1113204)

27 (drug adj4 admin* adj4 route*).tw. (2045)

28 (drug adj4 deliver* adj4 system*).tw. (34291)

29 Oral Drug Administration/ (386075)

30 exp Intravenous Drug Administration/ (355715)

31 (oral* or intravenous or IV).tw. (1679900)

32 ((vein or venous) adj4 (infus* or inject* or drip or transfus*)).tw. (16820)

33 exp Intraosseous Drug Administration/ (714)

34 ((intra-osseous or intraosseous or IO or intra-bone or intrabone or "intra bone" or system* or pump* or subcutan* or drip) adj4 (infus* or inject* or admin* or appl*)).tw. (211062)

35 infusor*.tw. (410)

36 (perfusion adj4 pump*).tw. (799)

37 Subcutaneous Drug Administration/ or Hypodermoclysis/ (92822)

38 hypodermoclys*.tw. (139)

39 exp Infusion Pump/ (8775)

40 exp Digestive Tract Intubation/ (5879)

41 (intubat* adj4 (gastrointestin* or gastro-intestin* or "gastro intestin*" or nasogastric*)).tw. (702)

42 (fluid bolus or two bag or ORT).tw. (2729)

43 Time Factor/ (32342)

44 (time adj4 factor*).tw. (30273)

45 exp Drug Administration/ (1186551)

46 (drug adj4 admin* adj4 schedul*).tw. (548)

47 (drug adj4 deliver* adj4 schedul*).tw. (115)

48 Acetic Acid/ or exp Inorganic Salt/ (840163)

49 (sodium* or salt*).tw. (582203)

50 (acetic adj4 acid).tw. (48842)

51 Chloride/ (40831)

52 (chloride* or chlorhydrate* or hydrochloride* or monochloride*).tw. (227860)

53 Glucose/ (392979)

54 (glucose or d-glucose or dextrose or l-glucose).tw. (607257)

55 (saline* or Na-Cl* or Na-Cl* or Nacl* or NaCl* or hartmann* or ringer*).tw. (325697)

56 (bicarbonate* or dicarbonate* or baros* or hydrocarbonate*).tw. (38749)

57 (hydrogen adj4 carbonate*).tw. (609)

58 (carbonic adj4 acid adj4 ion*).tw. (29)

59 (potassium or KCL or K39 or Kalium).tw. (178435)

60 (phosphate* or orthophosphate*).tw. (286237)

61 or/22-60 (5962035)

62 21 and 61 (16102)

63 nonhuman/ not human/ (4552889)

64 62 not 63 (14879)

65 limit 64 to english language (13389)

66 limit 65 to dc=20140601-20200213 (5832)

67 limit 66 to (conference abstract or conference paper or "conference review") (2751)

68 66 not 67 (3081)

69 exp Health Economics/ (827289)

70 exp "Health Care Cost"/ (285058)

71 exp Pharmacoeconomics/ (199133)

72 Monte Carlo Method/ (39076)

73 Decision Tree/ (12245)

74 econom$.tw. (355008)

75 cba.tw. (12591)

76 cea.tw. (33884)

77 cua.tw. (1450)

78 markov$.tw. (29397)

79 (monte adj carlo).tw. (46984)

80 (decision adj3 (tree$ or analys$)).tw. (22336)

81 (cost or costs or costing$ or costly or costed).tw. (745459)

82 (price$ or pricing$).tw. (55614)

83 budget$.tw. (37516)

84 expenditure$.tw. (72538)

85 (value adj3 (money or monetary)).tw. (3356)

86 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (8505)

87 or/69-86 (1707223)

88 "Quality of Life"/ (452733)

89 Quality Adjusted Life Year/ (25689)

90 Quality of Life Index/ (2721)

91 Short Form 36/ (27717)

92 Health Status/ (124395)

93 quality of life.tw. (421848)

94 quality adjusted life.tw. (18980)

95 (qaly$ or qald$ or qale$ or qtime$).tw. (19446)

96 disability adjusted life.tw. (3853)

97 daly$.tw. (3789)

98 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (40321)

99 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (2342)

100 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (9091)

101 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (57)

102 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (441)

103 (euroqol or euro qol or eq5d or eq 5d).tw. (19515)

104 (qol or hql or hqol or hrqol).tw. (92947)

105 (hye or hyes).tw. (131)

106 health$ year$ equivalent$.tw. (41)

107 utilit$.tw. (279405)

108 (hui or hui1 or hui2 or hui3).tw. (2197)

109 disutili$.tw. (897)

110 rosser.tw. (119)

111 quality of wellbeing.tw. (42)

112 quality of well-being.tw. (469)

113 qwb.tw. (244)

114 willingness to pay.tw. (8399)

115 standard gamble$.tw. (1090)

116 time trade off.tw. (1672)

117 time tradeoff.tw. (288)

118 tto.tw. (1619)

119 or/88-118 (954177)

120 87 or 119 (2509791)

121 68 and 120 (286)

1

Database: Econlit
Strategy used: Database: Econlit <1886 to January 30, 2020> Search Strategy: --- 1 [Diabetic Ketoacidosis/] (0) 2 (DK or DKA).tw. (18) 3 (DM adj4 (keto* or acidi* or gastropare*)).tw. (1) 4 or/1-3 (19) 5 [exp Diabetes Mellitus/] (0) 6 diabet*.tw. (584) 7 (DM adj4 ("type 1" or type1 or "type I" or "type one" or T1 or T-1 or TI or T-I)).tw. (1) 8 lada.tw. (0) 9 (dm1 or iddm or t1d* or dka).tw. (10) 10 (dm2 or t2d* or mody or niddm).tw. (46) 11 (DM adj4 ("type 2" or type2 or "type ii" or "type two" or T2 or T-2 or TII or T-II)).tw. (1) 12 (DM adj4 (autoimmun* or auto immun* or brittle or labile or insulin depend* or insulin deficien*)).tw. (0) 13 (DM adj4 onset* adj4 (maturit* or adult* or slow*)).tw. (0) 14 (DM adj4 depend* adj4 (non-insulin* or non insulin* or noninsulin*)).tw. (0) 15 (DM adj4 (earl* or sudden onset or juvenile or child*)).tw. (1) 16 or/5-15 (619) 17 [Ketosis/] (0) 18 (keto* or acidos* or acidoketos* or ketoacidaemi* or ketoacidemi* or hyperketo* or hyper-keto* or ketotic or ketonuri* or keton?emi* or acetonemi* or acetonuri*).tw. (4) 19 17 or 18 (4) 20 16 and 19 (2)

21 4 or 20 (21)

22 [exp Fluid Therapy/] (0)

23 [Rehydration Solutions/] (0)

24 [Water-Electrolyte Balance/] (0)

25 [Water-Electrolyte Imbalance/] (0)

26 (fluid* or solution* or electrolyte* or hydrat* or rehydrat* or re-hydrat* or "re hydrat*" or resuscitat*).tw. (34188)

27 [Drug Administration Routes/] (0)

28 (drug adj4 admin* adj4 route*).tw. (1)

29 (drug adj4 deliver* adj4 system*).tw. (2)

30 [Administration, Oral/] (0)

31 [Administration, Intravenous/] (0)

32 (oral* or intravenous or IV).tw. (6049)

33 ((vein or venous) adj4 (infus* or inject* or drip or transfus*)).tw. (0)

34 [Infusions, Intravenous/] (0)

35 [Infusions, Intraosseous/] (0)

36 ((intra-osseous or intraosseous or IO or intra-bone or intrabone or "intra bone" or system* or pump* or subcutan* or drip) adj4 (infus* or inject* or admin* or appl*)).tw. (3098)

37 infusor*.tw. (0)

38 (perfusion adj4 pump*).tw. (0)

39 [exp Infusions, Subcutaneous/] (0)

40 hypodermoclysis.tw. (0)

41 [Infusion Pump/] (0)

42 [Intubation, Gastrointestinal/] (0)

43 (intubat* adj4 (gastrointestin* or gastro-intestin* or "gastro intestin*" or nasogastric*)).tw. (0)

44 (fluid bolus or two bag or ORT).tw. (19)

45 [Time Factors/] (0)

46 (time adj4 factor*).tw. (1623)

47 [Drug Administration Schedule/] (0)

48 (drug adj4 admin* adj4 schedul*).tw. (0)

49 (drug adj4 deliver* adj4 schedul*).tw. (0)

50 [Sodium/] (0)

51 (sodium* or salt*).tw. (653)

52 (acetic adj4 acid).tw. (5)

53 [exp Chlorides/] (0)

54 (chloride* or chlorhydrate* or hydrochloride* or monochloride*).tw. (22)

55 [Glucose/ or Glucose Solution, Hypertonic/] (0)

56 (glucose or d-glucose or dextrose or l-glucose).tw. (47)

57 [Saline Solution, Hypertonic/] (0)

58 [Saline Solution/ or Ringer's Lactate/] (0)

59 (saline* or Na-Cl* or Na-Cl* or Nacl* or NaCl* or hartmann* or ringer*).tw. (888)

60 [exp Bicarbonates/] (0)

61 (bicarbonate* or dicarbonate* or baros* or hydrocarbonate*).tw. (3)

62 (hydrogen adj4 carbonate*).tw. (0)

63 (carbonic adj4 acid adj4 ion*).tw. (0)

64 [Potassium/ or Potassium Acetate/] (0)

65 (potassium or KCL or K39 or Kalium).tw. (46)

66 [Phosphates/] (0)

67 (phosphate* or orthophosphate*).tw. (106)

68 or/22-67 (46140)

69 21 and 68 (2)

70 [animals/ not humans/] (0)

71 69 not 70 (2)

72 limit 71 to english language [Limit not valid; records were retained] (2)

1

Database: CRD - NHS EED and HTA

Strategy used:

Line	Search	Hits	
1	(MeSH DESCRIPTOR Diabetic Ketoacidosis)	12	Delete
2	(((DK or DKA)))	520	Delete
3	((DM) AND ((keto* or acidi* or gastropare*)))	3	Delete
4	(#1 OR #2 OR #3)	532	Delete
5	(MeSH DESCRIPTOR Diabetes Mellitus EXPLODE ALL TREES)	2444	Delete
6	(diabet*)	4478	Delete
7	((DM) AND ("type 1" or type1 or "type I" or "type one" or T1 or T-1 or TI or T-I))	29	Delete
8	(lada)	1	Delete
9	(dm1 or iddm or t1d* or dka)	53	Delete
10	(dm2 or t2d* or mody or niddm)	83	Delete
11	((DM) AND (("type 2" or type2 or "type ii" or "type two" or T2 or T-2 or TII or T-II)))	53	Delete
12	((DM) AND ((autoimmun* or auto immun* or brittle or labile or insulin depend* or insulin deficien*)))	8	Delete
13	((DM) AND (onset*) AND ((maturit* or adult* or slow*)))	14	Delete
14	((DM) AND (depend*) AND ((non-insulin* or non insulin* or noninsulin*)))	4	Delete
15	((DM) AND ((earl* or sudden onset or juvenile or child*)))	118	Delete
16	(#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15)	4631	Delete
17	(MeSH DESCRIPTOR Ketosis)	3	Delete
18	(((keto* or acidos* or acidoketos* or ketoacidaemi* or ketoacidemi* or hyperketo* or hyper-keto* or ketotic or ketonuri* or keton?emi* or acetonemi* or acetonuri*)))	324	Delete
19	(#17 OR #18)	324	Delete
20	(#16 AND #19)	70	Delete

21	(#4 OR #20)	587	Delete
22	(MeSH DESCRIPTOR Fluid Therapy EXPLODE ALL TREES)	131	Delete
23	(MeSH DESCRIPTOR Rehydration Solutions)	19	Delete
24	(MeSH DESCRIPTOR Water-Electrolyte Balance)	5	Delete
25	(MeSH DESCRIPTOR Water-Electrolyte Imbalance)	1	Delete
26	(((fluid* or solution* or electrolyte* or hydrat* or rehydrat* or re-hydrat* or "re hydrat*" or resuscitat*)))	2135	Delete
27	(MeSH DESCRIPTOR Drug Administration Routes)	35	Delete
28	(((drug and admin* and route*)))	311	Delete
29	(((drug and deliver* and system*)))	1108	Delete
30	(MeSH DESCRIPTOR Administration, Oral)	726	Delete
31	(MeSH DESCRIPTOR Administration, Intravenous)	52	Delete
32	(((oral* or intravenous or IV)))	7863	Delete
33	(((vein or venous)) AND ((infus* or inject* or drip or transfus*)))	309	Delete
34	(MeSH DESCRIPTOR Infusions, Intravenous)	351	Delete
35	(MeSH DESCRIPTOR Infusions, Intraosseous)	3	Delete
36	(((intra-osseous or intraosseous or IO or intra-bone or intrabone or "intra bone" or system* or pump* or subcutan* or drip)) AND ((infus* or inject* or admin* or appl*)))	18089	Delete
37	(infusor*)	4	Delete
38	(perfusion and pump*)	14	Delete
39	(MeSH DESCRIPTOR Infusions, Subcutaneous EXPLODE ALL TREES)	21	Delete
40	(hypodermoclysis)	2	Delete
41	(MeSH DESCRIPTOR Infusion Pumps)	43	Delete
42	(MeSH DESCRIPTOR Intubation, Gastrointestinal)	57	Delete
43	((intubat*) AND (gastrointestin* or gastro-intestin* or "gastro intestin*" or nasogastric*))	77	Delete
44	(fluid bolus or two bag or ORT)	14	Delete
45	(MeSH DESCRIPTOR Time Factors)	3076	Delete

46	(time and factor*)	7112	Delete
47	(MeSH DESCRIPTOR Drug Administration Schedule)	815	Delete
48	(drug and admin* and schedul*)	1218	Delete
49	(drug and deliver* and schedul*)	134	Delete
50	(MeSH DESCRIPTOR Sodium)	13	Delete
51	(sodium* or salt*)	894	Delete
52	(acetic and acid)	42	Delete
53	(MeSH DESCRIPTOR Chlorides EXPLODE ALL TREES)	69	Delete
54	(((chloride* or chlorhydrate* or hydrochloride* or monochloride*)))	602	Delete
55	(MeSH DESCRIPTOR Glucose)	56	Delete
56	(MeSH DESCRIPTOR Glucose Solution, Hypertonic)	2	Delete
57	(((glucose or d-glucose or dextrose or l-glucose)))	1283	Delete
58	(MeSH DESCRIPTOR Saline Solution, Hypertonic)	24	Delete
59	(((saline* or Na-Cl* or Na-Cl* or Nacl* or NaCl* or hartmann* or ringer*)))	621	Delete
60	(MeSH DESCRIPTOR Bicarbonates EXPLODE ALL TREES)	22	Delete
61	(((bicarbonate* or dicarbonate* or baros* or hydrocarbonate*)))	73	Delete
62	(((hydrogen and carbonate*)))	0	Delete
63	(((carbonic and acid and ion*)))	0	Delete
64	(MeSH DESCRIPTOR Potassium)	23	Delete
65	(MeSH DESCRIPTOR Potassium Acetate)	0	Delete
66	(((potassium or KCL or K39 or Kalium)))	205	Delete
67	(MeSH DESCRIPTOR Phosphates)	32	Delete
68	(((phosphate* or orthophosphate*)))	189	Delete
69	(#22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68)	28822	Delete
70	(#21 AND #69)	217	Delete

71	((#70) WHERE LPD FROM 01/06/2014 TO 12/02/2020)	6	Delete

1

2

Database: Ovid Emcare

Strategy used:

Database: Ovid Emcare <1995 to 2020 week 06>

Search Strategy:

---

1 Diabetic Ketoacidosis/ (3417)

2 (DK or DKA).tw. (1250)

3 (DM adj4 (keto* or acidi* or gastropare*)).tw. (12)

4 or/1-3 (3986)

5 exp Diabetes Mellitus/ (215456)

6 diabet*.tw. (184022)

7 (DM adj4 ("type 1" or type1 or "type I" or "type one" or T1 or T-1 or TI or T-I)).tw. (502)

8 lada.tw. (177)

9 (dm1 or iddm or t1d* or dka).tw. (5731)

10 (dm2 or t2d* or mody or niddm).tw. (12425)

11 (DM adj4 ("type 2" or type2 or "type ii" or "type two" or T2 or T-2 or TII or T-II)).tw. (1652)

12 (DM adj4 (autoimmun* or auto immun* or brittle or labile or insulin depend* or insulin deficien*)).tw. (78)

13 (DM adj4 onset* adj4 (maturit* or adult* or slow*)).tw. (10)

14 (DM adj4 depend* adj4 (non-insulin* or non insulin* or noninsulin*)).tw. (29)

15 (DM adj4 (earl* or sudden onset or juvenile or child*)).tw. (307)

16 or/5-15 (240388)

17 Ketoacidosis/ (1266)

18 (keto* or acidos* or acidoketos* or ketoacidaemi* or ketoacidemi* or hyperketo* or hyper-keto* or ketotic or ketonuri* or keton?emi* or acetonemi* or acetonuri*).tw. (16402)

19 17 or 18 (16875)

20 16 and 19 (3897)

21 4 or 20 (5854)

22 exp Fluid Therapy/ or exp Infusion fluid/ (37230)

23 oral rehydration solution/ (954)

24 exp electrolyte balance/ or exp electrolyte/ (46925)

25 (fluid* or solution* or electrolyte* or hydrat* or rehydrat* or re-hydrat* or "re hydrat*" or resuscitat*).tw. (221493)

26 exp Drug Administration Route/ (86865)

27 (drug adj4 admin* adj4 route*).tw. (328)

28 (drug adj4 deliver* adj4 system*).tw. (3222)

29 Oral Drug Administration/ (21771)

30 exp Intravenous Drug Administration/ (27102)

31 (oral* or intravenous or IV).tw. (290648)

32 ((vein or venous) adj4 (infus* or inject* or drip or transfus*)).tw. (2146)

33 exp Intraosseous Drug Administration/ (254)

34 ((intra-osseous or intraosseous or IO or intra-bone or intrabone or "intra bone" or system* or pump* or subcutan* or drip) adj4 (infus* or inject* or admin* or appl*)).tw. (32164)

35 infusor*.tw. (62)

36 (perfusion adj4 pump*).tw. (123)

37 Subcutaneous Drug Administration/ or Hypodermoclysis/ (5703)

38 hypodermoclys*.tw. (69)

39 exp Infusion Pump/ (2611)

40 exp Digestive Tract Intubation/ (1699)

41 (intubat* adj4 (gastrointestin* or gastro-intestin* or "gastro intestin*" or nasogastric*)).tw. (155)

42 (fluid bolus or two bag or ORT).tw. (676)

43 Time Factor/ (1165)

44	(time adj4 factor*).tw. (7041)
45	exp Drug Administration/ (97925)
46	(drug adj4 admin* adj4 schedul*).tw. (94)
47	(drug adj4 deliver* adj4 schedul*).tw. (11)
48	Acetic Acid/ or exp Inorganic Salt/ (124456)
49	(sodium* or salt*).tw. (52046)
50	(acetic adj4 acid).tw. (3522)
51	Chloride/ (3547)
52	(chloride* or chlorhydrate* or hydrochloride* or monochloride*).tw. (16131)
53	Glucose/ (81096)
54	(glucose or d-glucose or dextrose or l-glucose).tw. (88868)
55	(saline* or Na-Cl* or Na-Cl* or Nacl* or NaCl* or hartmann* or ringer*).tw. (43420)
56	(bicarbonate* or dicarbonate* or baros* or hydrocarbonate*).tw. (3899)
57	(hydrogen adj4 carbonate*).tw. (39)
58	(carbonic adj4 acid adj4 ion*).tw. (1)
59	(potassium or KCL or K39 or Kalium).tw. (14715)
60	(phosphate* or orthophosphate*).tw. (24140)
61	or/22-60 (828600)
62	21 and 61 (3250)
63	nonhuman/ not human/ (392209)
64	62 not 63 (3135)
65	limit 64 to english language (2973)
66	limit 65 to dc=20140601-20200212 (1301)
67	limit 66 to (conference abstract or conference paper or "conference review") (31)
68	66 not 67 (1270)
69	exp Health Economics/ (285451)
70	exp "Health Care Cost"/ (121118)
71	exp Pharmacoeconomics/ (52835)

72 Monte Carlo Method/ (9058)

73 Decision Tree/ (2689)

74 econom$.tw. (102945)

75 cba.tw. (881)

76 cea.tw. (3286)

77 cua.tw. (170)

78 markov$.tw. (7017)

79 (monte adj carlo).tw. (9378)

80 (decision adj3 (tree$ or analys$)).tw. (6611)

81 (cost or costs or costing$ or costly or costed).tw. (198934)

82 (price$ or pricing$).tw. (16658)

83 budget$.tw. (11439)

84 expenditure$.tw. (25385)

85 (value adj3 (money or monetary)).tw. (1354)

86 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (3314)

87 or/69-86 (491128)

88 "Quality of Life"/ (150771)

89 Quality Adjusted Life Year/ (9780)

90 Quality of Life Index/ (1214)

91 Short Form 36/ (11756)

92 Health Status/ (53021)

93 quality of life.tw. (122237)

94 quality adjusted life.tw. (6735)

95 (qaly$ or qald$ or qale$ or qtime$).tw. (5629)

96 disability adjusted life.tw. (1429)

97 daly$.tw. (1230)

98 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (13125)

99 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (262)

100 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (3309)

101 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (9)

102 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (111)

103 (euroqol or euro qol or eq5d or eq 5d).tw. (5810)

104 (qol or hql or hqol or hrqol).tw. (23761)

105 (hye or hyes).tw. (53)

106 health$ year$ equivalent$.tw. (24)

107 utilit$.tw. (62991)

108 (hui or hui1 or hui2 or hui3).tw. (741)

109 disutili$.tw. (277)

110 rosser.tw. (48)

111 quality of wellbeing.tw. (19)

112 quality of well-being.tw. (250)

113 qwb.tw. (131)

114 willingness to pay.tw. (2971)

115 standard gamble$.tw. (501)

116 time trade off.tw. (684)

117 time tradeoff.tw. (150)

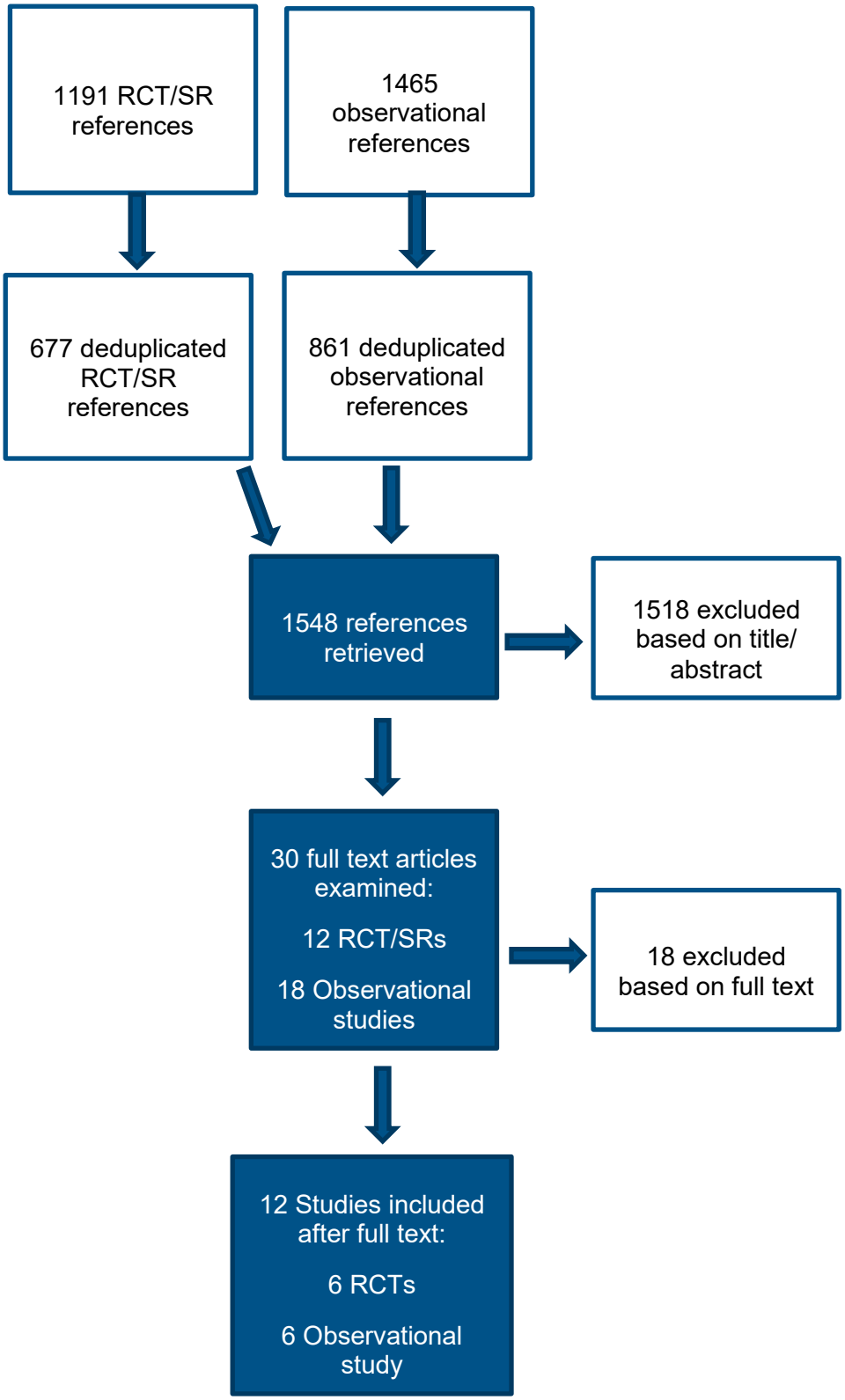
118 tto.tw. (538)

119 or/88-118 (285208)

120 87 or 119 (723040)

121 68 and 120 (139)

Appendix D – Effectiveness evidence study selection



Appendix E – Effectiveness evidence

Type of fluid – IV fluids

RCTs

Shafi 2018

Shafi, 2018

Bibliographic Reference	Shafi, Obeid; Kumar, Virendra; Initial Fluid Therapy in Pediatric Diabetic Ketoacidosis: A comparison of Hypertonic Saline Solution and Normal Saline Solution.; Pediatric endocrinology, diabetes, and metabolism; 2018; vol. 24 (no. 2); 56-64

Study details

Study type	**Randomised controlled trial (RCT)**
Study location	India
Study setting	Emergency and Pediatric Intensive Care Unit (PICU) of a tertiary care children's hospital
Study dates	November 2011 to April 2013
Duration of follow-up	The two groups were compared for: • Changes in heart rate, blood pressure (Systolic [SBP], Diastolic [DBP] and Mean [MBP]), respiratory rate, sodium levels, chloride levels, lactate, pH and blood sugar at 1, 2, 4, 6, 12, 24 and 48 hours. • Time needed for the correction of hyperglycemia (< 250 mg/dL). • Time needed for the resolution of ketoacidosis: defined as bicarbonate >18 mEq/L, venous pH ≥7.3, anion gap <14 mEq/L [any two]. • Cerebral edema: occurrence of an abnormal Glasgow Coma Scale (GCS<14) during the treatment.
Sources of funding	Not reported
Inclusion criteria	Subjects with age ≤18 years with a diagnosis of DKA were screened for the inclusion in the study and were included if they met the criteria for having moderate-severe DKA

Study type	Randomised controlled trial (RCT)
Exclusion criteria	Patients with a history suggestive of chronic systemic illnesses, Patients with underlying neurological abnormalities or concomitant head trauma, meningitis or other conditions which would affect mental status evaluation and monitoring, Patients who have already received intravenous fluid (≥ 5 mL/kg) prior to the enrolment into the study, refusal of consent
Sample size	20
Loss to follow-up	Not reported
Condition specific characteristics	Moderate -severe DKA defined as blood glucose >11 mmol/L (200 mg/dl) and pH<7.25 or bicarbonate <10 mmol/L and ketonemia and/or ketonuria
Interventions	**0.9% normal saline** Children randomised to the 0.9% saline received 20 ml/kg of solution during the initial 1 hour of fluid therapy. The rest of the fluid and management was per the written DKA management protocol followed by the treating unit, which is based on the ISPAD clinical practice consensus guidelines. After the initial fluid, all the patients received isotonic fluid (0.9% saline) solution for a duration of 4 hours followed by a solution consisting of 0.45% saline, with an aim to correct the dehydration over 48 hours. Insulin infusion was started after 1 hour, upon the completion of initial fluid therapy. The starting dose of insulin infusion for all patients was 0.1 unit/kg/hr and the solution was prepared by diluting 50 units of regular (soluble) insulin in 50 mL of normal saline. **Hypertonic Saline (3% NaCl)** Children randomised to the hypertonic saline (3% NaCl) received 20 ml/kg of solution during the initial 1 hour of fluid therapy. The rest of the fluid and management was per the written DKA management protocol followed by the treating unit, which is based on the ISPAD clinical practice consensus guidelines. After the initial fluid, all the patients received isotonic fluid (0.9% saline) solution for a duration of 4 hours followed by a solution consisting of 0.45% saline, with an aim to correct the dehydration over 48 hours. Insulin infusion was started after 1 hour, upon the completion of initial fluid therapy. The starting dose of insulin infusion for all patients was 0.1 unit/kg/hr and the solution was prepared by diluting 50 units of regular (soluble) insulin in 50 mL of normal saline.
Outcome measures	**Cerebral oedema** occurrence of an abnormal Glasgow Coma Scale (GCS < 14) during the treatment **Chloride concentration (mEq/L)** **Time needed for the correction of hyperglycaemia** hours. blood sugar <250 mg/dL **Time needed for the resolution of acidosis** hours. Defined as bicarbonate > 18 mEq/L, venous pH ≥ 7.3, anion gap < 14 mEq/L (any two)

1

2 **Study arms**

0.9% saline (N = 20)
hypertonic saline (3% NaCl) (N = 20)

1 **Characteristics**

2 **Study-level characteristics**

	Study (N = 40)
Age group (2-5 years) Percentage (%)	25
Age group (6-10 years) Percentage (%)	32.5
Age group (11-18 years) Percentage (%)	42.5
% Female Percentage (%)	57.5

3 **Arm-level characteristics**

	0.9% saline (N = 20)	hypertonic saline (3% NaCl) (N = 20)
Severity of DKA		
Severe		
No of events	n = 16 ; % = 80	n = 15 ; % = 75
Moderate		
No of events	n = 4 ; % = 20	n = 5 ; % = 25

4

Cochrane risk of bias tool 2.0 (RoB 2.0)		
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns (Baseline differences not specified for important factors such as age, sex, type of diabetes)
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Cochrane risk of bias tool 2.0 (RoB 2.0)		
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns (Baseline differences of some characteristics not reported)
	Overall Directness	Directly applicable

1

2 **Williams 2020**

Williams, 2020

3

Bibliographic Reference	Williams, V.; Jayashree, M.; Nallasamy, K.; Dayal, D.; Rawat, A.; 0.9% saline versus Plasma-Lyte as initial fluid in children with diabetic ketoacidosis (SPinK trial): A double-blind randomized controlled trial; Critical Care; 2020; vol. 24 (no. 1); 1

4 **Study details**

Study type	**Randomised controlled trial (RCT)**
Study location	India
Study setting	Pediatric Emergency and Intensive care units of a large tertiary, teaching and referral hospital
Study dates	August 2017 to December 2018
Duration of follow-up	Patients were followed up till discharge from PICU or ward or death, whichever was earlier. Post discharge, the children were assessed in the PICU and diabetic followup clinics.
Sources of funding	This study was supported by the Indian council of Medical Research (ICMR), as a part of DM dissertation
Inclusion criteria	All consecutive children > 1 month to < 12 years who presented to the pediatric emergency room with DKA as defined by the International Society of Pediatric and Adolescent Diabetes (ISPAD-2014) were enrolled into the study

Study type	Randomised controlled trial (RCT)
Exclusion criteria	Children with symptomatic cerebral edema (GCS < 8 at presentation) or known chronic kidney disease or liver disease or who had received pre-referral fluids and/or insulin at the time of hospital presentation were excluded.
Sample size	66
Loss to follow-up	2 patients lost at follow up
Condition specific characteristics	The severity of DKA was classified as mild if pH was between 7.2 and 7.3, moderate if pH was between 7.1 and 7.2, and severe if pH was < 7.1. DKA defined as blood glucose > 200 mg/dl and blood ketones >3 mmol/L and venous pH <7.3 or bicarbonate <15.mEg/L
Interventions	**0.9% normal saline** **DKA protocol:** volume calculated based on deficit (6.5-10%) and maintenance fluid as per Holliday Segar. Fluids given over 48 hours as hourly infusion. Eligible children who presented in shock [perfusion abnormalities with or without hypotension (blood pressure < 5th centile for age)], received trial fluid bolus of 20 ml/kg over an hour. Insulin was started at 0.05 U/kg/h in all after initial hour of fluid therapy. Fluids were changed to 0.45% saline and 5% dextrose once blood glucose fell below 250 mg/dl. In case of persistently high blood glucose, the clinician went through a checklist that included patency of intravenous cannula, insulin preparation and its shelf life, and appropriateness of dilution before increasing insulin to 0.1 U/kg/h. **Plasma-Lyte-A** **DKA protocol:** volume calculated based on deficit (6.5-10%) and maintenance fluid as per Holliday Segar. Fluids given over 48 hours as hourly infusion. Eligible children who presented in shock [perfusion abnormalities with or without hypotension (blood pressure < 5th centile for age)], received trial fluid bolus of 20 ml/kg over an hour. Insulin was started at 0.05 U/kg/h in all after initial hour of fluid therapy. Fluids were changed to 0.45% saline and 5% dextrose once blood glucose fell below 250 mg/dl. In case of persistently high blood glucose, the clinician went through a checklist that included patency of intravenous cannula, insulin preparation and its shelf life, and appropriateness of dilution before increasing insulin to 0.1 U/kg/h.
Outcome measures	**Incidence of acute kidney injury (AKI)** defined with either KDIGO or pRIFLE criteria **Healthcare utilisation - Need for renal replacement therapy (RRT)** Till discharge from PICU or ward or death, whichever was earlier **Healthcare utilisation- Need for ventilation** Till discharge from PICU or ward or death, whichever was earlier **Mortality in hospital** **Cerebral oedema** Till discharge from PICU or ward or death, whichever was earlier **Healthcare utilisation- Length of intensive care unit (ICU) stay**

Study type	**Randomised controlled trial (RCT)**
	Healthcare utilisation - length of hospital stay days

1 **Study arms**

Plasma-Lyte- A (N = 34)
0.9% Saline (N = 32)

2 **Characteristics**

3 **Arm-level characteristics**

	Plasma-Lyte- A (N = 34)	**0.9% Saline (N = 32)**
Age (years) Median IQR	7.8 (4 to 11.6)	6.6 (2.9 to 10.1)
% Female Sample Size	n = 16 ; % = 47	n = 17 ; % = 53
New onset of diabetes No of events	n = 17 ; % = 50	n = 24 ; % = 75
Duration of diabetes in known type 1 diabetes months MedianIQR	26.7 (7.2 to 47.8)	15.4 (6.1 to 32.2)
Severity of DKA		
Severe		
Number (%)	n = 20 ; % = 58.8	n = 20 ; % = 62.5
Moderate		
Number (%)	n = 11 ; % = 32.4	n = 11 ; % = 34.4
Mild		
Number (%)	n = 3 ; % = 8.8	n = 1 ; % = 3.1

4

Cochrane risk of bias tool 2.0 (RoB 2.0)		
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns (Significant difference between the number of children with new onset DKA)

Cochrane risk of bias tool 2.0 (RoB 2.0)		
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns (Significant difference between the number of children with new onset DKA)
	Overall Directness	Directly applicable

1 **Yung 2017**

Yung, 2017

2

Bibliographic Reference	Yung, Michael; Letton, Georgia; Keeley, Steve; Controlled trial of Hartmann's solution versus 0.9% saline for diabetic ketoacidosis.; Journal of paediatrics and child health; 2017; vol. 53 (no. 1); 12-17

3 **Study details**

Study type	**Randomised controlled trial (RCT)**
Study location	Australia
Study setting	Paediatric intensive care unit (PICU) or high dependency unit
Study dates	1st July 2007 and 31st August 2010
Duration of follow-up	During treatment - Vital signs were recorded, including GCS, hourly. Venous blood glucose hourly and blood gases, Na, K, Cl, lactate and haemoglobin every 2 h using the ABL725 blood gas analyser (Radiometer, Copenhagen). Study specifies that usual maintenance plus correction of deficit over 48 or 72 h if corrected Na is >150 mmol/L.
Sources of funding	Not specified.

Study type	Randomised controlled trial (RCT)
Inclusion criteria	Children with moderate to severe DKA admitted to the paediatric intensive care unit (PICU) or high-dependency unit with DKA were eligible.
Exclusion criteria	Exclusion criteria were as follows: a Glasgow coma score (GCS) <11, mechanical ventilation, hyponatremia, corrected Na <130 mmol/L (corrected sodium = Measured Na + 2 × ((Glucose − 5.5)/ 5.5) mmol/L), K+ >5.5 mmol/L or previous enrolment.
Sample size	77 children
Loss to follow-up	Not reported
Condition specific characteristics	Biochemical criteria for the diagnosis of moderate to severe DKA are hyperglycaemia (blood glucose >11 mmol/L), venous pH <7.3 and/or bicarbonate <15 mmol/L and ketonemia or ketonuria and glycosuria. Moderate DKA was defined as pH ≥7.1, HCO3 ≥ 5 mmol/L and severe DKA as pH <7.1, HCO3 < 5 mmol/L. If HCO3 did not correlate with pH, the pH determined the severity. Hypovolemic patients were given NS in boluses of 10 mL/kg (maximum 30 mL/kg). Hypovolemia was defined as either hypotension, systolic blood pressure < Age × 2 + 70, or reduced peripheral perfusion.
Interventions	**Hartmann's solution** After resuscitation, subjects were randomised to Hartmann's solution as their initial fluid for at least 12 hours. The rate of administration followed the hospital's DKA protocol: usual maintenance plus correction of deficit over 48 or 72 h if corrected Na is >150 mmol/L. We assumed a mean deficit of 6% for moderate and 10% for severe DKA as clinical signs of dehydration are unreliable in estimating dehydration in DKA. Fluids already received were subtracted from the deficit. After 12 h of study fluid, 0.45% saline was permitted if the corrected Na exceeded 150 mmol/L. When the initial corrected Na was >150 mmol/L, the fluid was changed to 0.45% saline if the corrected Na did not fall by at least 5 mmol/L in 12 h. KCl was added to study fluid unless hyperkalaemia (K >5.5 mmol/L) or anuria was present. KH2PO4 was allowed as an additional source of potassium after the first 24 h if hypophosphataemia occurred, and ionised calcium was monitored. Glucose was added after the blood glucose was <15 mmol/L or had fallen by >5 mmol/L/h, excluding the usual rapid fall with fluid boluses, by replacing 100 ml of the 1-L study fluid with 50% dextrose. Other aspects of treatment were guided by the hospital's DKA protocol and the treating clinicians, including the use of human soluble insulin, which was started after initial fluid resuscitation, when the potassium was known and appropriate replacement started. The initial dosing rate was 0.1 U/kg/h, or 0.05 U/kg/h for children <5 years old and those with known, partially treated diabetes. SC insulin was given when acidosis had resolved and oral intake was tolerated. **0.9% normal saline** After resuscitation, subjects were randomised to 0.9% normal saline as their initial fluid for at least 12 hours. The rate of administration followed the hospital's DKA protocol: usual maintenance plus correction of deficit over 48 or 72 h if corrected Na is >150 mmol/L. We assumed a mean deficit of 6% for moderate and 10% for severe DKA as clinical signs of dehydration are unreliable in estimating dehydration in DKA. Fluids already received were subtracted from the deficit. After 12 h of study fluid, 0.45% saline was permitted if the corrected Na exceeded 150 mmol/L. When the initial corrected Na was >150 mmol/L, the fluid was changed to 0.45% saline if the corrected Na did not fall by at least 5 mmol/L in 12 h. KCl was added to study fluid unless hyperkalaemia (K >5.5 mmol/L) or anuria was present. KH2PO4 was allowed as an additional source of potassium after the first 24 h if hypophosphataemia

Study type	**Randomised controlled trial (RCT)**
	occurred, and ionised calcium was monitored. Glucose was added after the blood glucose was <15 mmol/L or had fallen by >5 mmol/L/h, excluding the usual rapid fall with fluid boluses, by replacing 100 ml of the 1-L study fluid with 50% dextrose. Other aspects of treatment were guided by the hospital's DKA protocol and the treating clinicians, including the use of human soluble insulin, which was started after initial fluid resuscitation, when the potassium was known and appropriate replacement started. The initial dosing rate was 0.1 U/kg/h, or 0.05 U/kg/h for children <5 years old and those with known, partially treated diabetes. SC insulin was given when acidosis had resolved and oral intake was tolerated.
Outcome measures	**Minimum sodium concentration** **Maximum chloride concentration** **Altered conscious state** Glasgow coma scale (GCS) deterioration Acute renal failure **Healthcare utilisation- Paediatric intensive care unit (PICU) or high-dependency unit (HDU) stay** Hours

1 **Study arms**

Hartmann's solution (N = 38)
0.9% normal saline (N = 39)

2 **Characteristics**

3 **Arm-level characteristics**

	Hartmann's solution (N = 38)	0.9% normal saline (N = 39)
Age (years) MedianIQR	12.9 (11.4 to 15.1)	12.4 (8.5 to 15)
% Female Sample Size	n = 15 ; % = 63.2	n = 15 ; % = 38.5
Previously known diabetes Unclear if its T1DM or T2DM Sample Size	n = 19; % = 50	n = 19 ; % = 49

4

Cochrane risk of bias tool 2.0 (RoB 2.0)		
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
	Overall Directness	Directly applicable (Directly applicable for outcomes: minimum sodium concentration, maximum chloride concentration, acute renal failure and Healthcare utilisation- Paediatric intensive care unit (PICU) or high-dependency unit (HDU) stay) Indirectly applicable (Outcome 'altered conscious state' not specified in the review protocol but did include fall in GCS.)

1 **Observational studies**

2 **Basnet 2014**

Basnet, 2014

3

Bibliographic Reference	Basnet, Sangita; Venepalli, Preethi K; Andoh, Jennifer; Verhulst, Steven; Koirala, Janak; Effect of normal saline and half normal saline on serum electrolytes during recovery phase of diabetic ketoacidosis.; Journal of intensive care medicine; 2014; vol. 29 (no. 1); 38-42

1 **Study details**

Study type	**Retrospective cohort study**
Study location	USA
Study setting	Paediatric intensive care unit
Study dates	2005 and 2010
Duration of follow-up	For majority of the patients, we found that plasma glucose was checked every hour; sodium, potassium, and bicarbonate every 2 hours; and serum chloride every 6 to 8 hours
Sources of funding	Not reported
Inclusion criteria	Children between the age of 1 and 18 years with initial serum pH <7.3 and serum bicarbonate <15 meq/L with hyperglycemia and ketonuria
Exclusion criteria	Patients in shock requiring pressors for management
Sample size	121
Condition specific characteristics	DKA defined as initial serum pH <7.3 and serum bicarbonate <15 meq/L with hyperglycemia and ketonuria.
Interventions	**0.9% saline** Used a post-bolus re-hydration fluid during the recovery phase of DKA **0.45% saline** Used a post-bolus re-hydration fluid during the recovery phase of DKA
Outcome measures	**Healthcare utilisation - Mean PICU stay (hours)** **Change in corrected sodium (meq/L)** **Rate of change of glucose (mg/dL/h)**

2 **Study arms**

0.9% saline (N = 47)
0.45% saline (N = 41)

3 **Characteristics**

4 **Arm-level characteristics**

	0.9% saline (N = 47)	0.45% saline (N = 41)
Age (years) Mean/SD	12.9 (4.1)	9.9 (4.4)
% Female Nominal	62	61

1

ROBINS-I Tool		
Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate (no information on confounders or of methods to control for any post-intervention variables that could have been affected by the intervention.)
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate (No information on co-interventions e.g. initial fluid used, rate and volume or type of additives.)
5. Bias due to missing data	Risk of bias judgement for missing data	Low
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Moderate (no information on confounders or of methods to control for any post-intervention variables that could have been affected by the intervention. No information on co-interventions e.g. initial fluid used, rate and volume or type of additives.)
	Directness	Directly applicable

1

2 **Bergmann 2018**

Bergmann, 2018

3

Bibliographic Reference	Bergmann, Kelly R; Abuzzahab, M Jennifer; Nowak, Jeffrey; Arms, Joe; Cutler, Gretchen; Christensen, Eric; Finch, Mike; Kharbanda, Anupam; Resuscitation With Ringer's Lactate Compared With Normal Saline for Pediatric Diabetic Ketoacidosis.; Pediatric emergency care; 2018

4 **Study details**

Study type	**Retrospective cohort study**
Study location	USA
Study setting	multicentre study which included patient, observation, or emergency department (ED) care
Study dates	January 1, 2005, and September 30, 2015
Sources of funding	Not reported
Inclusion criteria	children aged 0 to 17 years discharged from inpatient, observation, or emergency department (ED) care with a diagnosis of diabetes with ketoacidosis, type I (International Classification of Diseases, Ninth Revision [ICD-9] codes 250.11 and 250.13), between January 1, 2005, and September 30, 2015
Exclusion criteria	those with nonparenteral administration route, infused volume of less than 50 mL, or concentrations other than 0.9%for the NS group. We further excluded those without available cost records as not all hospitals reported it each year.
Sample size	49,737
Loss to follow-up	not reported
Condition specific characteristics	No definition provided.
Interventions	**Ringer's lactate** No information provided on DKA protocols used. **Normal saline** No information provided on DKA protocols used.
Outcome measures	**Cerebral oedema**

Study type	**Retrospective cohort study**
	Length of stay (days) **Healthcare utilisation - Mechanical ventilation**

1 **Study arms**

Normal saline (N = 43841)
Ringer's lactate (N = 1762)

2 **Characteristics**

3 **Arm-level characteristics**

	Normal saline (N = 43841)	Ringer's lactate (N = 1762)
% Female Percentage (%)	54.5	53.5
Age MedianIQR	12 (9 to 15)	12 (9 to 15)

4

ROBINS-I Tool		
Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate (Appropriate analysis method that controlled for all the important confounding domains not conducted)
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Serious (DKA protocols followed not defined.)
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Serious (DKA protocols followed not defined.)

ROBINS-I Tool		
5. Bias due to missing data	Risk of bias judgement for missing data	Low
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Serious (Appropriate analysis method that controlled for all the important confounding domains not conducted. DKA protocols followed not defined.)
	Directness	Partially Applicable (Definition of DKA not provided)

1 **Savaş-Erdeve 2011**

Savaş-Erdeve, 2011

2

Bibliographic Reference	Savaş-Erdeve Ş; Berberoğlu M; Oygar P; Şıklar Z; Kendirli T; Hacıhamdioğlu B; Bilir P; Öçal G; Efficiency of fluid treatments with different sodium concentration in children with type 1 diabetic ketoacidosis.; Journal of clinical research in pediatric endocrinology; 2011; vol. 3 (no. 3)

3 **Study details**

Study type	**Retrospective cohort study**
Study location	Turkey
Study setting	Paediatric intensive care unit
Study dates	2002 to 2009
Duration of follow-up	Samples of venous blood for blood gases and electrolytes were taken at admission and at the 4th, 8th, 16th and 24th hours after admission.
Inclusion criteria	Patients younger than 18 years of age who were admitted to the paediatric intensive care unit from 2002 to 2009
Exclusion criteria	Not reported

Study type	Retrospective cohort study
Sample size	32
Condition specific characteristics	DKA defined as having a glycemia >200 mg/dL (11.4 mmol/L), a venous pH <7.30 or a plasma bicarbonate level <15 mmol/L, and ketonuria (2).
Interventions	**75 mEq/L Sodium Chloride** Initial rehydration was performed with isotonic solutions in the first hour of treatment. Study does not specify the fluid used but did highlight that in Turkey treatment of DKA is initiated with 0.9% Na saline. The total volume to be given was calculated assuming a 10% deficit plus maintenance fluid. Amounts of fluids used in the initial resuscitation were subtracted from the total volume calculated for 48 hours and the infusion rate was adjusted accordingly. After initial rehydration, IV fluids were switched to solutions containing 5% dextrose and [Na+] 75 mEq/L. The patients in Group I had received IV fluids with a Na concentration of 75 mEq/L (1/2 isotonic NaCl plus 1/2 5% dextrose). During rehydration, the potassium concentration of the IV fluids was adjusted as 40 mEq/L. The patients were started on oral intake and subcutaneous insulin as soon as the acidosis was resolved, serum Na level became stable, and vomiting had stopped. After transition to oral intake, the amount of oral fluid was subtracted from the ongoing IV fluid treatment. **100 mEq/L Sodium Chloride** Initial rehydration was performed with isotonic solutions in the first hour of treatment. Study does not specify the fluid used but did highlight that in Turkey treatment of DKA is initiated with 0.9% Na saline. The total volume to be given was calculated assuming a 10% deficit plus maintenance fluid. Amounts of fluids used in the initial resuscitation were subtracted from the total volume calculated for 48 hours and the infusion rate was adjusted accordingly. After initial rehydration, IV fluids were switched to solutions containing 5% dextrose and [Na+] 100 mEq/L. The patients in Group II had received IV fluids with a Na concentration of 100 mEq/L (2/3 isotonic NaCl plus 1/3 5% dextrose). During rehydration, the potassium concentration of the IV fluids was adjusted as 40 mEq/L. The patients were started on oral intake and subcutaneous insulin as soon as the acidosis was resolved, serum Na level became stable, and vomiting had stopped. After transition to oral intake, the amount of oral fluid was subtracted from the ongoing IV fluid treatment.
Outcome measures	**Cerebral oedema** Definition not provided. **Blood glucose levels (mg/dL)** **Sodium concentration (mEq/L)**

1 **Study arms**

75 mEq/L Sodium chloride (N = 19)
100 mEq/L Sodium chloride (N = 13)

1 **Characteristics**

2 **Study-level characteristics**

	Study (N = 32)
No. of patients with new-onset diabetes Sample Size	n = 26; % = 81.3

3 **Arm-level characteristics**

	75 mEq/L Sodium chloride (N = 19)	**100 mEq/L Sodium chloride (N = 13)**
Age (years) Mean/SD	8.7 (4.1)	9.5 (4)
% Female No of events	n = 11 ; % = 57.9	n = 4; % = 30.8

4

ROBINS-I Tool		
Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate (Appropriate analysis method that controlled for all the important confounding domains not conducted.)
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low

ROBINS-I Tool		
5. Bias due to missing data	Risk of bias judgement for missing data	Low
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Moderate (Appropriate analysis method that controlled for all the important confounding domains not conducted.)
	Directness	Partially Applicable (Included mixed population. Data not separated out for type of diabetes. Outcome 'blood glucose' not specified in review protocol.) Directly applicable for other outcomes.

1

2

3 Type of fluid and rate of rehydration

4 RCTs

5 Kuppermann 2018

Kuppermann, 2018

6

Bibliographic Reference	Kuppermann, Nathan; Ghetti, Simona; Schunk, Jeff E; Stoner, Michael J; Rewers, Arleta; McManemy, Julie K; Myers, Sage R; Nigrovic, Lise E; Garro, Aris; Brown, Kathleen M; Quayle, Kimberly S; Trainor, Jennifer L; Tzimenatos, Leah; Bennett, Jonathan E; DePiero, Andrew D; Kwok, Maria Y; Perry, Clinton S 3rd; Olsen, Cody S; Casper, T Charles; Dean, J Michael; Glaser, Nicole S; PECARN DKA FLUID Study, Group; Clinical Trial of Fluid Infusion Rates for Pediatric Diabetic Ketoacidosis.; The New England journal of medicine; 2018; vol. 378 (no. 24); 2275-2287

1 **Study details**

Study type	**Randomised controlled trial (RCT)** **2-by-2 factorial design**
Study location	USA
Study setting	13 emergency departments
Study dates	February 2011 through September 2016
Duration of follow-up	Glasgow Coma Scale scores were assessed at enrolment and hourly thereafter. Glasgow Coma Scale scores of less than 14 were confirmed by repeating the test 15 minutes later. For children 3 years of age or older, digit-span tests were conducted at enrolment and every 4 hours thereafter during normal waking hours. Glasgow Coma Scale and digit-span assessments continued for 24 hours or until resolution of diabetic ketoacidosis (as defined by the transition to subcutaneous insulin) if diabetic ketoacidosis resolved before the 24-hour time point. Patients 3 to 18 years of age were asked to return 2 to 4 months after discharge from the hospital for neurocognitive assessment but were allowed to return up to 6 months after discharge.
Sources of funding	Supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (grant U01HD062417) and the Emergency Medical Services for Children Network Development Demonstration Program of the Maternal and Child Health Bureau, Health Resources and Services Administration, under cooperative agreement
Inclusion criteria	Children aged between 0 and 18 years of age and had a diagnosis of diabetic ketoacidosis
Exclusion criteria	underlying disorders that could affect mental status testing or neurocognitive evaluation; concurrent alcohol or narcotics use, head trauma, or other conditions that could affect neurologic function; diabetic ketoacidosis for which the patient had already received substantial treatment; known pregnancy; or factors for which treating physicians determined that a specific fluid and electrolyte therapy was necessary. Children who presented with a Glasgow Coma Scale score of 11 or lower (on a scale ranging from 3 to 15, with lower scores indicating worse mental status) were excluded after year 2 because many participating clinicians believed that fluid regimens for such children should not be determined on the basis of randomization.
Sample size	1389 participants
Condition specific characteristics	Ketoacidosis defined as a blood glucose level of >300 mg per deciliter [16.7 mmol per liter] and either a venous pH of <7.25 or a serum bicarbonate level of <15 mmol per liter)
Interventions	**Fast administration of 0.45% sodium chloride** **Standard initial bolus:** 10 ml per kilogram bolus of 0.9% sodium chloride solution. Initial fluid bolus volumes were subtracted from the fluid deficit that was used to calculate the rate of fluid replacement. Fluid boluses could be repeated at the discretion of the treating physician to restore peripheral perfusion and hemodynamic stability. Insulin treatment was initiated after the initial intravenous fluid boluses as a continuous intravenous infusion at a rate of 0.1 U per kilogram of body weight per hour. Dextrose was added to the intravenous fluids when the serum glucose level declined to below 200 to 300 mg per deciliter (11.1 to 16.7 mmol per liter) to maintain the serum glucose level between 100 and 200 mg per deciliter (5.6 to 11.1 mmol per liter).

Study type	**Randomised controlled trial (RCT)** **2-by-2 factorial design**
	Additional intravenous fluid bolus: 10 ml per kilogram of 0.9% sodium chloride solution **Assumed deficit:** 10% of body weight. **Process of replacement of deficit:** During the initial 12 hours, replace half the fluid deficit, plus maintenance fluids. Then replace remaining deficit, plus maintenance fluids, during the subsequent 24 hours. **Fluid used for replacement of deficit:** 0.45% sodium chloride solution. Potassium salts used for replacement were identical among the groups at each site but varied among the trial sites. **Slow administration of 0.45% sodium chloride** **Standard initial bolus:** 10 ml per kilogram bolus of 0.9% sodium chloride solution. Initial fluid bolus volumes were subtracted from the fluid deficit that was used to calculate the rate of fluid replacement. Fluid boluses could be repeated at the discretion of the treating physician to restore peripheral perfusion and hemodynamic stability. Insulin treatment was initiated after the initial intravenous fluid boluses as a continuous intravenous infusion at a rate of 0.1 U per kilogram of body weight per hour. Dextrose was added to the intravenous fluids when the serum glucose level declined to below 200 to 300 mg per deciliter (11.1 to 16.7 mmol per liter) to maintain the serum glucose level between 100 and 200 mg per deciliter (5.6 to 11.1 mmol per liter). **Additional intravenous fluid bolus:** No additional bolus. **Assumed deficit:** 5% of body weight. **Process of replacement of deficit:** Replace deficit, plus maintenance fluids, evenly during a period of 48 hours. **Fluid used for replacement of deficit:** 0.45% sodium chloride solution. Replacement of potassium was provided with the use of an equal mixture of potassium chloride and potassium phosphate or an equal mixture of potassium acetate and potassium phosphate. Potassium salts used for replacement were identical among the groups at each site but varied among the trial sites. **Fast administration of 0.9% sodium chloride** **Standard initial bolus:** 10 ml per kilogram bolus of 0.9% sodium chloride solution. Initial fluid bolus volumes were subtracted from the fluid deficit that was used to calculate the rate of fluid replacement. Fluid boluses could be repeated at the discretion of the treating physician to restore peripheral perfusion and hemodynamic stability. Insulin treatment was initiated after the initial intravenous fluid boluses as a continuous intravenous infusion at a rate of 0.1 U per kilogram of body weight per hour. Dextrose was added to the intravenous fluids when the serum glucose level declined to below 200 to 300 mg per deciliter (11.1 to 16.7 mmol per liter) to maintain the serum glucose level between 100 and 200 mg per deciliter (5.6 to 11.1 mmol per liter). **Additional intravenous fluid bolus:** 10 ml per kilogram of 0.9% sodium chloride solution. **Assumed deficit:** 10% of body weight. **Process of replacement of deficit:** During the initial 12 hours, replace half the fluid deficit, plus maintenance fluids. Then replace remaining deficit, plus maintenance fluids, during the subsequent 24 hours.

Study type	**Randomised controlled trial (RCT)** **2-by-2 factorial design**
	Fluid used for replacement of deficit: 0.9% sodium chloride solution. Potassium salts used for replacement were identical among the groups at each site but varied among the trial sites. **<u>Slow administration of 0.9% sodium chloride</u>** **Standard initial bolus:** 10 ml per kilogram bolus of 0.9% sodium chloride solution. Initial fluid bolus volumes were subtracted from the fluid deficit that was used to calculate the rate of fluid replacement. Fluid boluses could be repeated at the discretion of the treating physician to restore peripheral perfusion and hemodynamic stability. Insulin treatment was initiated after the initial intravenous fluid boluses as a continuous intravenous infusion at a rate of 0.1 U per kilogram of body weight per hour. Dextrose was added to the intravenous fluids when the serum glucose level declined to below 200 to 300 mg per deciliter (11.1 to 16.7 mmol per liter) to maintain the serum glucose level between 100 and 200 mg per deciliter (5.6 to 11.1 mmol per liter). **Additional intravenous fluid bolus**: No additional bolus. **Assumed deficit:** 5% of body weight. **Process of replacement of deficit:** Replace deficit, plus maintenance fluids, evenly during a period of 48 hours. **Fluid used for replacement of deficit:** 0.9% sodium chloride solution. Replacement of potassium was provided with the use of an equal mixture of potassium chloride and potassium phosphate or an equal mixture of potassium acetate and potassium phosphate. Potassium salts used for replacement were identical among the groups at each site but varied among the trial sites.
Outcome measures	**Confirmed decline in Glasgow Come Scale Score** as evidenced by two consecutive Glasgow Coma Scale scores of <14 during any hour within the first 24 hours of treatment for diabetic ketoacidosis **Clinically apparent brain injury** defined as a deterioration in neurologic status leading to initiation of hyperosmolar therapy or endotracheal intubation or resulting in death **IQ** IQ was evaluated with the use of the Wechsler Abbreviated Scale of Intelligence (in patients 6 years of age or older) and the Wechsler Preschool and Primary Scale of Intelligence short form (in patients 3 to 5 years of age) **Renal failure** **Death** **Time to DKA resolution** time from randomisation until transition to subcutaneous insulin administration if within 24 hours; time until anion gap ≤ 12 if transition to SC was after 24 hours; time until transition to SC insulin in anion gap ≤12 not documented **Time to hospital discharge (hours)**

1 **Study arms**

Fast administration of 0.45% sodium chloride solution (N = 344)
Slow administration of 0.45% sodium chloride solution (N = 345)
Fast administration of 0.9% sodium chloride solution (N = 351)
Slow administration of 0.9% sodium chloride solution (N = 349)

2 **Characteristics**

3 **Arm-level characteristics**

	Fast administration of 0.45% sodium chloride solution (N = 344)	Slow administration of 0.45% sodium chloride solution (N = 345)	Fast administration of 0.9% sodium chloride solution (N = 351)	Slow administration of 0.9% sodium chloride solution (N = 349)
Age (years) Mean/SD	11.5 (4.06)	11.6 (4.09)	11.8 (4.26)	11.6 (3.89)
Age < 6 years No of events	n = 43; % = 12.5	n = 42; % = 12.2	n = 42; % = 12	n = 35; % = 10
% Female No of events	n = 179; % = 52	n = 187; % = 54.2	n = 187; % = 53.3	n = 186; % = 53.3
Previous diagnosis of diabetes No of events	n = 174; % = 50.6	n = 185; % = 53.6	n = 182; % = 51.9	n = 192; % = 55

4

Cochrane risk of bias tool 2.0 (RoB 2.0)		
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Cochrane risk of bias tool 2.0 (RoB 2.0)		
intended interventions (effect of assignment to intervention)		
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
	Overall Directness	Directly applicable For all other outcomes Indirectly applicable (Outcome brain injury not specified in review protocol but the authors hypothesised that rapid administration of IV fluids results in brain injury.)

1 IV fluids + Additives

2 Observational studies

3 Green 1998

Green, 1998

4

Bibliographic Reference	Green SM; Rothrock SG; Ho JD; Gallant RD; Borger R; Thomas TL; Zimmerman GJ; Failure of adjunctive bicarbonate to improve outcome in severe pediatric diabetic ketoacidosis.; Annals of emergency medicine; 1998; vol. 31 (no. 1)

5 **Study details**

Study type	Retrospective cohort study
Study location	USA
Study setting	University medical centre

Study type	Retrospective cohort study
Study dates	January 1st 1979 to December 31st 1994
Duration of follow-up	Till discharge
Sources of funding	Not reported
Inclusion criteria	Children aged 15 years or younger with a hospital diagnosis of severe DKA at a tertiary university medical centre over a 16-year period (January 1, 1979, through December 31, 1994)
Exclusion criteria	If initial arterial pH was more than 7.15, the initial serum glucose concentration less than 300 mg/dL (16.7mmol/L), or if either of these measurements were not obtained at the time of initial resuscitation. if DKA was a secondary condition with a more serious primary diagnosis.
Sample size	106 children
Loss to follow-up	not reported
Condition specific characteristics	Severe DKA defined as initial pH greater than or equal to 7.15 and glucose concentration ³300 mg/dL [16.7 mmol/L]
Interventions	**Sodium bicarbonate** Children received standard DKA therapy with hydration and intravenous insulin infusion. Adjunctive bicarbonate therapy was administered by treating physicians in doses ranging from 7 to 238 mEq and from 0.53 to 7.37 mEq/kg (mean 2.08, median 1.66 mEq) **No sodium bicarbonate** Children received standard DKA therapy with hydration and intravenous insulin infusion.
Outcome measures	Cerebral oedema Healthcare utilisation - Duration of hospitalisation Number of hours from the arterial blood gas value obtained at the time of initial resuscitation to actual discharge

1 **Study arms**

No sodium bicarbonate (N = 49)
Sodium bicarbonate (N = 57)

2 **Characteristics**

3 **Arm-level characteristics**

	No sodium bicarbonate (N = 49)	Sodium bicarbonate (N = 57)
Age (years)		
Mean/SD	10.1 (3.8)	9.6 (4.8)
% Female		
No of events	n = 26; % = 53	n = 35; % = 61

1

ROBINS-I Tool		
Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate (No adjustments for time varying confounding.)
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Moderate (Adjustments techniques not used to correct for the presence of selection bias.)
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Moderate (No information on DKA protocol followed (e.g. type of fluid, rate or volume))
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Serious (No information on co-interventions. Sodium bicarbonate was given at physicians discretion.)
5. Bias due to missing data	Risk of bias judgement for missing data	Low
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Serious (No adjustments for time varying confounding. Adjustments techniques not used to correct for the presence of selection bias. No information on DKA protocol followed (e.g. type of fluid, rate or volume). No information on co-interventions. Sodium bicarbonate was given at physicians discretion.)

ROBINS-I Tool		
	Directness	Directly applicable

1 **Mar 1981**

Mar, 1981

2

Bibliographic Reference	Mar TJ; Traisman HS; Traisman ES; Typlin B; Ban S; Juvenile ketoacidosis. The use of sodium bicarbonate in the treatment of diabetic children.; The Journal of the Kansas Medical Society; 1981; vol. 82 (no. 6)

3 **Study details**

Study type	**Retrospective cohort study**
Study location	USA
Study setting	Hospital setting
Study dates	1950 to 1973
Duration of follow-up	During treatment
Sources of funding	Not reported
Inclusion criteria	Children with diabetes with DKA with at least one episode of DKA
Exclusion criteria	Not reported
Sample size	131
Split between study groups	Study included 5 arms 1. Sodium bicarbonate or sodium bicarbonate and saline 2. Lactate Ringers or Lactate ringers with saline 3. Saline 4. Sodium bicarbonate and saline and Lactate ringers or sodium bicarbonate and lactate ringers 5. Other Arms 2 and 4 were included in the review.
Loss to follow-up	Not reported

Study type	Retrospective cohort study
Condition specific characteristics	No definition provided. Definition of DKA not provided
Interventions	Sodium bicarbonate and saline and lactate Ringers or sodium bicarbonate and Lactate Ringers No information about DKA protocol provided. Lactate Ringers or Lactate Ringers with saline No information about DKA protocol provided.
Outcome measures	Length of stay (days) Duration of acidosis (hours)

1 **Study arms**

Sodium bicarbonate and saline and lactate Ringers or sodium bicarbonate and Lactate Ringers (N = 8) Iv solution with sodium bicarbonate
Lactate Ringers or Lactate Ringers with saline (N = 41) No sodium bicarbonate

2

ROBINS-I Tool		
Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate (Appropriate analysis to control confounding not conducted.))
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Moderate (Adjustment techniques were not used to correct the presence of selection bias)
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Moderate (Adjustment techniques were not used to correct the presence of selection bias)
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate (DKA protocols followed not defined.))
5. Bias due to missing data	Risk of bias judgement for missing data	Low

ROBINS-I Tool		
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Serious (Appropriate analysis to control confounding not conducted. Adjustment techniques were not used to correct the presence of selection bias, DKA protocols followed not defined.)
	Directness	Partially Applicable (Definition of DKA not provided, Outcome 'duration of acidosis' not specified in the review protocol.)

1 # Rate of rehydration

2 ## RCTs

3 ### Glaser 2013

Glaser, 2013

4

Bibliographic Reference	Glaser NS; Wootton-Gorges SL; Buonocore MH; Tancredi DJ; Marcin JP; Caltagirone R; Lee Y; Murphy C; Kuppermann N; Subclinical cerebral edema in children with diabetic ketoacidosis randomized to 2 different rehydration protocols.; Pediatrics; 2013; vol. 131 (no. 1)

5 **Study details**

Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	Emergency department
Study dates	2008 and 2011
Duration of follow-up	Vital signs were evaluated hourly. Neurologic status was assessed hourly by using an age-appropriate Glasgow Coma Scale (GCS)14 for all patients, and every 30 minutes for patients with altered mental status.

Study type	Randomised controlled trial (RCT)
	Serum electrolyte concentrations, venous pH, and PCO2 were measured at presentation and every 3 hours, and blood glucose concentrations were measured hourly until the intravenous insulin infusion was discontinued. Patients underwent DWI at 3 time points: (1) 3 to 6 hours after the initiation of DKA treatment (defined by the administration of the first fluid bolus), (2) 9 to 12 hours after the initiation of DKA treatment, and (3) after recovery from DKA (≥72 hours after initiation of treatment)
Sources of funding	Supported by the National Institutes of Health (grant R01 NS048610 to Dr Glaser). Funded by the National Institutes of Health (NIH).
Inclusion criteria	Children aged 8 to 18 years old, were diagnosed with type 1 diabetes and had DKA
Exclusion criteria	Children were excluded if they had dental hardware that could interfere with MRI or cognitive deficits that would limit ability to cooperate with imaging. Children transferred to the study center after beginning DKA treatment were also excluded.
Sample size	18 patients
Condition specific characteristics	DKA defined as serum glucose >300 mg/ dL, venous pH <7.25, or serum bicarbonate <15 mEq/L, and a positive test for urine ketones
Interventions	**Rapid rate** **Intravenous fluid bolus**: 20 mL/Kg **Assumed fluid deficit:** 10% of body weight **Rate of deficit replacement:** Two-thirds over first 24 h; One-third over next 24 h **Urine output replacement:** Half of urine vol replaced while serum glucose level is >250 mg/dL **Fluid type:** 0.9% saline while serum glucose is >250 mg/dL, followed by 0.45% saline. For both protocols, insulin was initiated after the first fluid bolus as a continuous infusion of 0.1 U/Kg/hour. Potassium was administered as an equal mixture of potassium chloride and potassium phosphate. To optimize patient safety, regardless of protocol assignment, additional fluid boluses could be administered if these were thought necessary based on circulatory status. Similarly, treating physicians were able to adjust fluid infusion rates if it was felt that the rate prescribed by the study protocol might compromise patient safety. **Slower rate** **Intravenous fluid bolus:** 10 mL/Kg **Assumed fluid deficit:** 7% of body weight **Rate of deficit replacement:** Evenly over 48 h **Urine output replacement:** None

Study type	**Randomised controlled trial (RCT)**
	Fluid type: 0.9% saline while serum glucose is >250 mg/dL, followed by 0.45% saline. For both protocols, insulin was initiated after the first fluid bolus as a continuous infusion of 0.1 U/Kg/hour. Potassium was administered as an equal mixture of potassium chloride and potassium phosphate. To optimize patient safety, regardless of protocol assignment, additional fluid boluses could be administered if these were thought necessary based on circulatory status. Similarly, treating physicians were able to adjust fluid infusion rates if it was felt that the rate prescribed by the study protocol might compromise patient safety
Outcome measures	**Treated for suspected cerebral oedema** **Risk of cerebral oedema** High risk defined as SUN in the upper quartile (≥27 mg/dL) and/ or pH in the lower quartile (≤6.97)

1 **Study arms**

Rapid rate (N = 8)
Slower rate (N = 10)

2 **Characteristics**

3 **Arm-level characteristics**

	Rapid rate (N = 8)	Slower rate (N = 10)
Age (years) MedianIQR	11.5 (9 to 14)	15 (9 to 18)
% Female Percentage (%)	62	40
New onset diabetes (%) No of events	n = 1 ; % = 12	n = 1; % = 10

4

Cochrane risk of bias tool 2.0 (RoB 2.0)		
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns (Significant difference in age of children in the two arms. Slower rate group had older children.)
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns (Randomisation- Significant difference in age of children in the two arms. Slower rate group had older children.)
	Overall Directness	Indirectly applicable (Intravenous bolus volume was different in the two arms. Outcomes not specified in review protocol.)

1 ## Observational studies

2 ### Felner 2001

Felner, 2001

3

Bibliographic Reference	Felner EI; White PC; Improving management of diabetic ketoacidosis in children.; Pediatrics; 2001; vol. 108 (no. 3)

4 **Study details**

Study type	**Retrospective cohort study**
Study location	USA

Study type	Retrospective cohort study
Study setting	Children's medical centre. Study states at almost all patients admitted with DKA were initially evaluated in the emergency department. They patients were admitted to a regular hospital floor when stable. Patients who are obtunded, have severe acidosis were admitted to the intensive care unit.
Study dates	Group 1: September 1st 1994 to June 30th 1997. Group 2: July 1st 1997 to March 31st 2000.
Duration of follow-up	During treatment.
Sources of funding	The work was supported by the National Institutes of Health Grants.
Inclusion criteria	Patients within insulin-dependent diabetes mellitus who received DKA therapy under a traditional fluid protocol (group 1)were identified from a list of patients at Children's Medical Centre of Dallas who has discharge diagnoses of 'diabetic ketosis/ ketoacidosis'' and admission dates from September 1st 1994 to June 30th 1997, whereas patients treated under the revised fluid protocol (group 2) were identified from a list of patients admitted from July 1st 1997 to March 31st 2000.
Exclusion criteria	Not reported
Sample size	60
Loss to follow-up	Not reported
Condition specific characteristics	No definition provided for DKA.
Interventions	**Fast rate** On presentation to the emergency department, all patients received a 20 mL/kg bolus infusion of 0.9% NaCl (normal saline, 150 mmol/L of Na) over 30 to 45 minutes. This was repeated if necessary to maintain adequate peripheral perfusion, defined as normal peripheral pulses and normal capillary refill time. After completion of bolus infusions, patients from both treatment groups received regular human insulin in a premixed solution at a rate of 0.1 U/kg/hour IV. The fluid deficit was calculated by multiplying the percentage of dehydration (7-10%, determined clinically on initial presentation) by the patient's weight. The fluid deficit was added to 1.5 times the patient's total fluid requirement. Half of the total required fluid was ordered over the first 12 hours of treatment and the remaining 50% over the next 24 hours. In both groups patients were changed to subcutaneous insulin regimen and allowed to eat and drink ad libitum at the first meal time after resolution of acidosis, defined as a venous pH >7.30. After initial fluid bolus infusions, patients in group1 received 0.45% NaCl. **Slow rate** On presentation to the emergency department, all patients received a 20 mL/kg bolus infusion of 0.9% NaCl (normal saline, 150 mmol/L of Na) over 30 to 45 minutes. This was repeated if necessary to maintain adequate peripheral perfusion, defined as normal

Study type	**Retrospective cohort study**
	peripheral pulses and normal capillary refill time. After completion of bolus infusions, patients from both treatment groups received regular human insulin in a premixed solution at a rate of 0.1 U/kg/hour IV. Total fluids were delivered at 2.5 times the maintenance rate regardless of the degree of dehydration. Fluid were decreased to 1 to 1.5 times the maintenance rate after 24 hours of treatment (or earlier if acidosis resolved) until urine ketones were negative. In both groups patients were changed to subcutaneous insulin regimen and allowed to eat and drink ad libitum at the first meal time after resolution of acidosis, defined as a venous pH >7.30. After initial fluid bolus infusions, patients in group1 received 0.675% NaCl.
Outcome measures	**Time acidosis resolved (hours)** **Change in sodium concentration** **Change in chloride concentration**

1 **Study arms**

Fast rate (N = 30) Group 1 was further divided into group 1A (the initial 0.45% NaCl solution was discontinued and replaced with an identical solution containing an appropriate amount of glucose to provide 4:1 glucose to insulin ratio, and this was changed as necessary to control the level and rate of decrease of serum glucose. 2 bag system. In group 1B, 10g/dL of glucose was added to separate solution that was otherwise identical to the initial fluid. the rate of infusion of each of the 2 solutions was varied as necessary to control the level and rate of decrease of serum glucose, with both the insulin and total fluid delivery remaining constant. Therefore 3 separate IV solutions including the insulin solution (3-bag protocol) were needed. Data from group 1B was used as comparator group also used a 3 bag protocol.
Slow rate (N = 30) The use of 3 bag protocol was mandated.

2 **Characteristics**

3 **Arm-level characteristics**

	Fast rate (N = 30)	**Slow rate (N = 30)**
Age (years) Mean/SD	10.9 (4.5)	11.4 (4.6)
% Female No of events	n = 16; % = 53.3	n = 14; % = 46.6

	Fast rate (N = 30)	Slow rate (N = 30)
New onset diabetes (%) No of events	n = 8; % = 26.7	n = 9; % = 30

1

ROBINS-I Tool		
Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate (Appropriate analysis to control confounding not conducted.)
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Moderate (Adjustment techniques were not used to correct the presence of selection bias.)
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low
5. Bias due to missing data	Risk of bias judgement for missing data	Low
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Serious (Appropriate analysis to control confounding not conducted. Adjustment techniques were not used to correct the presence of selection bias.)
	Directness	Partially Applicable (Type of fluid used were different between the two groups. Definition of DKA not provided.)

Volume of rehydration

RCTs

Bakes 2016

Bakes, 2016

Bibliographic Reference	Bakes, Katherine; Haukoos, Jason S; Deakyne, Sara J; Hopkins, Emily; Easter, Josh; McFann, Kim; Brent, Alison; Rewers, Arleta; Effect of Volume of Fluid Resuscitation on Metabolic Normalization in Children Presenting in Diabetic Ketoacidosis: A Randomized Controlled Trial.; The Journal of emergency medicine; 2016; vol. 50 (no. 4); 551-9

Study details

Study type	**Randomised controlled trial (RCT)**
Study location	USA
Study setting	Paediatric emergency department and inpatient units of an academic freestanding children's hospital
Study dates	December 2007 until June 2010
Duration of follow-up	Variables measured included demographic characteristics (i.e., age, sex, and race/ethnicity) and laboratory values. Laboratory values, which included venous blood gas, basic chemistries (i.e., glucose, sodium, chloride, bicarbonate, potassium, blood urea nitrogen, creatinine, magnesium, phosphate, and b-hydroxybutyrate) were sent hourly during the first 4 h.
Sources of funding	Not specified.
Inclusion criteria	Children were eligible for participation if they were between 0 and 18 years of age, had type 1 diabetes mellitus plus the presence of DKA
Exclusion criteria	Patients were excluded from the study if they 1) required additional fluid resuscitation for treatment of hemodynamic instability, given at the discretion of the treating attending physician; or 2) weighed >70 kg.
Sample size	50
Loss to follow-up	No loss to follow up.
Condition specific characteristics	DKA defined as glucose >250 mg/dL, presence of ketone bodies in the blood, and metabolic acidosis (venous pH < 7.30 or serum bicarbonate < 15 mmol/L)

Study type	Randomised controlled trial (RCT)
	DKA severity was classified according to the Lawson Wilkins Pediatric Endocrine Society Consensus Statement: severe DKA (venous pH < 7.10 or bicarbonate < 5 mmol/L), moderate DKA (venous pH 7.10 to7.19 or bicarbonate 5 to < 10 mmol/L), and mild DKA (venous pH 7.20 to 7.29 or bicarbonate between 10 and < 15 mmol/L)
Interventions	**High volume IV fluid** The high-volume IV fluid group, received a 20 mL/kg of IV 0.9% saline bolus over the first hour followed by 0.675% saline + potassium replacement at 1.5 times maintenance. In both groups, dextrose was added to the IV fluids when serum glucose values reached 250–300 mg/dL. Dextrose content in IV fluids was adjusted depending on hourly glucose measurements. Potassium replacement was conducted as per International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines. Both groups received an insulin infusion (0.1 U/kg/h) upon completion of the initial saline bolus. If safe glucose levels could not be maintained by adjusting dextrose (5%–10%), insulin infusion was adjusted per protocol. **Low volume IV fluid** Low-volume IV fluid group, received a 10 mL/kg of IV 0.9% saline bolus over the first hour followed by 0.675% saline + potassium replacement at 1.25 times maintenance. In both groups, dextrose was added to the IV fluids when serum glucose values reached 250–300 mg/dL. Dextrose content in IV fluids was adjusted depending on hourly glucose measurements. Potassium replacement was conducted as per International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines. Both groups received an insulin infusion (0.1 U/kg/h) upon completion of the initial saline bolus. If safe glucose levels could not be maintained by adjusting dextrose (5%–10%), insulin infusion was adjusted per protocol.
Outcome measures	**Cerebral oedema** **Time to metabolic normalisation** serum bicarbonate >15 mmol/L and pH> 7.30. **Healthcare utilisation - length of treatment** Defined as the duration of hospital stay after the start of IV fluid infusion. **Time to discharge**

1 **Study arms**

High volume infusion (N = 25)
Low volume infusion (N = 25)

2 **Characteristics**

3 **Arm-level characteristics**

	High volume infusion (N = 25)	Low volume infusion (N = 25)
Age (years) MedianIQR	9 (6 to 12)	10 (8 to 13)
% Female No of events	n = 18; % = 72	n = 12; % = 48
New onset DM No of events	n = 12; % = 48	n = 15; % = 60
Severity of DKA		
Mild		
Number (%)	n = 9; % = 36	n = 12; % = 48
Moderate		
Number (%)	n = 9; % = 36	n = 11; % = 44
Severe		
Number (%)	n = 7; % = 28	n = 2; % = 8

1

Cochrane risk of bias tool 2.0 (RoB 2.0)		
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High (Study states that the treating attending physician identified potential subjects, followed by laboratory confirmation of

Cochrane risk of bias tool 2.0 (RoB 2.0)		
		DKA. Additionally there were more children with severe DKA in the high volume arm. Furthermore the study states that there is a possibility of selection bias, as many potential study patients were initially fluid resuscitated at an outside facility before transfer to our study site, thus making them ineligible for study enrolment.)
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High (Study states that the treating attending physician identified potential subjects, followed by laboratory confirmation of DKA. Additionally there were more children with severe DKA in the high volume arm. Furthermore the study states that there is a possibility of selection bias, as many potential study patients were initially fluid resuscitated at an outside facility before transfer to our study site, thus making them ineligible for study enrollment.)
	Overall Directness	Indirectly applicable (Rate of infusion of maintenance dose was different in the two groups. Outcome time to metabolic normalisation not specified in review protocol)

Appendix F - Forest plots

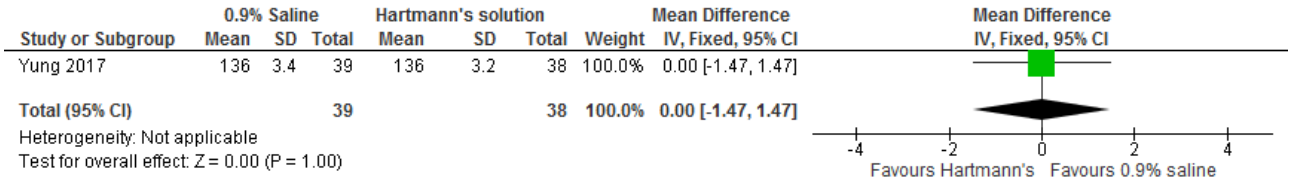
Type of fluid – IV fluids

Moderate to severe DKA

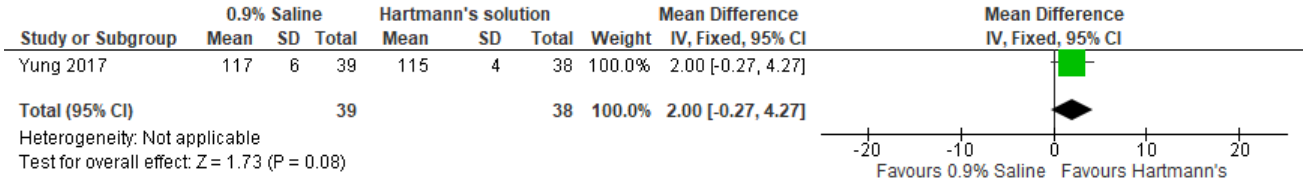
0.9% Saline vs Hartmann's solution as initial IV fluid

Outcomes during treatment of DKA

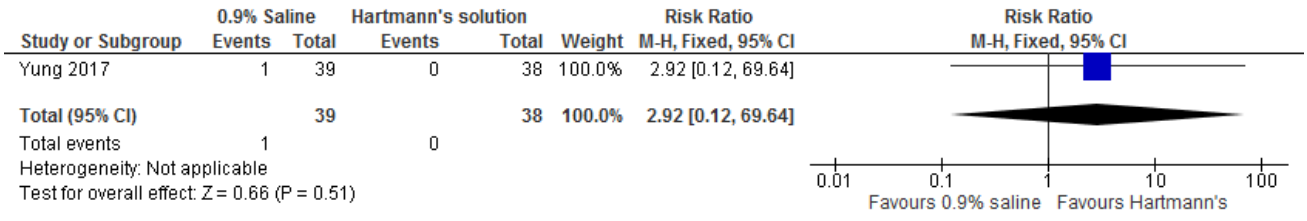
Minimum sodium concentration (Higher value =better outcome)



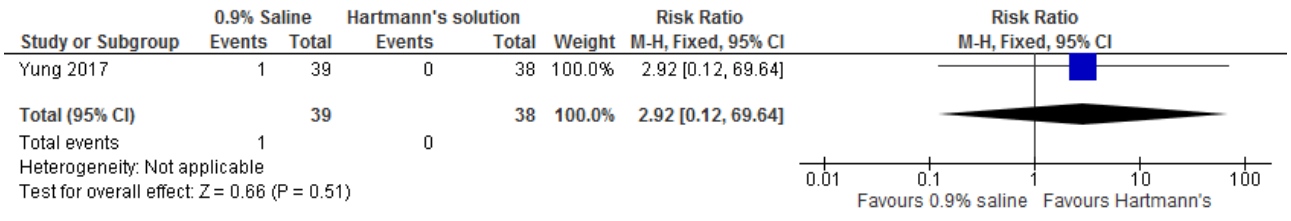
Maximum chloride concentration (Lower value =better outcome)



Altered conscious state



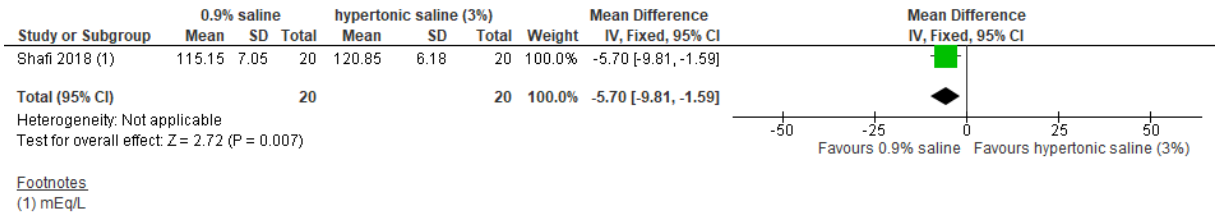
Acute renal failure



0.9% saline vs hypertonic saline (3% NaCl) as initial IV fluid

Outcomes during 1 hour of treatment

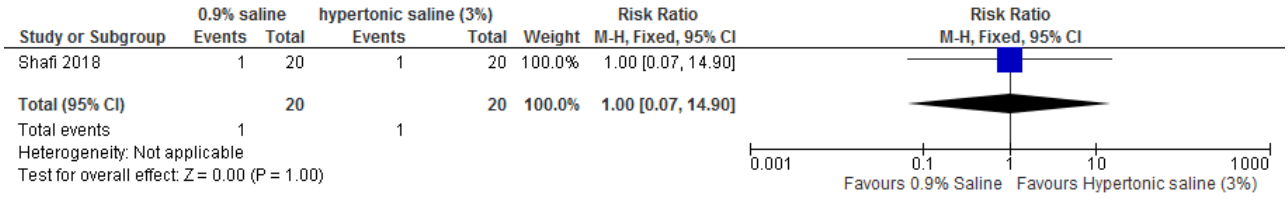
Chloride concentration (Lower value =better outcome)



Footnotes
(1) mEq/L

Outcomes during 12 hours of treatment

Cerebral oedema

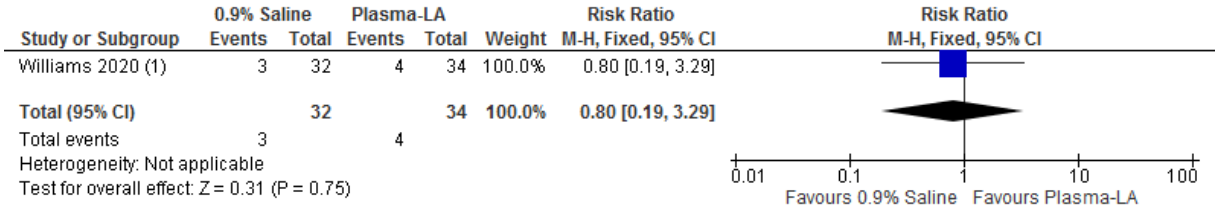


All severities of DKA

0.9% saline vs Plasma-Lyte-A as initial IV fluid

Outcomes during 24 hours of treatment

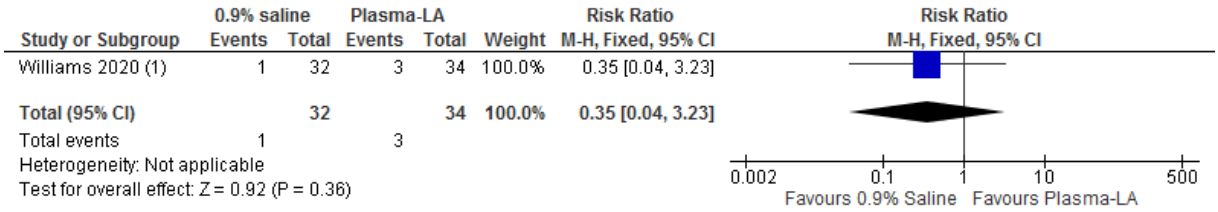
Incidence of acute kidney injury (AKI)



Footnotes
(1) defined with either KDIGO or pRIFLE criteria

Outcomes during 48 hours of treatment

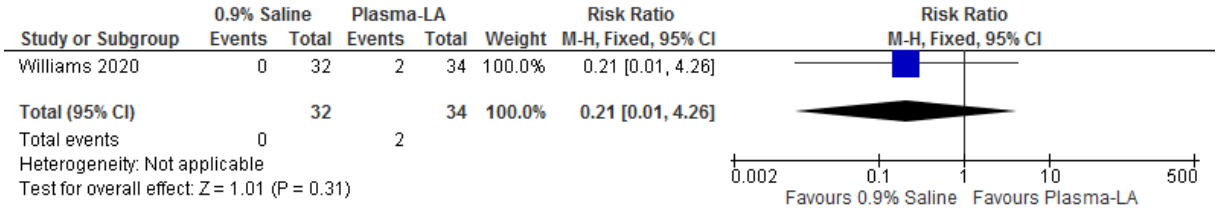
Incidence of acute kidney injury (AKI)



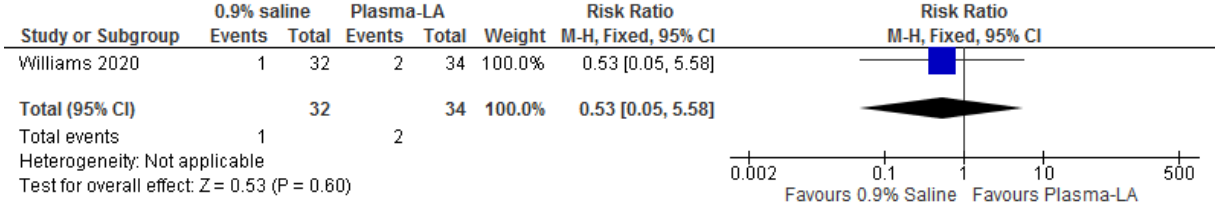
Footnotes
(1) defined with either KDIGO or pRIFLE criteria

Outcomes till discharge

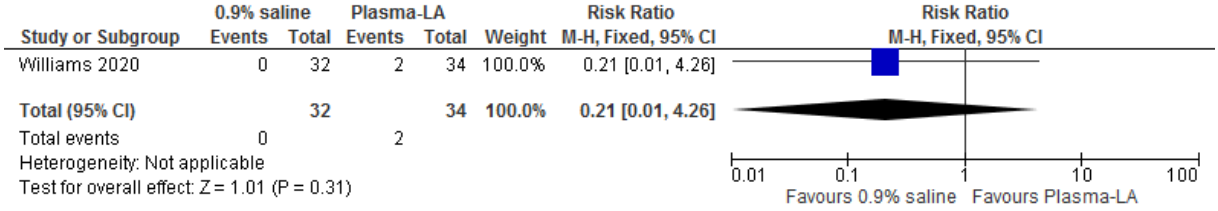
Healthcare utilisation – Need for renal replacement therapy (RRT)



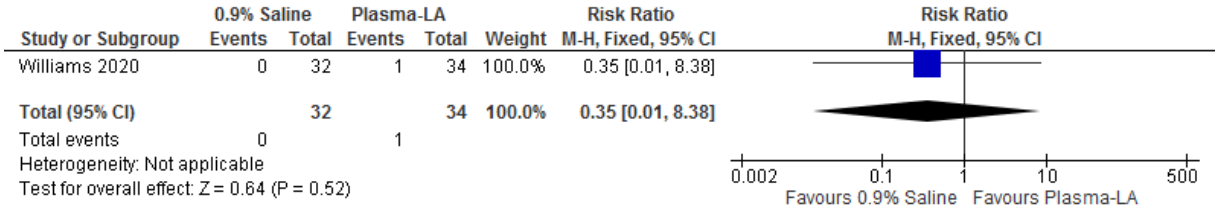
Healthcare utilisation – Need for ventilation



All-cause mortality in hospital



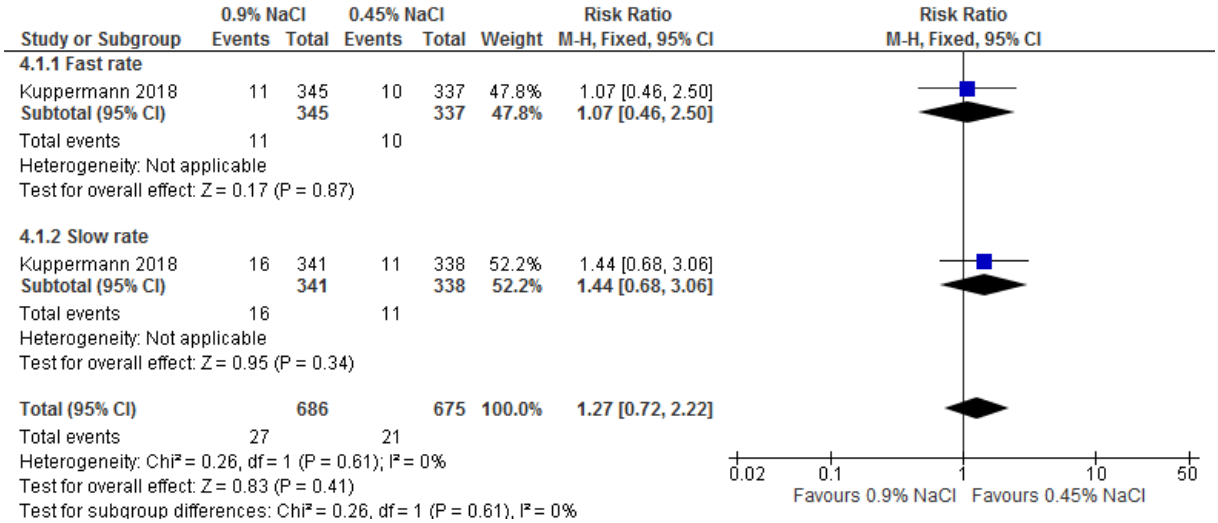
Cerebral oedema



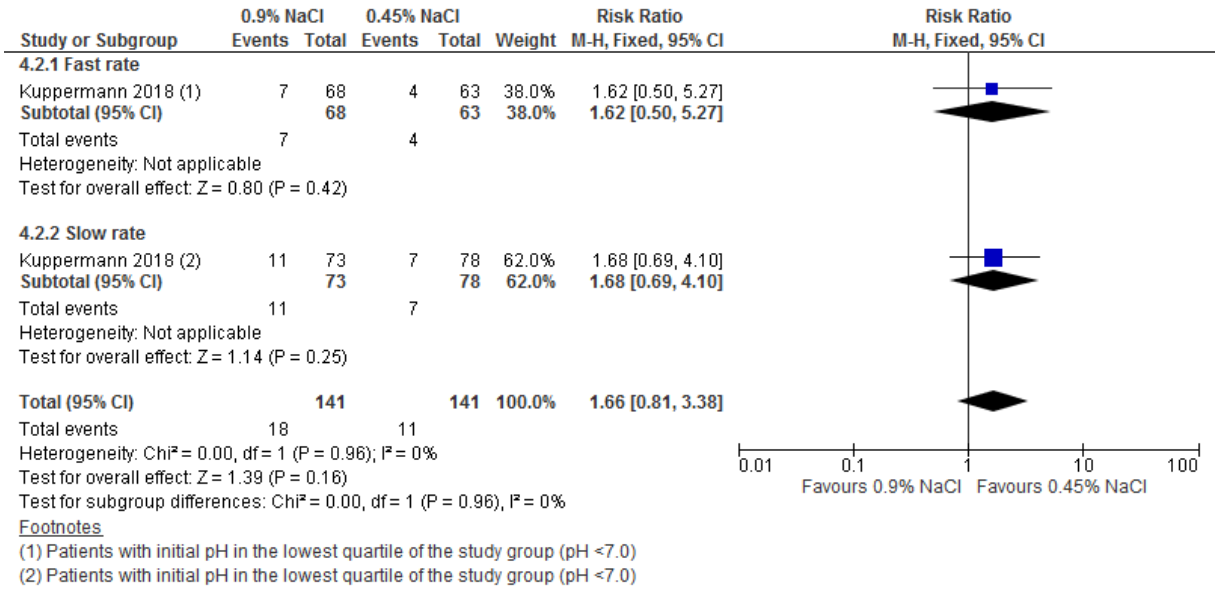
0.9% saline vs 0.45% saline for replacement of deficit

Outcomes during treatment of DKA

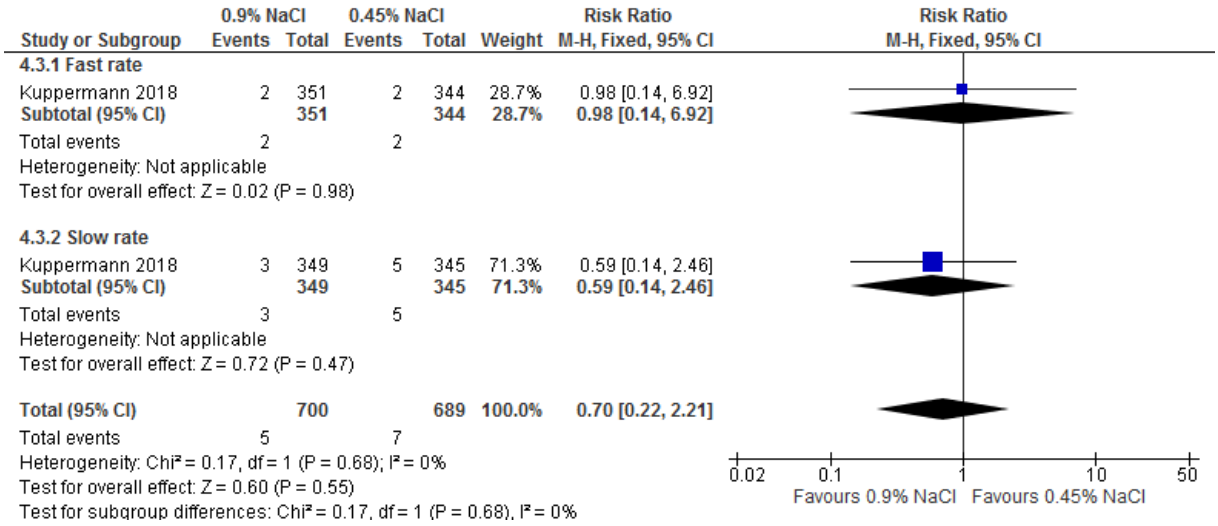
Confirmed decline in Glasgow Coma Scale score to <14



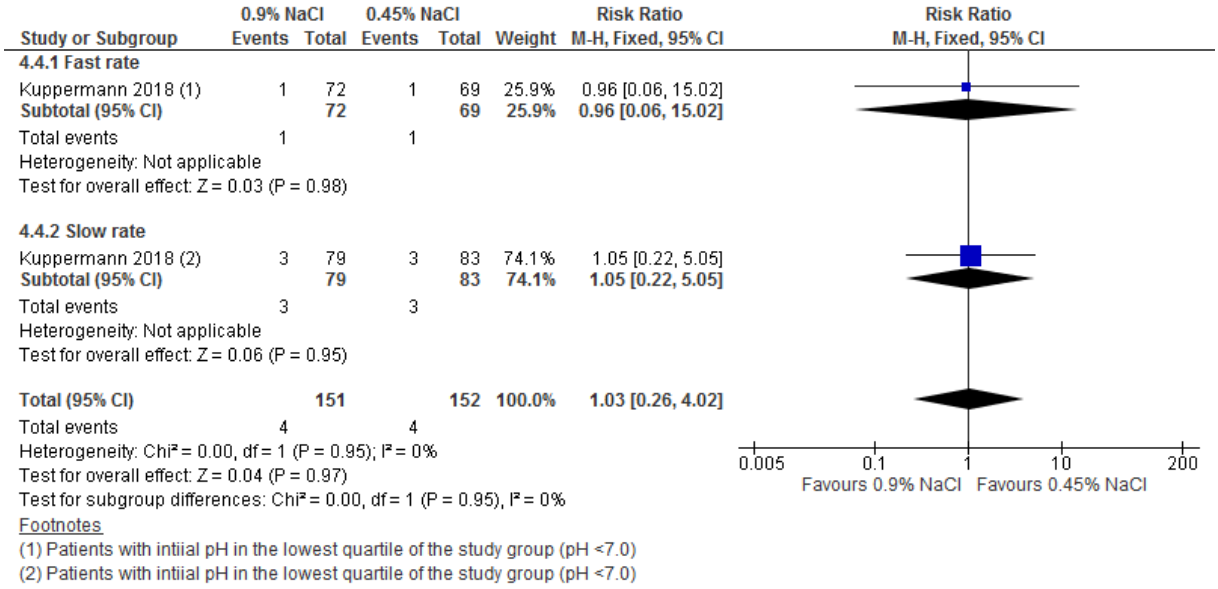
Confirmed decline in Glasgow Coma Scale score < 14 - in patients who had more severe DKA (Patients with initial pH in the lowest quartile of the study group (pH <7.0))



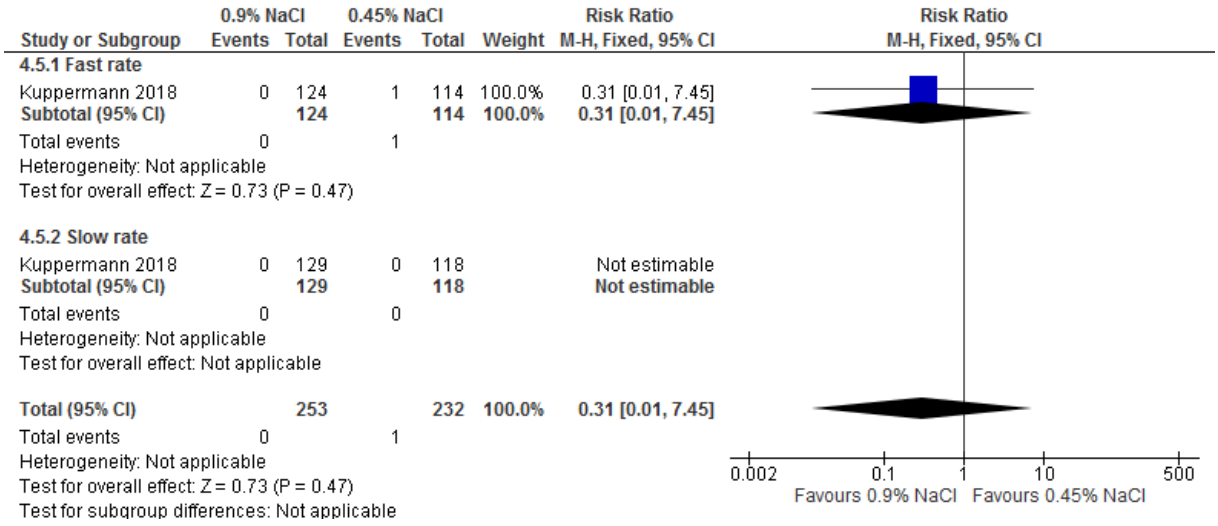
Clinically apparent brain injury



Clinically apparent brain injury- in patients who had more severe DKA (Patients with initial pH in the lowest quartile of the study group (pH <7.0))

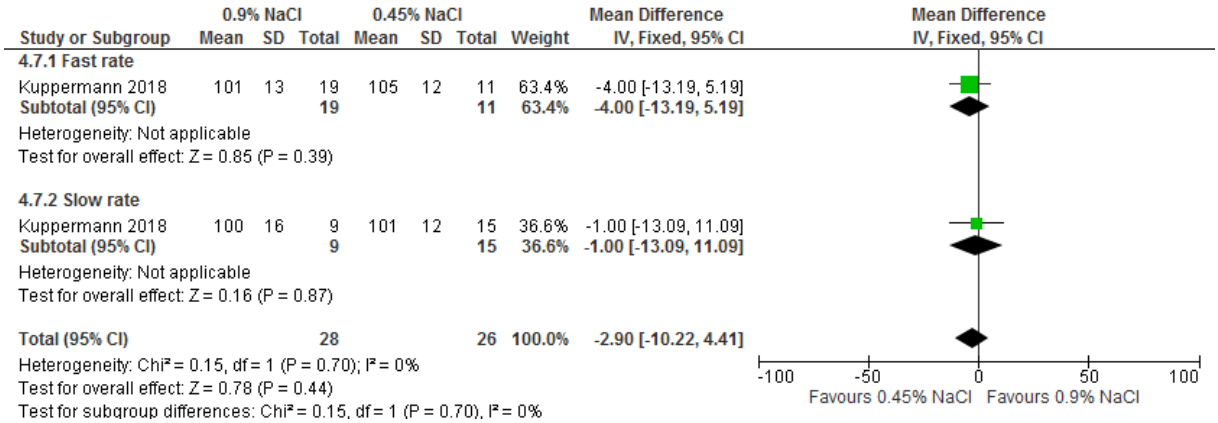


Mortality

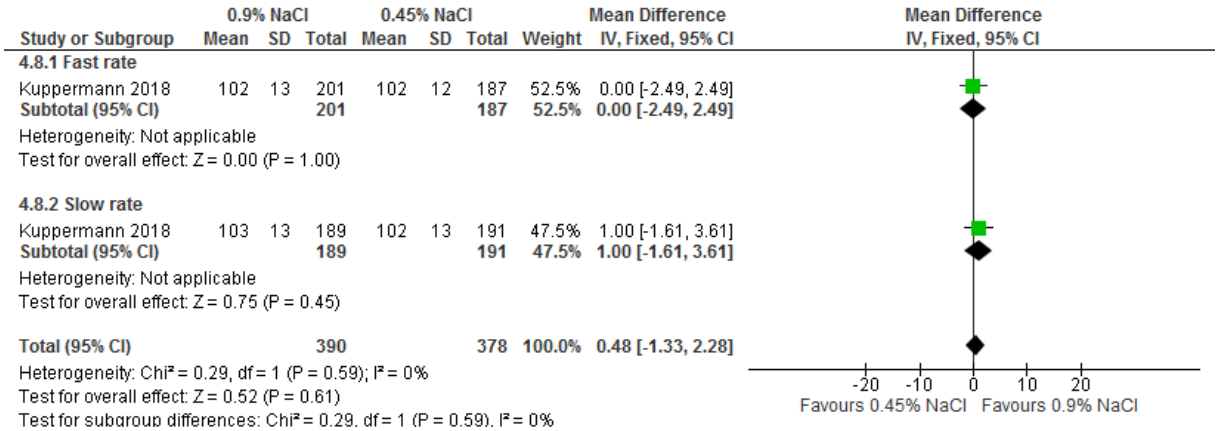


Outcomes 2 to 6 months after hospitalisation

IQ (in children aged 3 to 5 years)



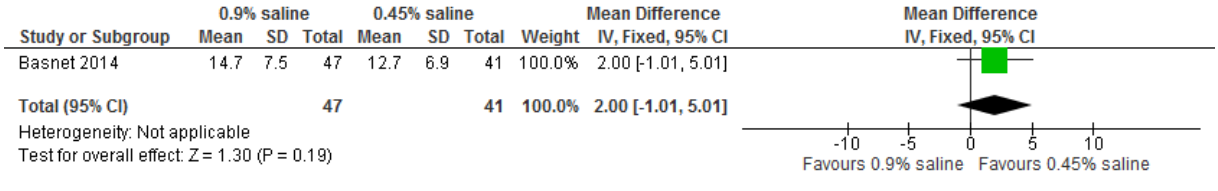
IQ (in children aged 6 to 18 years)



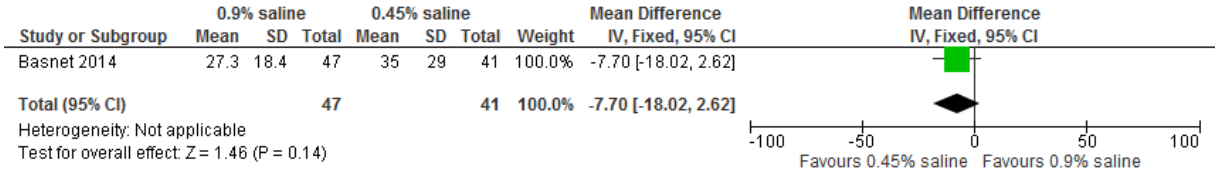
0.9% saline vs 0.45% saline as post-bolus re-hydration fluid

Outcomes during treatment of DKA

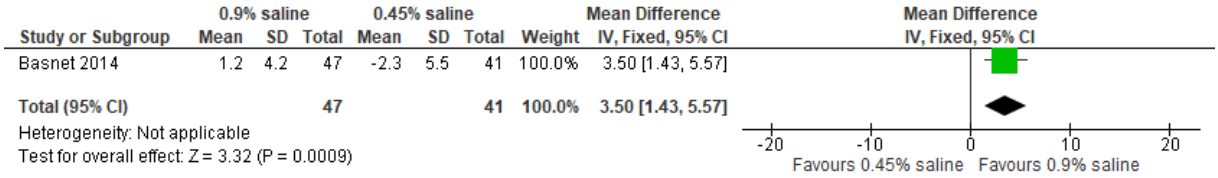
Healthcare utilisation- Mean PICU length of stay (hours)



Rate of change of glucose (mg/dL/h)



Change in corrected sodium from baseline (meq/L)

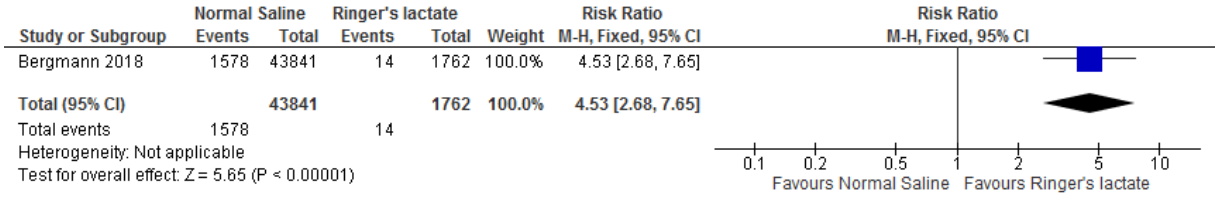


Normal saline vs Ringer's lactate

Outcomes during treatment of DKA

Healthcare utilisation – mechanical ventilation

Cerebral oedema

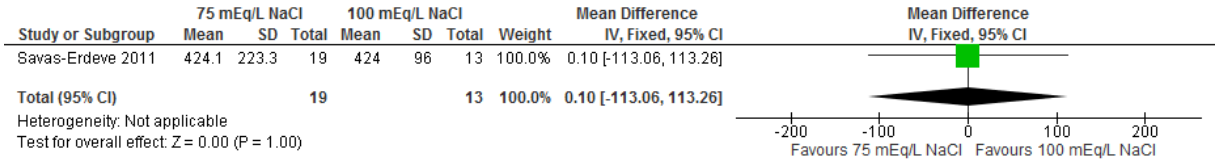


Type 1 diabetes - All severities of DKA

75 mEq/L NaCl vs 100 mEq/L NaCl after initial rehydration

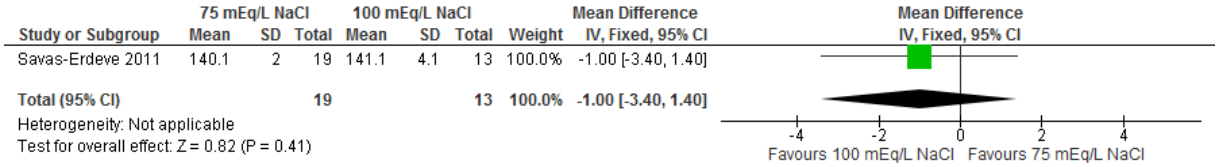
Outcomes during 1 hour of treatment

Blood glucose levels



Outcomes during 24 hours of treatment

Change in corrected sodium from baseline (meq/L)



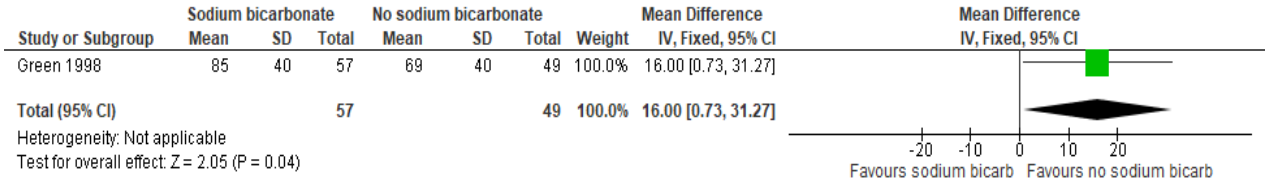
IV + Additives

Severe DKA

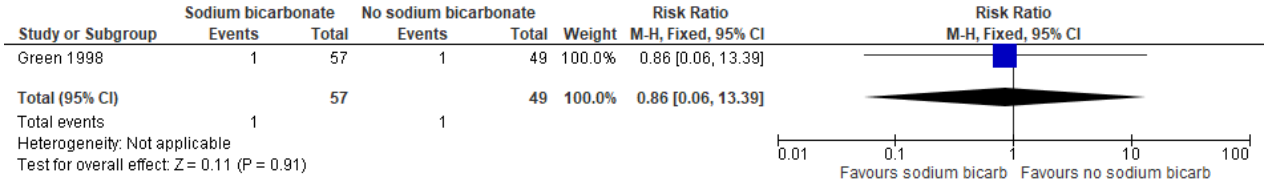
IV fluid + sodium bicarbonate vs IV fluid+ no sodium bicarbonate

Outcomes till discharge

Duration of hospitalisation (hours)



Cerebral oedema

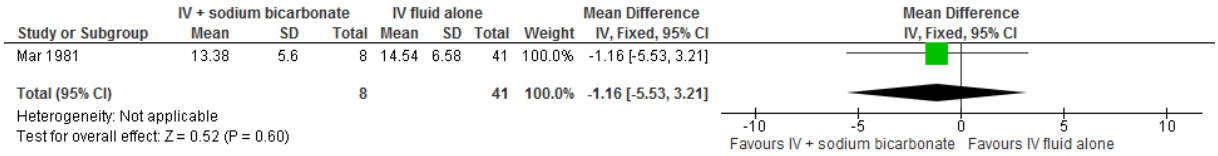


All severities of DKA

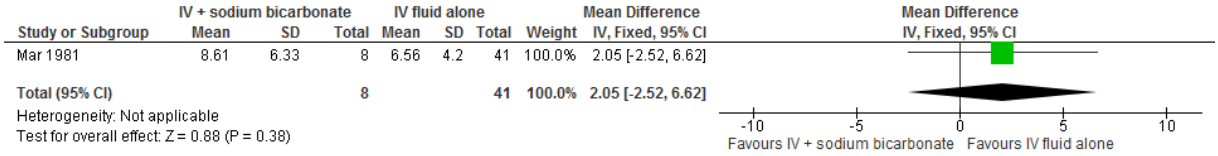
IV fluid (Lactate Ringers or Lactate Ringers with saline) with sodium bicarbonate vs IV fluid (Lactate Ringers or Lactate Ringers with saline) alone

Outcomes during treatment of DKA

Duration of acidosis



Length of hospital stay



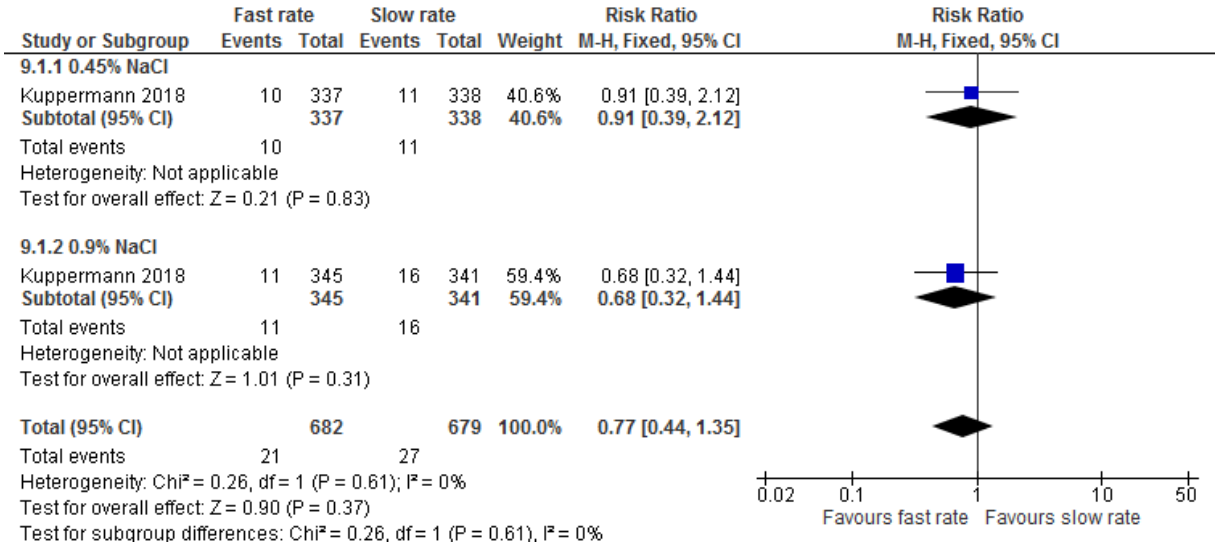
Rate of rehydration

All severities of DKA

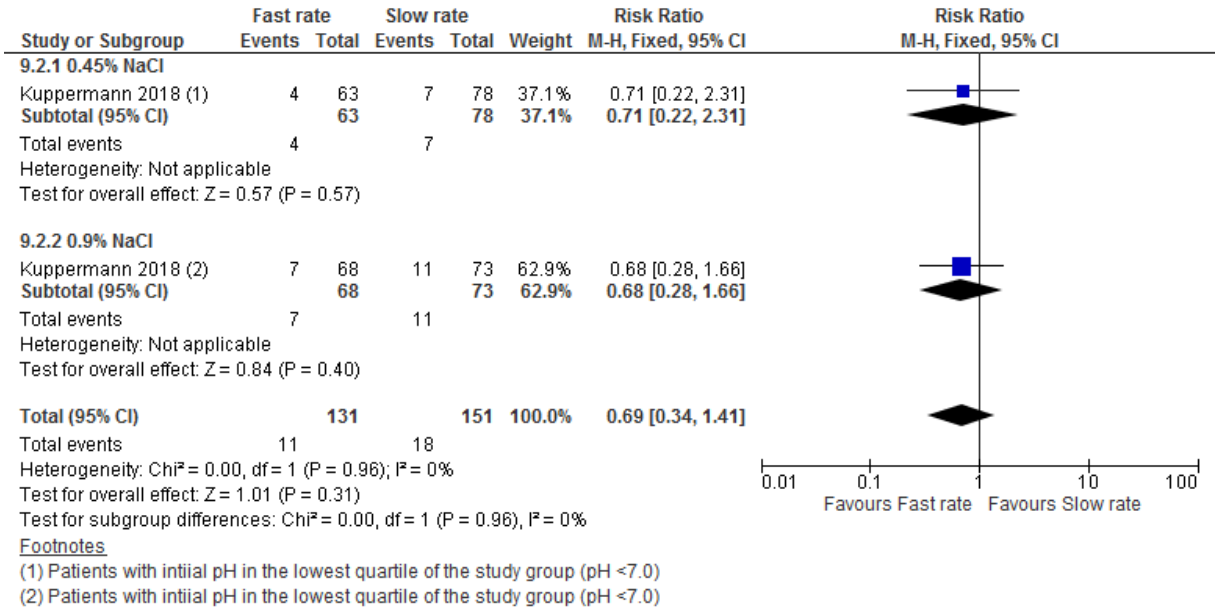
Fast rate vs slow rate for the replacement of deficit

Outcomes during treatment of DKA

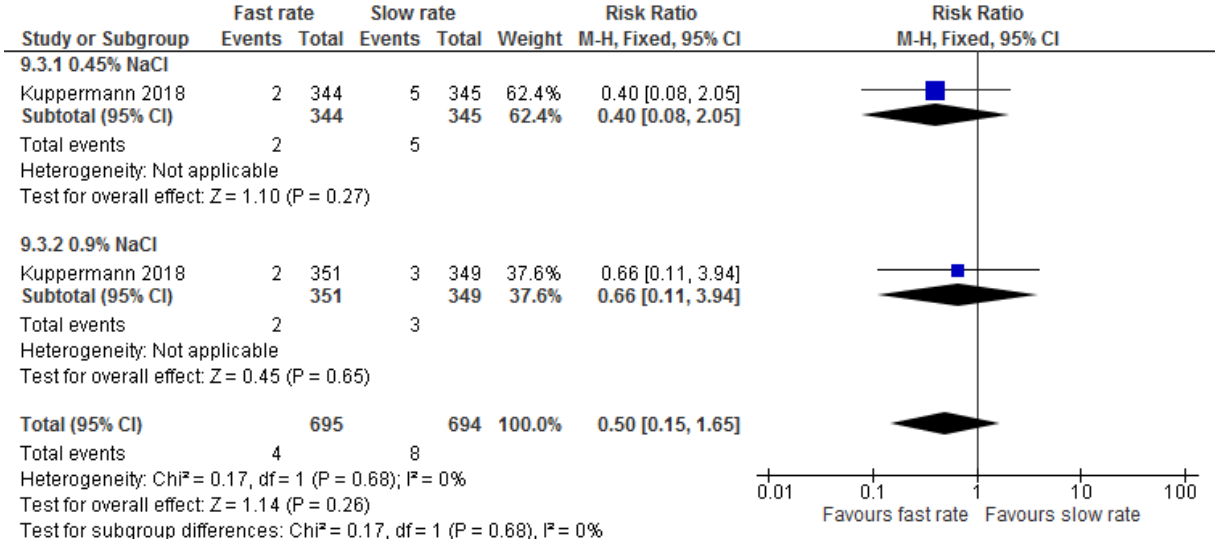
Confirmed decline in Glasgow Coma Scale score to <14



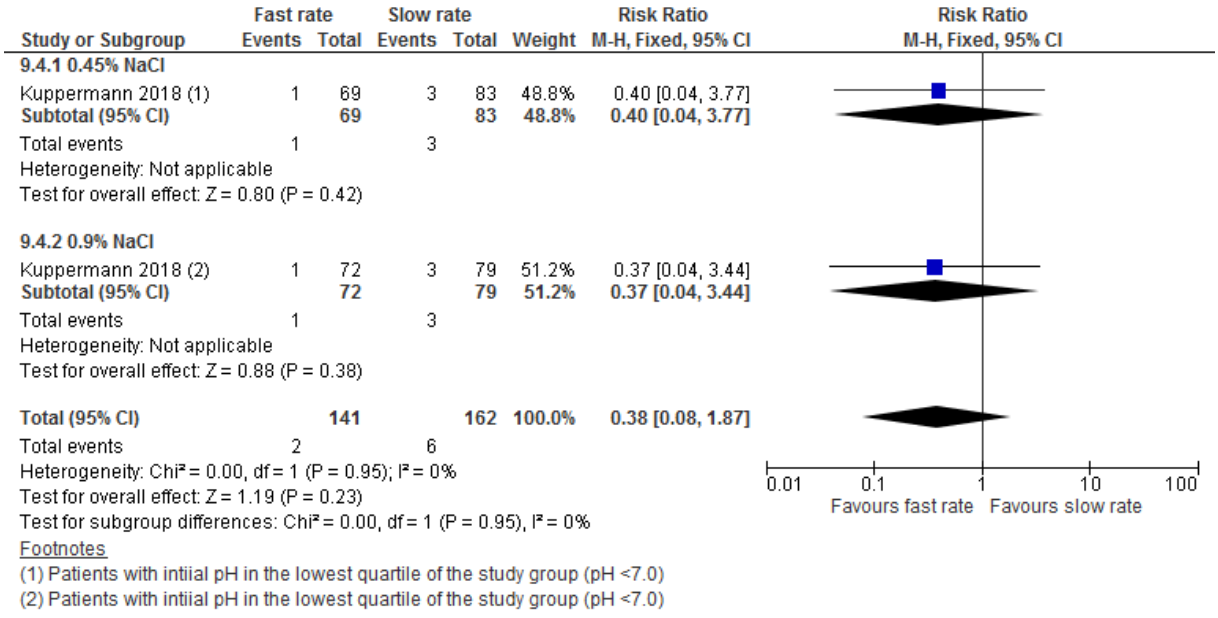
Confirmed decline in Glasgow Coma Scale score < 14 - in patients who had more severe DKA (Patients with initial pH in the lowest quartile of the study group (pH <7.0))



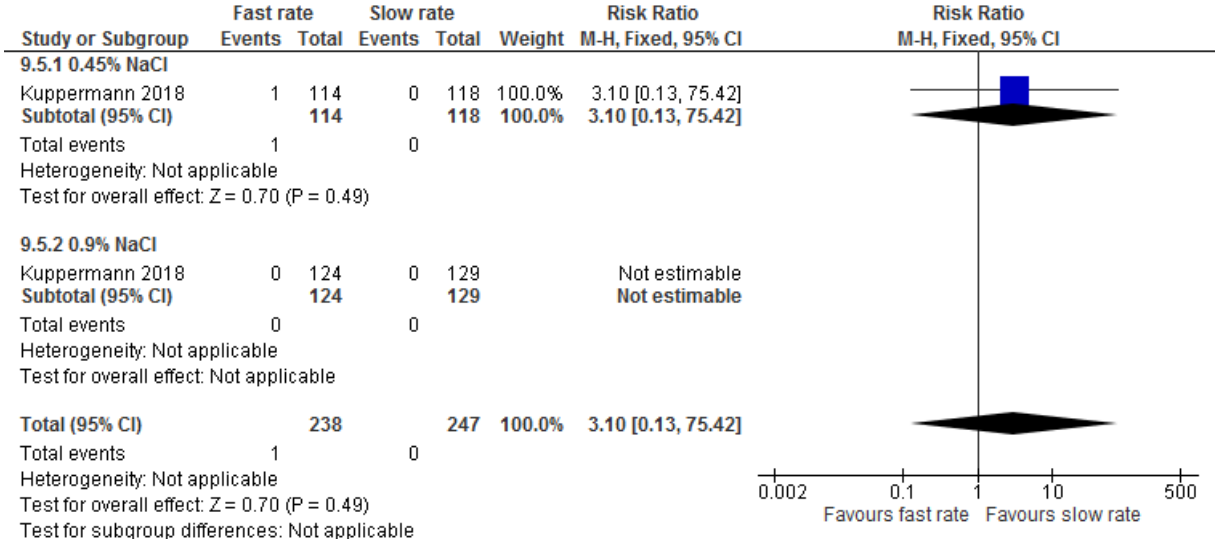
Clinically apparent brain injury



Clinically apparent brain injury- in patients who had more severe DKA (Patients with initial pH in the lowest quartile of the study group (pH <7.0))

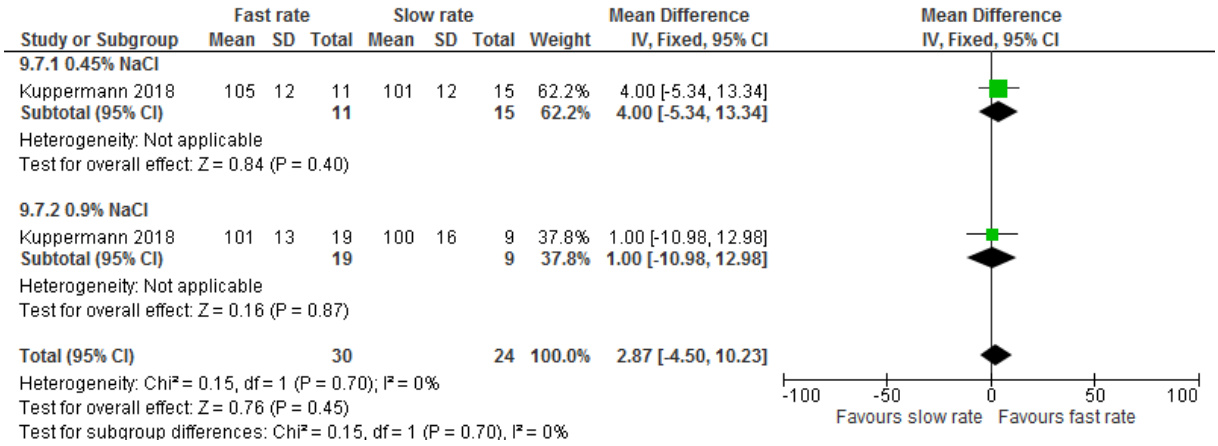


Mortality

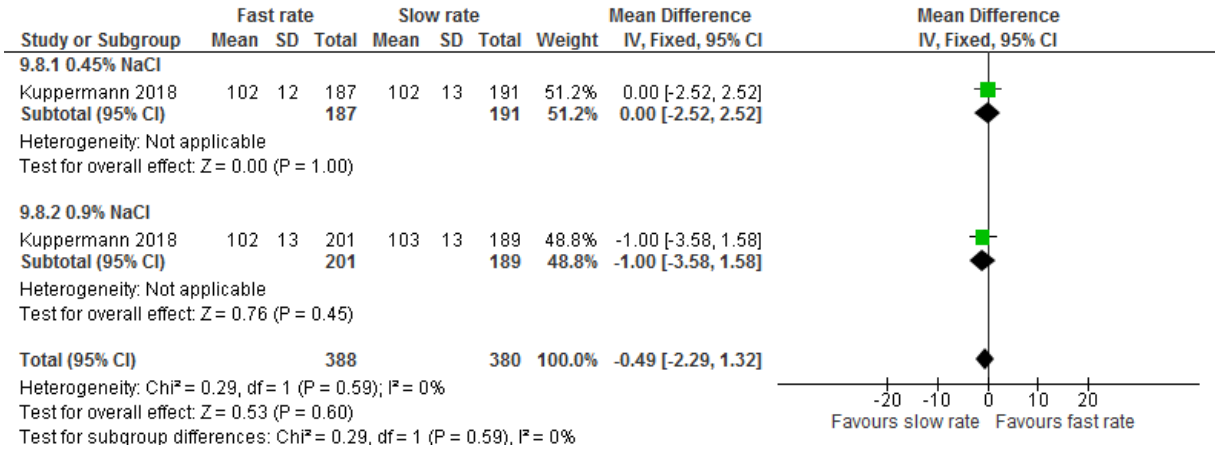


Outcomes 2 to 6 months after hospitalisation

IQ (in children aged 3 to 5 years)



IQ (in children aged 6 to 18 years)

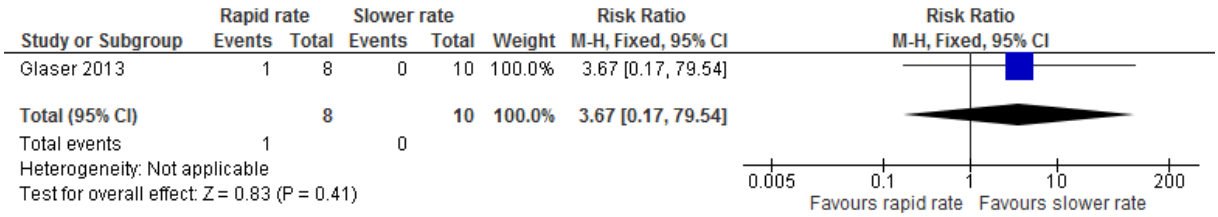


Type 1 diabetes- All severities of DKA

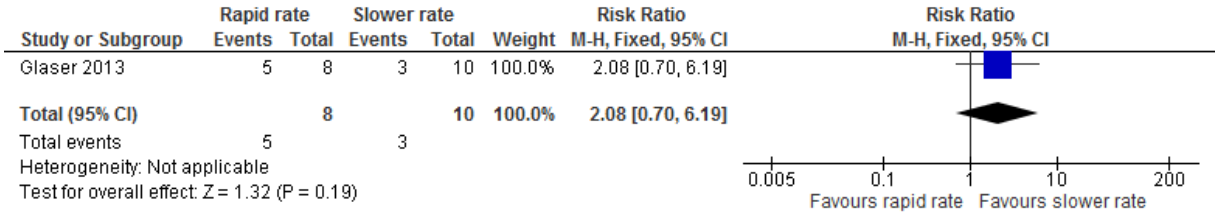
Rapid rate vs slower rate

Outcomes during the treatment of DKA

Treated for suspected cerebral oedema



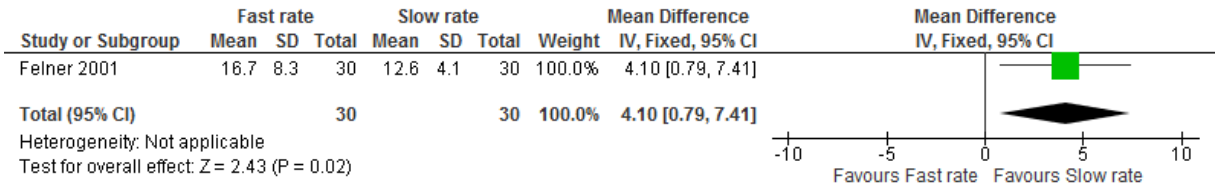
High risk of cerebral oedema



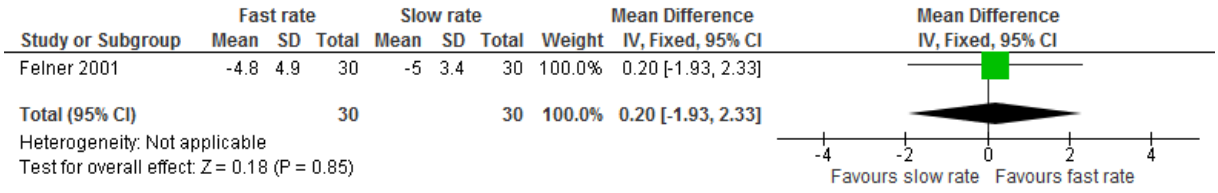
Fast rate vs slow rate

Outcomes during the treatment of DKA

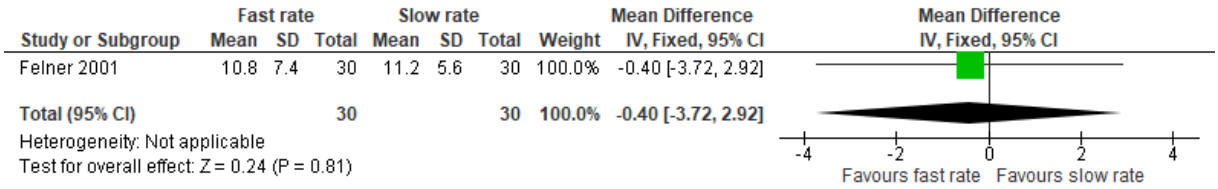
Time in which acidosis resolved (hours)



Change in sodium concentration (mmol/L)



Change in chloride concentration (mmol/L)



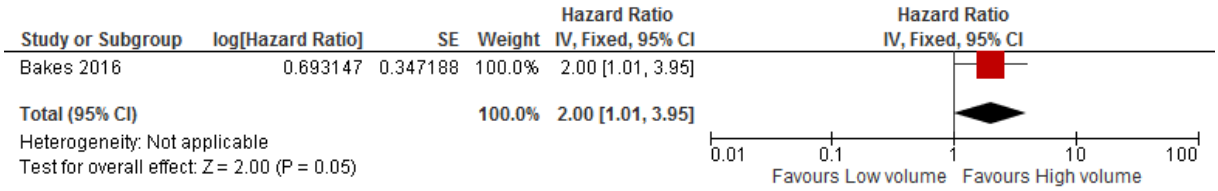
Volume

Type 1 diabetes- All severities of DKA

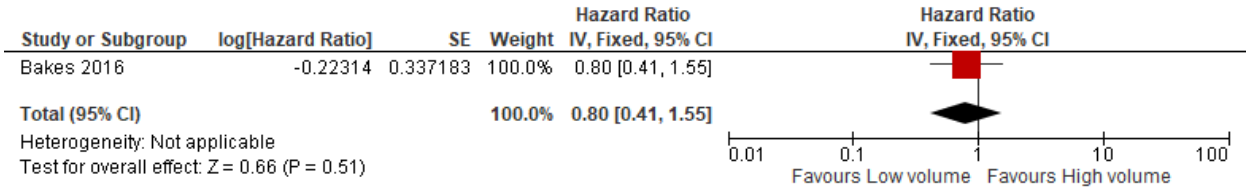
High volume vs low volume

Outcomes during treatment of DKA

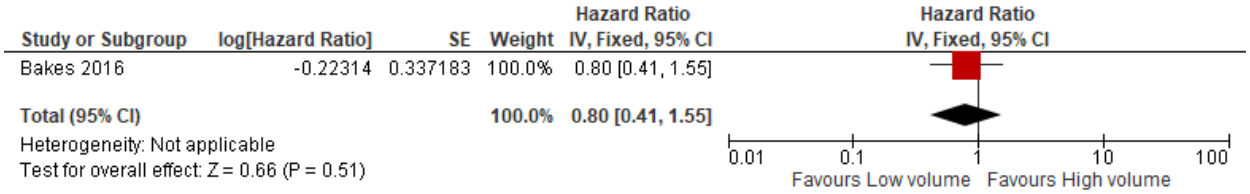
Metabolic normalisation (hours)



Length of treatment (hours)



Hospital discharge (hours)



Appendix G - Additional data

Type of fluids

Moderate to severe DKA

0.9% Saline vs Hartmann's solution as initial IV fluid

Outcomes during treatment of DKA

Study name	0.9% saline	Hartmann's solution	P value*	Notes
Paediatric intensive care unit (PICU) or high-dependency unit (HDU) stay (hours)				
Yung 2017	23.8 (15.8, 26.4)	17.3 (14.0, 23.3)	0.026	**Risk of bias:** No serious **Directness:** No serious
Data presented as median (interquartile range) *Used Student's t-test or the Wilcoxon rank-sum test				

0.9% Saline vs Hypertonic saline (3% NaCl) as initial IV fluid

Outcomes during treatment of DKA

Study name	0.9% saline	Hypertonic saline	P value*	Notes
Average time needed for the correction of hyperglycaemia (hours)				**Risk of bias:** Serious[1] **Directness:** No serious
Shafi 2018	7.13	7.15	0.974	
Time needed for the resolution of acidosis (hours)				
Shafi 2018	17.35	18	0.782	
Data presented as mean (SD not reported) [1] Baseline differences (e.g. age, sex, type of diabetes) between arms not reported. *Used Mann-Whitney U test. P-value of 0.05 was considered to indicate statistical significance.				

All severities of DKA

0.9% Saline vs Plasma-Lyte-A as initial IV fluid

Outcomes during treatment of DKA

Study name	0.9% saline	Plasma-lyte-A	P value*	Notes
Length of intensive care unit (ICU) stay (hours)				**Risk of bias:** Serious[1] **Directness:** No serious
Williams 2020	48 (48, 60)	47 (24, 54)	0.276	
Length of hospital stay (days)				
Williams 2020	9 (8, 12)	10.0 (8.25, 11)	0.396	
Data presented as median (interquartile range) [1]There was a significant difference in the number of participants with new onset diabetes in the two arms of the trial				

Study name	0.9% saline	Plasma-lyte-A	P value*	Notes
Length of intensive care unit (ICU) stay (hours)				**Risk of bias:** Serious[1] **Directness:** No serious
Williams 2020	48 (48, 60)	47 (24, 54)	0.276	
Length of hospital stay (days)				
Williams 2020	9 (8, 12)	10.0 (8.25, 11)	0.396	
*Used unpaired student's t-test or the Wilcoxon rank-sum test. P-value (two-tailed)<0.05 was taken as significant.				

1

0.9% Saline vs 0.45% saline for replacement of deficit

Outcomes during treatment of DKA

Study name	0.9% saline	0.45% saline	P value*	Notes
Time to resolution of DKA (hours)– fast rate				
Kuppermann 2018	14.0 (9.8-18.3)	14.0 (10.2- 18.3)	0.48	**Risk of bias:** No serious **Directness:** No serious
Time to resolution of DKA (hours)– slow rate				
Kuppermann 2018	13.6 (10.0-18.5)	14.9 (9.8-18.6)	0.48	**Risk of bias:** No serious **Directness:** No serious
Time to hospital discharge (hours)- fast rate				
Kuppermann 2018	47.4 (26.6-67.2)	46.3 (27.3-66.3)	0.71	**Risk of bias:** No serious **Directness:** No serious
Time to hospital discharge (hours)- slow rate				
Kuppermann 2018	46.4 (27.2-69.0)	48.6 (28.0-68.8)	0.71	**Risk of bias:** No serious **Directness:** No serious
Data presented as median (25th and 75th percentile) *p values are from a Van Elteren test				

Normal saline vs Ringer's lactate

Outcomes during treatment of DKA

Study name	Normal saline	Ringer's lactate	P value	Notes
Length of hospital stay (days)				
Bergmann 2018	2 (1-3)	2 (1-3)	Not reported	**Risk of bias:** Serious[1] **Directness:** Serious[2]
Data presented as median and interquartile range. [1] DKA protocol (e.g. co-interventions) were not described in the study [2] Definition of DKA not provided.				

Rate of rehydration

All severities of DKA

0.9% Saline vs 0.45% saline for replacement of deficit

Outcomes during treatment of DKA

Study name	Fast rate	Slow rate	P value*	Notes
Time to resolution of DKA (hours)– 0.45% saline				
Kuppermann 2018	14.0 (10.2 - 18.3)	14.9 (9.9-18.6)	0.28	**Risk of bias:** No serious **Directness:** No serious
Time to resolution of DKA (hours)– 0.9% saline				
Kuppermann 2018	14.0 (9.8-18.3)	13.6 (10.0-18.5)	0.28	**Risk of bias:** No serious **Directness:** No serious
Time to hospital discharge (hours)- 0.45% saline				
Kuppermann 2018	46.3 (27.3-66.3)	48.6 (28.0-68.8)	0.34	**Risk of bias:** No serious **Directness:** No serious
Time to hospital discharge (hours)- 0.9% saline				
Kuppermann 2018	47.4 (26.6-67.2)	46.4 (27.2-69.0)	0.34	**Risk of bias:** No serious **Directness:** No serious
Data presented as median (25th and 75th percentile) *p values are from a Van Elteren test				

1

2 Appendix H – GRADE tables

3 Type of fluid – IV fluids

4 Moderate to severe DKA

5 0.9% Saline vs Hartmann's solution as initial IV fluid

6 ***Outcomes during treatment of DKA***

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Minimum sodium concentration – MD greater than 1 favours 0.9% saline											
Yung 2017	RCT	77	0.00 (-1.47, 1.47)	-	-	1.6 [1]	No serious	NA[3]	No serious	No serious	High
Maximum chloride concentration – MD less than 1 favours 0.9% saline											
Yung 2017	RCT	77	2.00 (-0.27, 4.27)	-	-	2[2]	No serious	NA[3]	No serious	Serious[4]	Moderate
Altered conscious state (defined as deterioration in Glasgow Coma Scale (CGS))– RR less than 1 favours 0.9% saline											
Yung 2017	RCT	77	2.92 (0.12, 69.64)	0 per 100 children and young people	0 per 100 children and young people	-	No serious	NA[3]	Serious[5]	Serious[6]	Low
Acute renal failure - RR less than 1 favours 0.9% saline											

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Yung 2017	RCT	77	2.92 (0.12, 69.64)	0 per 100 children and young people	0 per 100 children and young people	-	No serious	NA[3]	No serious	Serious[6]	Moderate

[1] MID = 0.5 of the median standard deviation of the comparison group (SD= 3.2).
[2] MID= 0.5 of the median standard deviation of the comparison group (SD= 4).
[3] Inconsistency not applicable for single study.
[4] Downgrade 1 level for serious imprecision. 95% confidence interval crosses one end of the estimated MID.
[5] Downgrade 1 level for indirectness. Outcome was not specified in review protocol.
[6] Downgrade 1 level for serious imprecision. 95% confidence interval crosses the line of no effect.
* Derived by taking the overall number of event/ total number of participants and multiplying by 100.

1

2 **0.9% Saline vs hypertonic saline (3% NaCl) as initial IV fluid**

3 ***Outcomes during 1 hour of treatment***

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Chloride concentration (mEq/L) - MD less than 1 favours 0.9% saline											
Shafi 2018	RCT	40	-5.70 (-9.81, -1.59)	-	-	3.09[1]	Serious[2]	NA[3]	No serious	Serious[4]	Low

[1] MID = 0.5 of the median standard deviation of the comparison group (SD= 6.18).
[2] Baseline differences (e.g. age, sex, type of diabetes) between arms not reported. Downgrade 1 level for serious risk of bias.
[3] Inconsistency not applicable for single study.
[4] Downgrade 1 level for serious imprecision. 95% confidence interval crosses one end of the estimated MID.

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
* Derived by taking the overall number of event/ total number of participants and multiplying by 100.											

1 ***Outcomes during 12 hours of treatment***

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Cerebral oedema - RR less than 1 favours 0.9% saline											
Shafi 2018	RCT	40	1.00 (0.07, 14.90)	5 per 100 children and young people	5 per 100 children and young people (0 less, 75 more)	-	Serious[2]	NA[3]	No serious	Serious[4]	Low

[1] MID = 0.5 of the median standard deviation of the comparison group (SD= 6.18).
[2] Baseline differences (e.g. age, sex, type of diabetes) between arms not reported. Downgrade 1 level for serious risk of bias.
[3] Inconsistency not applicable for single study.
[4] Downgrade 1 level for serious imprecision. 95% confidence interval crosses the line of no effect.
* Derived by taking the overall number of event/ total number of participants and multiplying by 100.

All severities of DKA

0.9% Saline vs Plasma-Lyte-A as initial IV fluid

Outcomes during 24 hours of treatment

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Incidence of acute kidney injury (AKI) (defined with either KDIGO or pRIFLE criteria)– RR less than 1 favours 0.9% saline											
Williams 2020	RCT	66	0.80 (0.19, 3.29)	12 per 100 children and young people	12 per 100 children and young people (2 less, 39 more)	-	Serious[1]	NA[2]	No serious	Serious[3]	Low

[1] There was a significant difference in the number of participants with new onset diabetes in the two arms of the trial. Downgrade 1 level for serious risk of bias.
[2] Inconsistency not applicable for single study.
[3] Downgrade 1 level for serious imprecision. 95% confidence interval crosses the line of no effect.
* Derived by taking the overall number of event/ total number of participants and multiplying by 100.

Outcomes during 48 hours of treatment

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Incidence of acute kidney injury (AKI) (defined with either KDIGO or pRIFLE criteria)– RR less than 1 favours 0.9% saline											
Williams 2020	RCT	66	0.35 (0.04, 3.23)	9 per 100 children and young people	7 less per 100 children and young people (2 less, 29 more)	-	Serious[1]	NA[2]	No serious	Serious[3]	Low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality

[1] There was a significant difference in the number of participants with new onset diabetes in the two arms of the trial. Downgrade 1 level for serious risk of bias.
[2] Inconsistency not applicable for single study.
[3] Downgrade 1 level for serious imprecision. 95% confidence interval crosses the line of no effect.
* Derived by taking the overall number of event/ total number of participants and multiplying by 100.

1 ***Outcomes till discharge***

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Healthcare utilisation – Need for renal replacement therapy - RR less than 1 favours 0.9% saline											
Williams 2020	RCT	66	0.21 (0.01, 4.26)	6 per 100 children and young people	1 less per 100 children and young people (0 less, 25 more)	-	Serious[1]	NA[2]	No serious	Serious[3]	Low
Healthcare utilisation – Need for ventilation - RR less than 1 favours 0.9% saline											
Williams 2020	RCT	66	0.53 (0.05, 5.58)	6 per 100 children and young people	3 less per 100 children and young people (0 less, 33 more)	-	Serious[1]	NA[2]	No serious	Serious[3]	Low
All-cause mortality in hospital - RR less than 1 favours 0.9% saline											
Williams 2020	RCT	66	0.21 (0.01, 4.26)	6 per 100 children and young people	1 less per 100 children and young people (0	-	Serious[1]	NA[2]	No serious	Serious[3]	Low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
					less, 25 more)						
Cerebral oedema - RR less than 1 favours 0.9% saline											
Williams 2020	RCT	66	0.35 (0.01, 8.38)	3 per 100 children and young people	1 less per 100 children and young people (0 less, 25 more)	-	Serious[1]	NA[2]	No serious	Serious[3]	Low

[1] There was a significant difference in the number of participants with new onset diabetes in the two arms of the trial. Downgrade 1 level for serious risk of bias.
[2] Inconsistency not applicable for single study.
[3] Downgrade 1 level for serious imprecision. 95% confidence interval crosses the line of no effect.
* Derived by taking the overall number of event/ total number of participants and multiplying by 100.

0.9% Saline vs 0.45% saline for replacement of deficit

Outcomes during treatment of DKA

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Confirmed decline in Glasgow Coma Scale score to <14 - RR less than 1 favours 0.9% saline											
Kuppermann 2018	RCT	1361	1.27 (0.72, 2.22)	3 per 100 children and young people	4 more per 100 children and young people (2 less, 7 more)	-	No serious	NA[1]	No serious	Serious[2]	Moderate

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Confirmed decline in Glasgow Coma Scale score to <14 - RR less than 1 favours 0.9% saline – fast rate											
Kuppermann 2018	RCT	682	1.07 (0.46, 2.50)	3 per 100 children and young people	3 per 100 children and young people (1 less, 7 more)	-	No serious	NA[1]	No serious	Serious[2]	Moderate
Confirmed decline in Glasgow Coma Scale score to <14 - RR less than 1 favours 0.9% saline– slow rate											
Kuppermann 2018	RCT	679	1.44 (0.68, 3.06)	3 per 100 children and young people	5 more per 100 children and young people (2 less, 10 more)	-	No serious	NA[1]	No serious	Serious[2]	Moderate
Confirmed decline in Glasgow Coma Scale score to <14 - RR less than 1 favours 0.9% saline - in children with severe DKA (defined as with initial pH in the lowest quartile of the study group (pH <7.0))											
Kuppermann 2018	RCT	282	1.66 (0.81, 3.38)	8 per 100 children and young people	13 more per 100 children and young people (6 less, 26 more)	-	No serious	NA[1]	No serious	Serious[2]	Moderate
Confirmed decline in Glasgow Coma Scale score to <14 - RR less than 1 favours 0.9% saline - in children with severe DKA (defined as with initial pH in the lowest quartile of the study group (pH <7.0))- fast rate											
Kuppermann 2018	RCT	131	1.62 (0.50, 5.27)	6 per 100 children and young people	10 more per 100 children and young people (3 less, 33 more)	-	No serious	NA[1]	No serious	Serious[2]	Moderate

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Confirmed decline in Glasgow Coma Scale score to <14 - RR less than 1 favours 0.9% saline - in children with severe DKA (defined as with initial pH in the lowest quartile of the study group (pH <7.0))- slow rate											
Kuppermann 2018	RCT	151	1.68 (0.69, 4.10)	9 per 100 children and young people	15 more per 100 children and young people (6 less, 37 more)	-	No serious	NA[1]	No serious	Serious[2]	Moderate
Clinically apparent brain injury - RR less than 1 favours 0.9% saline											
Kuppermann 2018	RCT	1389	0.70 (0.22, 2.21)	1 per 100 children and young people	1 per 100 children and young people (0 less, 2 more)	-	No serious	NA[1]	Serious[3]	Serious[2]	Low
Clinically apparent brain injury - RR less than 1 favours 0.9% saline – fast rate											
Kuppermann 2018	RCT	695	0.98 (0.14, 6.92)	1 per 100 children and young people	1 per 100 children and young people (0 less, 4 more)	-	No serious	NA[1]	Serious[3]	Serious[2]	Low
Clinically apparent brain injury - RR less than 1 favours 0.9% saline – slow rate											
Kuppermann 2018	RCT	694	0.59 (0.14, 2.46)	1 per 100 children and young people	1 per 100 children and young people (0 less, 4 more)	-	No serious	NA[1]	Serious[3]	Serious[2]	Low
Clinically apparent brain injury - RR less than 1 favours 0.9% saline - in children with severe DKA (defined as with initial pH in the lowest quartile of the study group (pH <7.0))											

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Kuppermann 2018	RCT	303	1.03 (0.26, 4.02)	3 per 100 children and young people	3 per 100 children and young people (1 less, 11 more)	-	No serious	NA[1]	Serious[3]	Serious[2]	Low
Clinically apparent brain injury - RR less than 1 favours 0.9% saline - in children with severe DKA (defined as with initial pH in the lowest quartile of the study group (pH <7.0))- fast rate											
Kuppermann 2018	RCT	141	0.96 (0.06, 15.02)	1 per 100 children and young people	1 per 100 children and young people (0 less, 22 more)	-	No serious	NA[1]	Serious[3]	Serious[2]	Low
Clinically apparent brain injury - RR less than 1 favours 0.9% saline - in children with severe DKA (defined as with initial pH in the lowest quartile of the study group (pH <7.0))- slow rate											
Kuppermann 2018	RCT	162	1.05 (0.22, 5.05)	4 per 100 children and young people	4 per 100 children and young people (1 less, 18 more)	-	No serious	NA[1]	Serious[3]	Serious[2]	Low
Mortality- RR less than 1 favours 0.9% saline											
Kuppermann 2018	RCT	485	0.31 (0.01, 7.45)	1 per 100 children and young people	0 less per 100 children and young people (0 less, 7 more)	-	No serious	NA[1]	No serious	Serious[2]	Moderate
Mortality- RR less than 1 favours 0.9% saline – fast rate											

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Kuppermann 2018	RCT	238	0.31 (0.01, 7.45)	1 per 100 children and young people	1 per 100 children and young people (0 less, 22 more)	-	No serious	NA[1]	No serious	Serious[2]	Moderate
Mortality- RR less than 1 favours 0.9% saline – slow rate											
Kuppermann 2018	RCT	247	RR not estimable due to zero event in both arms				No serious	NA[1]	No serious	Very serious[4]	Low
Renal failure - RR less than 1 favours 0.9% saline											
Kuppermann 2018	RCT	1389	RR not estimable due to zero event in both arms				No serious	NA[1]	No serious	Very serious[4]	Low

[1] Inconsistency not applicable for single study.

[2] Downgrade 1 level for serious imprecision. 95% confidence interval crosses the line of no effect.

[3] Downgrade 1 level due to indirectness. Outcome was not specified in review protocol.

[4] Downgrade 2 levels for very serious imprecision. Effect size could not be calculated.

* Derived by taking the overall number of event/ total number of participants and multiplying by 100.

1 ***Outcomes 2 to 6 months after hospitalisation***

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
IQ (in children aged 3 to 5 years) - MD greater than 0 favours 0.9% saline											
Kuppermann 2018	RCT	54	-2.90 (-10.22, 4.41)	-	-	6[1]	No serious	NA[2]	No serious	Serious[3]	Moderate
IQ (in children aged 3 to 5 years) - MD greater than 0 favours 0.9% saline – fast rate											

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Kuppermann 2018	RCT	30	-4.00 (-13.19, 5.19)	-	-	6[1]	No serious	NA[2]	No serious	Serious[3]	Moderate
IQ (in children aged 3 to 5 years) - MD greater than 0 favours 0.9% saline – slow rate											
Kuppermann 2018	RCT	24	-1.00 (-13.09, 11.09)	-	-	6[1]	No serious	NA[2]	No serious	Very serious[4]	Low
IQ (in children aged 6 to 18 years) - MD greater than 0 favours 0.9% saline											
Kuppermann 2018	RCT	768	0.48 (-1.33, 2.28)	-	-	6.5[5]	No serious	NA[2]	No serious	No serious	High
IQ (in children aged 6 to 18 years) - MD greater than 0 favours 0.9% saline- fast rate											
Kuppermann 2018	RCT	388	0.00 (-2.49, 2.49)	-	-	6[1]	No serious	NA[1]	No serious	No serious	High
IQ (in children aged 6 to 18 years) - MD greater than 0 favours 0.9% saline- slow rate											
Kuppermann 2018	RCT	380	1.00 (-1.61, 3.61)	-	-	6.5[6]	No serious	NA[1]	No serious	Serious[3]	Moderate

[1] MID = 0.5 of the median standard deviation of the comparison group (SD= 12).
[2] Inconsistency not applicable for single study.
[3] Downgrade 1 level for serious imprecision. 95% confidence interval crosses one end of the estimated MID.
[4] Downgrade 2 levels for serious imprecision. 95% confidence interval crosses both ends of the estimated MID.
[5] Pooled data – most conservative SD chosen. MID = 0.5 of the median standard deviation of the comparison group (SD= 13).
[6] MID = 0.5 of the median standard deviation of the comparison group (SD= 13).

1 **0.9% Saline vs 0.45% saline post-bolus re-hydration fluid**

2 ***Outcomes during treatment of DKA***

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Healthcare utilisation- Mean PICU length of stay (hours) -MD less than 0 favours 0.9% saline											
Basnet 2014	Retrospective cohort study	88	2.00 (-1.01, 5.01)	-	-	3.45[1]	Serious[2]	NA[3]	No serious	Serious[4]	Low
Rate of change of glucose (mg/dL/h) - MD greater than 0 favours 0.9% saline											
Basnet 2014	Retrospective cohort study	88	-7.70 (-18.02, 2.62)	-	-	14.5[5]	Serious[2]	NA[3]	No serious	Serious[4]	Low
Change in corrected sodium from baseline (meq/L) -MD less than 0 favours 0.9% saline											
Basnet 2014	Retrospective cohort study	88	3.50 (1.43, 5.57)	-	-	2.75[6]	Serious[2]	NA[3]	No serious	Serious[4]	Low

[1] MID = 0.5 of the median standard deviation of the comparison group (SD= 6.9).

[2]. No information was provided on co-interventions provided to participants (e.g. initial fluid used, rate and volume of fluid and use of additives. Downgrade 1 level for serious risk of bias.

[3] Inconsistency not applicable for single study.

[4] Downgrade 1 level for serious imprecision. 95% confidence interval crosses one end of the estimated MID.

[5] MID = 0.5 of the median standard deviation of the comparison group (SD= 29).

[6] MID = 0.5 of the median standard deviation of the comparison group (SD= 5.5).

1 **Normal saline vs Ringer's lactate**

2 ***Outcomes during treatment of DKA***

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Healthcare utilisation – mechanical ventilation – RR less than 1 favours normal saline											
Bergmann 2018	Retrospective cohort study	45603	0.93 (0.59, 1.46)	1 per 100 children and young people	1 per 100 children and young people (1 less, 2 more)	-	Very serious[1]	NA[2]	Serious[3]	Serious[4]	Very low
Cerebral oedema – RR less than 1 favours normal saline											
Bergmann 2018	Retrospective cohort study	45603	4.53 (3.68, 7.65)	1 per 100 children and young people	4 more per 100 children and young people (2 less, 6 more)	-	Very serious[1]	NA[2]	Serious[3]	No serious	Very low

[1] DKA protocol (e.g. co-interventions) was not described in the study. Additionally, appropriate analysis method that controlled for all the important confounding domains not conducted. Downgrade 2 level for very serious risk of bias

[2] Inconsistency not applicable for single study.

[3] Downgrade 1 level for indirectness. Definition of DKA not provided.

[4] Downgrade 1 level for serious imprecision. 95% confidence interval crosses the line of no effect.

* Derived by taking the overall number of event/ total number of participants and multiplying by 100.

Type 1 diabetes - All severities of DKA

75 mEq/L NaCl vs 100 mEq/L NaCl after initial rehydration

Outcomes during 1 hour of treatment

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Blood glucose levels – MD less than 0 favours 75 mEq/L of NaCl											
Savaş-Erdeve 2011	Retrospective cohort study	32	0.10 (-113.06, 113.26)	-	-	48[1]	Serious[2]	NA[3]	No serious	Very serious[4]	Very low

[1] MID = 0.5 of the median standard deviation of the comparison group (SD= 96).

[2] Appropriate analysis method that controlled for all the important confounding domains not conducted. Downgrade 1 level for serious risk of bias.

[3] Inconsistency not applicable for single study.

[4] Downgrade 2 levels for serious imprecision. 95% confidence interval crosses both ends of the estimated MID.

Outcomes during 24 hours treatment

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Change in corrected sodium from baseline (meq/L) – MD greater than 0 favours 75 mEq/L of NaCl											
Savaş-Erdeve 2011	Retrospective cohort study	32	-1.00 (-3.40, 1.40)	-	-	2.05[1]	Serious[2]	NA[3]	No serious	Serious[4]	Low
Cerebral oedema – RR less than 1 favours 75 mEq/L of NaCl											
Savaş-Erdeve 2011	Retrospective cohort study	32	RR not estimable due to zero event in both arms				Serious[2]	NA[3]	No serious	Very serious[5]	Very low

[1] MID = 0.5 of the median standard deviation of the comparison group (SD= 4.1).

[2] Appropriate analysis method that controlled for all the important confounding domains not conducted. Downgrade 1 level for serious risk of bias.

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
[3] Inconsistency not applicable for single study. [4] Downgrade 1 level for serious imprecision. 95% confidence interval crosses one end of the estimated MID. [5] Downgrade 2 levels for very serious imprecision. Effect size could not be calculated.											

IV + Additives

Severe DKA

IV fluid (not specified) with sodium bicarbonate vs IV fluid (not specified) with no sodium bicarbonate

Outcomes till discharge

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Duration of hospitalisation (hours) – MD less than 0 favours IV +sodium carbonate											
Green 1998	Retrospective cohort study	106	16.00 (0.73, 31.27)	-	-	20[1]	Very serious[2]	NA[3]	No serious	Serious[4]	Very low
Cerebral oedema – RR less than 1 favours IV +sodium carbonate											
Green 1998	Retrospective cohort study	106	0.86 (0.06, 13.39)	2 per 100 children and young people	2 per 100 children and young people (0 less, 27 more)	-	Very serious[2]	NA[3]	No serious	Serious[5]	Very low
[1] MID = 0.5 of the median standard deviation of the comparison group (SD= 40).											

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
[2] DKA protocols and co-interventions followed not defined. Additionally, no adjustments made for time varying confounding and adjustment techniques not used to correct for presence of selection bias. Downgrade 2 level for serious risk of bias.. [3] Inconsistency not applicable for single study. [4] Downgrade 1 level for serious imprecision. 95% confidence interval crosses one end of the estimated MID. [5] Downgrade 1 level for serious imprecision. 95% confidence interval crosses the line of no effect. * Derived by taking the overall number of event/ total number of participants and multiplying by 100.											

1

2 **All severities of DKA**

3 **IV fluid (Lactate Ringers or Lactate Ringers with saline) with sodium bicarbonate vs IV fluid (Lactate Ringers or Lactate Ringers with**
4 **saline) alone**

5 ***Outcomes during treatment of DKA***

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Duration of acidosis – MD less than 0 favours IV +sodium carbonate											
Mar 1981	Retrospective cohort study	49	-1.16 (-5.53, 3.21)	-	-	3.29[1]	Very serious[2]	NA[3]	Very serious[4]	Serious[5]	Very low
Length of hospital stay – MD less than 0 favours IV +sodium carbonate											
Mar 1981	Retrospective cohort study	49	2.05 (-2.52, 6.62)	-	-	2.1[6]	Very serious[1]	NA[3]	Serious[7]	Very serious[8]	Very low
[1] MID = 0.5 of the median standard deviation of the comparison group (SD= 6.58). [2] DKA protocols followed not defined. Additionally, appropriate analysis to control confounding not conducted and adjustments not used to correct the presence of selection bias. Downgrade 2 levels for very serious risk of bias.											

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality

[3] Inconsistency not applicable for single study.
[4] Downgrade 2 levels for indirectness. Outcome was not specified in review protocol and definition of DKA was not provided.
[5] Downgrade 1 level for serious imprecision. 95% confidence interval crosses one end of the estimated MID.
[6] MID = 0.5 of the median standard deviation of the comparison group (SD= 4.2).
[7] Downgrade 1 level for indirectness. Definition of DKA was not provided.
[8] Downgrade 2 levels for serious imprecision. 95% confidence interval crosses both ends of the defined MID.

1 Rate of rehydration

2 All severities of DKA

3 Fast rate vs slow rate for the replacement of deficit

4 *Outcomes during treatment of DKA*

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Confirmed decline in Glasgow Coma Scale score to <14 - RR less than 1 favours fast rate											
Kuppermann 2018	RCT	1361	0.77 (0.44, 1.35)	4 per 100 children and young people	3 less per 100 children and young people (2 less, 5 more)	-	No serious	NA[1]	No serious	Serious[2]	Moderate
Confirmed decline in Glasgow Coma Scale score to <14 - RR less than 1 favours fast rate- 0.45% NaCl											
Kuppermann 2018	RCT	675	0.91 (0.39, 2.12)	3 per 100 children and	3 per 100 children and young	-	No serious	NA[1]	No serious	Serious[2]	Moderate

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
				young people	people (1 less, 7 more)						
Confirmed decline in Glasgow Coma Scale score to <14 - RR less than 1 favours fast rate – 0.9% NaCl											
Kuppermann 2018	RCT	686	0.68 (0.32, 1.44)	5 per 100 children and young people	3 less per 100 children and young people (2 less, 7 more)	-	No serious	NA[1]	No serious	Serious[2]	Moderate
Confirmed decline in Glasgow Coma Scale score to <14 - RR less than 1 favours fast rate - in children with severe DKA (defined as with initial pH in the lowest quartile of the study group (pH <7.0))											
Kuppermann 2018	RCT	282	0.69 (0.34, 1.41)	12 per 100 children and young people	4 less per 100 children and young people (4 less, 17 more)	-	No serious	NA[1]	No serious	Serious[2]	Moderate
Confirmed decline in Glasgow Coma Scale score to <14 - RR less than 1 favours fast rate - in children with severe DKA (defined as with initial pH in the lowest quartile of the study group (pH <7.0))- 0.45% saline											
Kuppermann 2018	RCT	141	0.71 (0.22, 2.31)	9 per 100 children and young people	6 less per 100 children and young people (2 less, 21 more)	-	No serious	NA[1]	No serious	Serious[2]	Moderate
Confirmed decline in Glasgow Coma Scale score to <14 - RR less than 1 favours fast rate – in children with severe DKA (defined as with initial pH in the lowest quartile of the study group (pH <7.0))- 0.9% saline											
Kuppermann 2018	RCT	141	0.68 (0.28, 1.66)	15 per 100 children	10 less per 100 children and young	-	No serious	NA[1]	No serious	Serious[2]	Moderate

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
				and young people	people (4 less, 25 more)						
Clinically apparent brain injury - RR less than 1 favours fast rate											
Kuppermann 2018	RCT	1389	0.50 (0.15,1.65)	1 per 100 children and young people	1 per 100 children and young people (0 less,2 more)	-	No serious	NA[1]	Serious[3]	Serious[2]	Low
Clinically apparent brain injury - RR less than 1 favours fast rate – 0.45% NaCl											
Kuppermann 2018	RCT	689	0.40 (0.08, 2.05)	1 per 100 children and young people	1 per 100 children and young people (0 less, 3 more)	-	No serious	NA[1]	Serious[3]	Serious[2]	Low
Clinically apparent brain injury - RR less than 1 favours fast rate – 0.9% NaCl											
Kuppermann 2018	RCT	700	0.66 (0.11, 3.94)	1 per 100 children and young people	1 per 100 children and young people (0 less, 3 more)	-	No serious	NA[1]	Serious[3]	Serious[2]	Low
Clinically apparent brain injury - RR less than 1 favours fast rate - in children with severe DKA (defined as with initial pH in the lowest quartile of the study group (pH <7.0))											
Kuppermann 2018	RCT	303	0.38 (0.08, 1.87)	4 per 100 children and young people	1 less per 100 children and young people (0 less, 7 more)	-	No serious	NA[1]	Serious[3]	Serious[2]	Low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Clinically apparent brain injury - RR less than 1 favours fast rate - in children with severe DKA (defined as with initial pH in the lowest quartile of the study group (pH <7.0))- 0.45% NaCl											
Kuppermann 2018	RCT	152	0.40 (0.04, 3.77)	4 per 100 children and young people	1 less per 100 children and young people (0 less, 14 more)	-	No serious	NA[1]	Serious[3]	Serious[2]	Low
Clinically apparent brain injury - RR less than 1 favours fast rate – in children with severe DKA (defined as with initial pH in the lowest quartile of the study group (pH <7.0))- 0.9% NaCl											
Kuppermann 2018	RCT	151	0.37 (0.04, 3.44)	4 per 100 children and young people	1 less per 100 children and young people (0 less, 13 more)	-	No serious	NA[1]	Serious[3]	Serious[2]	Low
Mortality- RR less than 1 favours fast rate											
Kuppermann 2018	RCT	485	3.10 (0.13, 75.42)	0 per 100 children and young people	0 per 100 children and young people	-	No serious	NA[1]	No serious	Serious[2]	Moderate
Mortality- RR less than 1 favours fast rate – 0.45% NaCl											
Kuppermann 2018	RCT	238	3.10 (0.13, 75.42)	0 per 100 children and young people	0 per 100 children and young people	-	No serious	NA[1]	No serious	Serious[2]	Moderate
Mortality- RR less than 1 favours fast rate – 0.9%NaCl											

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Kuppermann 2018	RCT	247	RR not estimable due to zero event in both arms				No serious	NA[1]	No serious	Very serious[4]	Low
Renal failure - RR less than 1 favours fast rate											
Kuppermann 2018	RCT	1389	RR not estimable due to zero event in both arms				No serious	NA[1]	No serious	Very serious[4]	Low

[1] Inconsistency not applicable for single study.
[2] Downgrade 1 level for serious imprecision. 95% confidence interval crosses the line of no effect.
[3] Downgrade 1 levels for serious indirectness. Outcome was not specified in review protocol.
[4] Downgrade 2 levels for very serious imprecision. Effect size could not be calculated.
[*]Derived by taking the overall number of event/ total number of participants and multiplying by 100.

1 ***Outcomes 2 to 6 months after hospitalisation***

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
IQ (in children aged 3 to 5 years) - MD greater than 0 favours fast rate											
Kuppermann 2018	RCT	54	2.87 (-4.50, 10.23)	-	-	8[1]	No serious	NA[2]	No serious	Serious[3]	Moderate
IQ (in children aged 3 to 5 years) - MD greater than 0 favours fast rate – 0.45% NaCl											
Kuppermann 2018	RCT	30	4.00 (-5.34, 13.34)	-	-	6[4]	No serious	NA[2]	No serious	Serious[3]	Moderate
IQ (in children aged 3 to 5 years) - MD greater than 0 favours fast rate – 0.9% NaCl											
Kuppermann 2018	RCT	24	1.00 (-10.98, 12.98)	-	-	8[1]	No serious	NA[2]	No serious	Very serious[5]	Low
IQ (in children aged 6 to 18 years) - MD greater than 0 favours fast rate											

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Kuppermann 2018	RCT	768	-0.49 (-2.29, 1.32)	-	-	6.5[6]	No serious	NA[2]	No serious	No serious	High
IQ (in children aged 6 to 18 years) - MD greater than 0 fast rate- 0.4% NaCl											
Kuppermann 2018	RCT	388	0.00 (-2.52, 2.52)	-	-	6.5[7]	No serious	NA[1]	No serious	No serious	High
IQ (in children aged 6 to 18 years) - MD greater than 0 favours fast rate- 0.9% NaCl											
Kuppermann 2018	RCT	380	-1.00 (-3.58, 1.58)	-	-	6.5[7]	No serious	NA[1]	No serious	No serious	High

[1] Pooled data – most conservative SD chosen. MID = 0.5 of the median standard deviation of the comparison group (SD= 16).
[2] Inconsistency not applicable for single study.
[3] Downgrade 1 level for serious imprecision. 95% confidence interval crosses one end of the estimated MID
[4] MID = 0.5 of the median standard deviation of the comparison group (SD= 12).
[5] Downgrade 2 levels for serious imprecision. 95% confidence interval crosses both ends of the estimated MID.
[6] Pooled data – most conservative SD chosen. MID = 0.5 of the median standard deviation of the comparison group (SD= 13).
[7] MID = 0.5 of the median standard deviation of the comparison group (SD= 13).

1 **Type 1 diabetes- All severities of DKA**

2 **Rapid rate vs slower rate**

3 ***Outcomes during treatment of DKA***

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Treated for suspected cerebral oedema – RR less than 1 favours rapid rate											

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Glaser 2013	RCT	18	3.67 (0.17, 79.54)	0 per 100 children and young people	0 per 100 children and young people	-	Serious[1]	NA[2]	Very serious[3]	Serious[4]	Very low
High risk of cerebral oedema (High risk defined as SUN in the upper quartile (≥27 mg/dL) and/ or pH in the lower quartile (≤6.97))– RR less than 1 favours rapid rate											
Glaser 2013	RCT	18	2.08 (0.70, 6.19)	30 per 100 children and young people	62 more per 100 children and young people (21 less, 186 more)	-	Serious[1]	NA[2]	Very serious[3]	Serious[4]	Very low

[1] Downgrade 1 level for serious risk of bias. There was a significant difference in the age of children in the two arms. There were more older children in slower rate group.

[2] Inconsistency not applicable for single study.

[3] Downgrade 2 levels for serious indirectness. Intravenous bolus volume and assumed fluid deficit were different in both arms. Additionally, outcome was not specified in review protocol.

[4] Downgrade 1 level for serious imprecision. 95% confidence interval crosses the line of no effect.

* Derived by taking the overall number of event/ total number of participants and multiplying by 100.

1

2 **Fast rate vs slow rate**

3 ***Outcomes during treatment of DKA***

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Time in which acidosis resolved (hours) – MD less than 0 favours fast rate											

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Felner 2001	Retrospective cohort study	60	4.10 (0.79, 7.47)	-	-	2.05[1]	Serious[2]	NA[3]	Very serious[4]	Serious[5]	Very low
Change in sodium concentration (mmol/L)– MD greater than 0 favours fast rate											
Felner 2001	Retrospective cohort study	60	0.20 (-1.93, 2.33)	-	-	1.7[6]	Serious[2]	NA[3]	Very serious[4]	Very serious[7]	Very low
Change in chloride concentration (mmol/L)– MD less than 0 favours fast rate											
Felner 2001	Retrospective cohort study	60	-0.40 (-3.72. 2.92)	-	-	2.8[8]	Serious[2]	NA[3]	Very serious[4]	Very serious[7]	Very low

[1] MID = 0.5 of the median standard deviation of the comparison group (SD= 4.1).

[2] Appropriate analysis to control confounding not conducted. Additionally, adjustment techniques were not used to correct the presence of selection bias. Downgrade 1 level for serious risk of bias.

[3] Inconsistency not applicable for single study.

[4] Type of fluid used were different between the two groups. Definition of DKA not provided. Downgrade 2 levels due to indirectness.

[5] Downgrade 1 level for serious imprecision. 95% confidence interval crosses one end of the estimated MID.

[6] MID = 0.5 of the median standard deviation of the comparison group (SD= 3.4).

[7] Downgrade 2 levels for serious imprecision. 95% confidence interval crosses both ends of the estimated MID.

[8] MID = 0.5 of the median standard deviation of the comparison group (SD= 5.6).

Volume of rehydration

Type 1 diabetes- All severities of DKA

High volume vs low volume

Outcomes during treatment of DKA

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Metabolic normalisation– HR greater than 1 favours high volume											
Bakes 2016	RCT	50	2.00 (1.01, 3.95)	-	-	-	Serious[1]	NA[2]	Very serious[3]	No serious	Very low
Length of treatment – HR greater than 1 favours high volume											
Bakes 2016	RCT	50	0.80 (0.41, 1.55)	-	-	-	Serious[1]	NA[2]	Serious[4]	Serious[5]	Very low
Hospital discharge – HR greater than 1 favours high volume											
Bakes 2016	RCT	50	0.80 (0.41, 1.55)	-	-	-	Serious[1]	NA[2]	Serious[4]	Serious[5]	Very low
Cerebral oedema – RR less than 1 favours high volume											
Bakes 2016	RCT	50	RR not estimable due to zero event in both arms				Serious[1]	NA[2]	Serious[4]	Very serious[6]	Very low

[1] Downgrade 1 level for serious risk of bias. Imbalance between arms. There were more children with severe DKA in the high-volume arm.

[2] Inconsistency not applicable for single study.

[3] Downgrade 2 levels for very serious indirectness. Rate of infusion of maintenance dose was different in the two arms. Outcome not specified in review protocol.

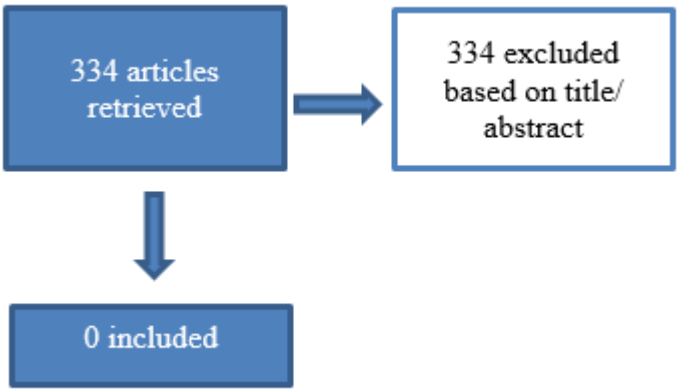
[4] Downgrade 1 level for serious indirectness. Rate of infusion of maintenance dose was different in the two arms

[5] Downgrade 1 level for serious imprecision. 95% confidence interval crosses the line of no effect.

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Estimated MID for MD	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
[6] Downgrade 2 levels for very serious imprecision. Effect size could not be calculated.											

1

Appendix I – Economic evidence study selection



Appendix J – Economic evidence tables

None

Appendix K - Health economic model

This question was not prioritised for health economic modelling.

The cost of managing an episode of DKA is very high when compared to the price of the fluids. As a result, the effectiveness of the fluids will determine the most cost-effective option.

Appendix L - Excluded studies

RCTs

Study	Code [Reason]
Antequera Martín, AM, Barea Mendoza, JA, Muriel, A et al. (2019) Buffered solutions versus 0.9% saline for resuscitation in critically ill adults	- Systematic review does not include population of interest

Study	Code [Reason]
and children. Cochrane Database of Systematic Reviews	
Carcillo, Joseph A (2014) Intravenous fluid choices in critically ill children. Current opinion in critical care 20(4): 396-401	- Review article but not a systematic review
Dhochak, N; Jayashree, M; Singhi, S (2018) A randomized controlled trial of one bag vs. two bag system of fluid delivery in children with diabetic ketoacidosis: Experience from a developing country. Journal of critical care 43: 340-345	- Study does not contain a relevant intervention [Study compared one bag system (IV fluids with desired dextrose) with two bag system (first bag with no dextrose and second bag with dextrose).]
Glaser, Nicole and Kuppermann, Nathan (2019) Fluid treatment for children with diabetic ketoacidosis: How do the results of the pediatric emergency care applied research network Fluid Therapies Under Investigation in Diabetic Ketoacidosis (FLUID) Trial change our perspective? Pediatric diabetes 20(1): 10-14	- Review article but not a systematic review [Review of PECARN trial]
Koves, Ildiko H, Leu, Michael G, Spencer, Suzanne et al. (2014) Improving care for pediatric diabetic ketoacidosis. Pediatrics 134(3): e848-56	- Comparator in study does not match that specified in protocol [Cohort study with a historical control. The control arm represented treatment before the implementation of a DKA protocol. Before the protocol there was no consistent treatment of DKA.]
Usman, A., Bakry, M.M., Mustafa, N. et al. (2019) Correlation of acidosis-adjusted potassium level and cardiovascular outcomes in diabetic ketoacidosis: A systematic review. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy 12: 1323-1338	- Systematic review does not include population of interest

1 Observational studies

2 Studies highlighted in bold were included in the previous (2015) update.

Study	Code [Reason]
Becker DJ, Brown DR, Steranka BH et al. (1983) Phosphate replacement during treatment of diabetic ketosis. Effects on calcium and phosphorus homeostasis. American journal of diseases of children (1960) 137(3): 241-246	- Comparator in study does not match that specified in protocol [Control group consisted of children who were neither acidotic nor clinically dehydrated on admission and were treated with subcutaneous crystalline insulin, oral fluids and a diabetic diet without potassium or phosphorus supplements]
Edge JA, Jakes RW, Roy Y et al. (2006) The UK case-control study of cerebral oedema complicating diabetic ketoacidosis in children. Diabetologia 49(9): 2002-2009	- Not a relevant study design [Case control study] - Study does not contain a relevant intervention [Cases defined as patients with cerebral oedema and control as those without cerebral oedema]

Study	Code [Reason]
Flood, Kayla, Nour, Munier, Holt, Tanya et al. (2019) Implementation and Evaluation of a Diabetic Ketoacidosis Order Set in Pediatric Type 1 Diabetes at a Tertiary Care Hospital: A Quality-Improvement Initiative. Canadian journal of diabetes 43(5): 297-303	- Study does not contain a relevant intervention [Study assessed update of a new DKA protocol (details of new protocol not provided)]
Glaser N, Barnett P, McCaslin I et al. (2001) Risk factors for cerebral edema in children with diabetic ketoacidosis. The Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics. The New England journal of medicine 344(4): 264-269	- Not a relevant study design [Case control study]
Hsia, Daniel S, Tarai, Sarah G, Alimi, Amir et al. (2015) Fluid management in pediatric patients with DKA and rates of suspected clinical cerebral edema. Pediatric diabetes 16(5): 338-44	- Study does not contain a relevant intervention [Study compared two different protocols that differed in type of fluid, rate and additives.]
Lawrence SE, Cummings EA, Gaboury I et al. (2005) Population-based study of incidence and risk factors for cerebral edema in pediatric diabetic ketoacidosis. The Journal of pediatrics 146(5): 688-692	- Not a relevant study design [Case control study]
Mahoney CP; Vlcek BW; DelAguila M (1999) Risk factors for developing brain herniation during diabetic ketoacidosis. Pediatric neurology 21(4): 721-727	- Not a relevant study design [Chart review]
Munir, I., Fargo, R., Garrison, R. et al. (2017) Comparison of a 'two-bag system' versus conventional treatment protocol ('one-bag system') in the management of diabetic ketoacidosis. BMJ Open Diabetes Research and Care 5(1): e000395	- Wrong population [Study included adults]
Pruitt, L.G., Jones, G., Musso, M. et al. (2019) Intravenous fluid bolus rates and pediatric diabetic ketoacidosis resolution. American Journal of Emergency Medicine 37(12): 2239-2241	- Not a relevant study design [Retrospective chart review]
Ronsley, Rebecca, Islam, Nazrul, Ronsley, Claire et al. (2018) Adherence to a pediatric diabetic ketoacidosis protocol in children presenting to a tertiary care hospital. Pediatric diabetes 19(2): 333-338	- Study does not contain a relevant intervention [Study examined the adherence of a DKA protocol]
Velasco Md, Jacqueline P, Fogel PhD, Joshua, Levine Md PhD, Robert L et al. (2017) Potential Clinical Benefits of a Two-bag System for Fluid Management in Pediatric Intensive Care Unit Patients with Diabetic Ketoacidosis. Pediatric endocrinology, diabetes, and metabolism 23(1): 6-13	- Study does not contain a relevant intervention [Compared one bag system (IV fluid with electrolytes used and new bag ordered with appropriate glucose content when first bag is depleted) with two bag system (two bags with identical electrolyte content but with different dextrose concentrations that are administered simultaneously).]
Veverka, Megan, Marsh, Kourtney, Norman, Susan et al. (2016) A Pediatric Diabetic	- Comparator in study does not match that specified in protocol

Study	Code [Reason]
Ketoacidosis Management Protocol Incorporating a Two-Bag Intravenous Fluid System Decreases Duration of Intravenous Insulin Therapy. The journal of pediatric pharmacology and therapeutics: JPPT: the official journal of PPAG 21(6): 512-517	[Study compared people receiving two-bag protocol to those who did not receive protocol. It is unclear what intervention the control group received]

1
2

Appendix M - Research recommendations – full details

None