

IV fluids in children

Intravenous fluid therapy in children and young people in hospital

Appendix C

May 2015

Draft for Consultation

*Commissioned by the National Institute for
Health and Care Excellence*

Disclaimer

Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and/or their guardian or carer.

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Contents

Appendix C: Review protocols	5
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Appendix C: Review protocols

C.1 Clinical evidence reviews

C.1.1 Assessment and monitoring

C.1.1.1 Methods of assessing IV fluid requirements

C.1.1.1.1 *Body weight versus body surface area*

Table 1: Body weight versus body surface area

Review question	How effective is assessing body weight compared with body surface area for predicting IV fluid requirements in children?
Guideline condition and its definition	IV fluids in neonates born at term, infants, children and young people (up to their 16 th birthday) in hospital
Objectives	To generate recommendation on the effectiveness of measuring body surface area to predict fluid requirements in children
Review population	Neonates born at term, infants, children and young people up to their 16 th birthday receiving IV fluids in hospital
	Line of therapy not an inclusion criterion
Interventions and comparators: generic/class; specific/drug (All interventions will be compared with each other, unless otherwise stated)	Measuring body weight Measuring body surface area
Outcomes	<p>Critical</p> <ul style="list-style-type: none"> • Mortality (dichotomous) • Adverse effects (including hypovolaemia, dehydration, hypervolemia, neurological complications) (dichotomous) • Fluid balance (continuous) <p>Important</p> <ul style="list-style-type: none"> • Quality of life (continuous)
Study design	<p>Order of preference for study designs:</p> <ul style="list-style-type: none"> • Systematic reviews of RCTs which meet our PICOs • Randomised control trials <p>Where no RCTs are available, we will consider:</p> <ul style="list-style-type: none"> • Abstracts on RCTs <p>Where no RCTs or abstracts of RCTs are available, we will consider:</p> <ul style="list-style-type: none"> • Non-randomised trials: prospective or retrospective cohort studies of 50 children or more. • Non-blinded, single + double-blinded trials will be included.
Unit of randomisation	Patient Hospital ward
Crossover study	Permitted

Minimum duration of study	Not defined
Other inclusions	Hospital
Sample size exclusion criteria	No limitations on sample size in any one group
Other exclusions	Pre-mature neonates (corrected gestational age less than 40 weeks)
Population stratification	Stratify by age: Neonates (children under 28 days), infant (to 1 year), children (1-16 years). Stratify by: Polyuric Oliguric
Reasons for stratification	The percentage of the body composed of water is higher for a term neonate than it is for an older child. Furthermore, insensible water loss (water loss that is not readily measured) varies with gestational age; the earlier the gestational age of the preterm infant, the greater the insensible water loss. Finally, neonates have a decreased capacity to concentrate or dilute urine in response to changes in intravascular fluid status and are at risk for dehydration or fluid overload.
Sensitivity/other analysis	High risk of bias
Subgroup analyses if there is heterogeneity	Coexisting medical condition (gastroenteritis; diabetic ketoacidosis; meningitis; malaria; sepsis; dengue fever; cardiovascular disease). Admission to intensive care (severe burns; severe blood loss)
Search criteria	Databases: Medline, Embase and the Cochrane Library Date limits for search: all years Language: English only

C.1.1.2 Methods of calculating IV fluid requirements

C.1.1.2.1 Measurement and documentation

Table 2: Fluid balance and/or prescription charts

Review question	What are the key components to be measured and documented on an IV fluid balance and/or prescription chart to ensure appropriate prescribing of IV fluids?
Guideline condition and its definition	IV fluids in neonates born at term, infants, children and young people up to their 16 th birthday, in hospital.
Objectives	To determine the key components which are required to be measured and documented to ensure appropriate prescription and management of IV fluids
Review population	Neonates born at term, infants, children and young people up to their 16 th birthday receiving IV fluids in hospital
Interventions and comparators: generic/class; specific/drug (All interventions will be compared with each other, unless otherwise stated)	Comparison of any fluid balance and/or prescription chart, including a combination of any of the following components (measures) to assess needs for fluid administration: <ul style="list-style-type: none"> • Weight or body surface area (previous day's/current/difference) • Clinical history: fluid intake in previous 24 hours, abnormal losses, any relevant comorbidities (for example renal, cardiovascular disease, neurological) • Clinical examination including pulse, blood pressure (BP), capillary refill, jugular vein pressure (JVP) in older children, level of dehydration, presence of pulmonary or peripheral oedema

	<ul style="list-style-type: none"> • Review switch to oral fluid or nasogastric administration • Results of laboratory assessments: full blood count (FBC), urea, creatinine, serum electrolyte levels (chloride, sodium, potassium), urinary electrolytes, acid base status (if in hypovolaemic shock) • Previous 24 hours input/output • Ongoing losses
Outcomes	<p>Critical</p> <ul style="list-style-type: none"> • Mortality (dichotomous) • Adverse effects (including hypovolaemia, dehydration, hypervolaemia, neurological complications, hypoglycaemia) • Logistic regression to fluid factors associated most closely with fluid requirements. <p>Important</p> <ul style="list-style-type: none"> • Quality of life • Hospital stay
Study design	<p>Study design:</p> <p>Order of preference for study designs:</p> <ul style="list-style-type: none"> • Systematic reviews of RCTs which meet our PICOs • Randomised control trials <p>Where no RCTs are available, we will consider:</p> <ul style="list-style-type: none"> • Abstracts on RCTs <p>Where no RCTs or abstracts of RCTs are available, we will consider:</p> <ul style="list-style-type: none"> • Non-randomised trials: prospective or retrospective cohort studies of 50 children or more. • Non-blinded, single + double-blinded trials will be included
Unit of randomisation	Patient
Crossover study	Not permitted
Minimum duration of study	Not defined
Population stratification	None
Sensitivity/other analysis	High risk of bias
Subgroup analyses if there is heterogeneity	<ul style="list-style-type: none"> • Intensive care chart • Renal • Cardiovascular
Search criteria	<p>Databases: Medline, Embase and the Cochrane Library</p> <p>Date limits for search: all years</p> <p>Language: English only</p>

C.1.1.2.2 *Laboratory-based methods versus point-of-care testing*

Table 3: Laboratory-based methods versus point-of-care testing

Review question	What is the clinical- and cost-effectiveness of laboratory-based methods versus point-of-care testing for assessing electrolyte estimations in children?
Guideline condition and its definition	IV fluids in neonates born at term, infants, children and young people (up to their 16 th birthday) in hospital
Objectives	To generate recommendations on the use of laboratory-based methods and point-of-care tests for assessing IV fluid requirements in children

Review population	Neonates born at term, infants, children and young people up to their 16 th birthday receiving IV fluids in hospital
	Line of therapy not an inclusion criterion
Interventions	Laboratory based testing for assessing fluid requirement including: <ul style="list-style-type: none"> • Plasma (albumin, sodium, potassium, chloride, urea, creatinine, pH, lactate bicarbonate and glucose) • Urine (sodium and potassium, osmolality)
Comparisons	Point-of-contact testing for assessing fluid requirement including: <ul style="list-style-type: none"> • Plasma (sodium, potassium, chloride, urea, creatinine, pH, lactate bicarbonate and glucose) • Urine (sodium and potassium)
Outcomes	<p>Critical</p> <ul style="list-style-type: none"> • Mortality • Test turnaround time • Adverse effects (including hypovolaemia, dehydration, hypervolaemia, neurological complications) <p>Important</p> <ul style="list-style-type: none"> • Fluid balance • Quality of life • Hospital stay
Study design	<p>Study design:</p> <p>Order of preference for study designs:</p> <ul style="list-style-type: none"> • Systematic reviews of RCTs which meet our PICOs • Randomised control trials <p>Where no RCTs are available, we will consider:</p> <ul style="list-style-type: none"> • Abstracts on RCTS <p>Where no RCTs or abstracts of RCTs are available, we will consider:</p> <ul style="list-style-type: none"> • Non-randomised trials: prospective or retrospective cohort studies of 50 children or more. • Non-blinded, single + double-blinded trials will be included <p>Where no randomised or non-randomised evidence in children are available, we will consider:</p> <ul style="list-style-type: none"> • Systematic Reviews of RCTs which meet our PICOs in adults • Randomised control trials in adults • Non-randomised trials: prospective or retrospective cohort studies of 50 adults or more.
Unit of randomisation	Patient Hospital ward
Crossover study	Permitted
Minimum duration of study	Not defined
Other inclusions	Hospital
Sample size exclusion criteria	No limitations on sample size in any one group

Other exclusions	Pre-mature neonates (corrected age less than 40 weeks)
Population stratification	Neonates (children under 28 days) Infants, children and young people (28 days until 16 years old)
Reasons for stratification	The percentage of the body composed of water is higher for a term neonate than it is for an older child. Furthermore, insensible water loss (water loss that is not readily measured) varies with gestational age; the earlier the gestational age of the preterm infant, the greater the insensible water loss. Finally, neonates have a decreased capacity to concentrate or dilute urine in response to changes in intravascular fluid status and are at risk for dehydration or fluid overload.
Sensitivity/other analysis	High risk of bias
Subgroup analyses if there is heterogeneity	Co-morbidity (renal/cardiovascular)
Search criteria	Databases: Medline, Embase and the Cochrane Library Date limits for search: all years Language: English only

C.1.1.2.3 Assessing dehydration and hypervolaemia

Table 4: Assessing dehydration and hypovolaemia

Review question	What are the most clinically- and cost-effective methods for assessing dehydration and hypovolaemia?
Guideline condition	IV fluids in neonates born at term, infants, children and young people (up to their 16 th birthday) in hospital
Objectives	To generate recommendations on methods to calculate IV fluid and electrolyte requirements to replace abnormal fluid losses and redistribution of fluids in children
Review population	Neonates born at term, infants, children and young people up to their 16 th birthday
	Line of therapy not an inclusion criterion
	Patients who need IV fluids to address existing deficits, ongoing losses, or abnormal fluid distribution including: chest tubes in place, uncontrolled vomiting, continuing diarrhoea, and drain losses or constant gastric losses
Interventions and comparators: generic/class; specific/drug (All interventions will be compared with each other, unless otherwise stated)	Measures to assess needs for fluid administration: Weight losses Clinical history: water intake in previous 24 hours, losses (fluid balance), any relevant comorbidities (for example renal, cardiovascular disease, neurological) Clinical examination including pulse, BP, capillary refill, JVP in older children, altered consciousness Pinch test (turgor) Other clinical examinations: sunken eyes, dry mucus membrane Combination of any chart including any of the components above

Outcomes	<p>Critical</p> <ul style="list-style-type: none"> • Mortality • Adverse effects (including hypervolaemia, dehydration, neurological complications, hypoglycaemia) • Logistics regression to fluid factors associated most closely with fluid requirements <p>Important</p> <ul style="list-style-type: none"> • Quality of life • Length of stay
Study design	<p>Study design: Order of preference for study designs:</p> <ul style="list-style-type: none"> • Systematic reviews of RCTs which meet our PICOs • Randomised control trials <p>Where no RCTs are available, we will consider:</p> <ul style="list-style-type: none"> • Abstracts on RCTs <p>Where no RCTs or abstracts of RCTs are available, we will consider:</p> <ul style="list-style-type: none"> • Non-randomised trials: prospective or retrospective cohort studies of 50 children or more. • Non-blinded, single + double-blinded trials will be included
Unit of randomisation	<p>Patient Hospital</p>
Crossover study	Not permitted
Minimum duration of study	Not defined
Subgroup analyses if there is heterogeneity	<ul style="list-style-type: none"> • Volaemic status on presentation (hypovolaemic; euvolaemic; hypervolaemic) • Suspected hypernatraemia (hypernatraemia; no hypernatraemia).
Search criteria	<p>Databases: Medline, Embase and the Cochrane Library Date limits for search: all years Language: English only</p>

C.1.2 IV fluid therapy for fluid resuscitation

C.1.2.1 Fluid type for fluid resuscitation

Table 5: Fluid type for IV fluid resuscitation

Review question	What is the most clinically- and cost-effective fluid type for fluid resuscitation in children?
Guideline condition and its definition	IV fluids in neonates born at term, infants, children and young people (up to their 16 th birthday) in hospital.
Objectives	To generate recommendations on the use of albumin versus crystalloids for fluid resuscitation in children
Review population	Neonates born at term, infants, children and young people up to their 16 th birthday; critically ill patients.
	Infants and children (term to 16 years)
	Line of therapy not an inclusion criterion
	Resuscitation definition - critically ill patients, for instance those undergoing surgery with expected blood loss > 10% blood volume, with severe sepsis or septic shock, severe burns, acute gastroenteritis, gastrointestinal haemorrhage, dengue shock syndrome, admitted to an intensive care and a trauma unit with

	<p>suspected hypovolaemia and/or hypotension and other electrolyte disturbances (for example hypernatraemia, hypokalaemia, metabolic acidosis or alkalosis).</p>
<p>Interventions and comparators: generic/class; specific/drug</p> <p>(All interventions will be compared with each other, unless otherwise stated)</p>	<p>Crystalloids</p> <p>Balanced crystalloid solutions; Hartmann's solution</p> <p>Balanced crystalloid solutions; Ringer's lactate solution</p> <p>Balanced crystalloid solutions; Plasma-Lyte</p> <p>Isotonic sodium chloride; 0.9% sodium chloride</p> <p>Hypertonic sodium chloride ; 1.8% - 7.5% sodium chloride</p> <p>Albumin</p> <p>Albumin; 4-5% albumin</p> <p>Synthetic colloid</p> <p>Gelatin; Polygeline - Haemaccel</p> <p>Gelatin; succinylated gelatin - Gelofusine</p> <p>Dextran; Dextran 60, Dextran 70</p>
<p>Outcomes</p>	<p>Critical</p> <ul style="list-style-type: none"> • Mortality at 28 days (dichotomous) • Neurological compromise (dichotomous) • Cardiovascular compromise (dichotomous) <p>Important</p> <ul style="list-style-type: none"> • Length of hospital stay (continuous) • Hyperchloraemic acidosis (dichotomous) • Quality of life (continuous) • Hypoglycaemia (dichotomous) • Hypernatraemia (dichotomous) • Hyponatraemia (dichotomous)
<p>Study design</p>	<p>Study design:</p> <p>Order of preference for study designs:</p> <p>Systematic reviews of RCTs which meet our PICOs</p> <p>Randomised control trials</p> <p>Where no RCTs are available, we will consider:</p> <p>Abstracts on RCTs</p> <p>Where no RCTs or abstracts of RCTs are available, we will consider:</p> <p>Non-randomised trials: prospective or retrospective cohort studies of 50 children or more.</p> <p>Where no randomised or non-randomised evidence in children is available, we will consider:</p> <p>Systematic reviews of RCTs which meet our PICOs in adults</p> <p>Randomised control trials in adults</p> <p>Where no RCTs in adults are available, we will consider:</p> <p>Abstracts on RCTs in adults</p> <p>Where no RCTs or abstracts of RCTs in adults are available, we will consider:</p> <p>Non-randomised trials: prospective or retrospective cohort studies of 1000 adults or more.</p> <p>Non-blinded, single + double-blinded trials will be included</p>
<p>Unit of randomisation</p>	<p>Patient</p>

Crossover study	Not permitted
Minimum duration of study	Not defined
Other inclusions	Babies born at term, children and young people receiving IV fluids in a hospital setting
Other exclusions	Adults aged 16 years or older Babies born prematurely whose corrected age is less than term
Population stratification	Aged 28 days to 16 years Aged 28 days and under Trauma Sepsis Perioperative
Reasons for stratification	Age (neonate < 28 days) have different treatment requirements than over 28 days as they are smaller and are at higher risk
Other stratifications	None
Subgroup analyses if there is heterogeneity	Different conditions (dengue fever; traumatic brain injury; hypoalbuminemia (albumin level < 25 g per litre); febrile children; malaria); may respond to treatment differently Different administration rate (low rate; high rate); different doses may explain heterogeneity
Search criteria	Databases: Medline, Embase and the Cochrane Library Date limits for search: all years Language: English only

C.1.2.2 Volume and rate of administration for fluid resuscitation

Table 6: Volume and rate of administration for fluid resuscitation

Review question	What is the most clinically- and cost-effective volume and rate of administration for IV fluid resuscitation?
Guideline condition and its definition	IV fluids in neonates born at term, infants, children and young people (up to their 16 th birthday) in hospital
Objectives	To generate recommendations on the use of albumin versus crystalloids for fluid resuscitation in children
Review population	Neonates born at term, infants, children and young people up to their 16 th birthday; critically ill patients
	Infants and children (term to 16 years)
	Line of therapy not an inclusion criterion
	Resuscitation definition - critically ill patients, for instance those undergoing surgery with expected blood loss > 10% blood volume, with severe sepsis or septic shock, severe burns, acute gastroenteritis, gastrointestinal haemorrhage, dengue shock syndrome, admitted to an intensive care and a trauma unit with suspected hypovolaemia and/or hypotension and other electrolyte disturbances (for example hypernatraemia, hypokalaemia, metabolic acidosis or alkalosis).
Interventions and comparators: generic/class; specific/drug	Isotonic crystalloid solution; 0.9% sodium chloride at "x" ml/kg/15 minutes Isotonic crystalloid solution; 0.9% sodium chloride at "y" ml/kg/15 minutes
(All interventions will be compared with each	

other, unless otherwise stated)	
Outcomes	<p>Critical</p> <ul style="list-style-type: none"> • Mortality at 28 days (dichotomous) • Neurological compromise (dichotomous) • Cardiovascular compromise (dichotomous) <p>Important</p> <ul style="list-style-type: none"> • Length of hospital stay (continuous) • Hyperchloraemic acidosis (dichotomous) • Quality of life (continuous) • Hypoglycaemia (dichotomous) • Hyponatraemia (dichotomous) • Hyponatraemia (dichotomous)
Study design	<p>Study design: Order of preference for study designs: Systematic reviews of RCTs which meet our PICOs Randomised control trials Where no RCTs are available, we will consider: Abstracts on RCTs Where no RCTs or abstracts of RCTs are available, we will consider: Non-randomised trials: prospective or retrospective cohort studies of 50 children or more. Non-blinded, single + double-blinded trials will be included</p> <p>Where no randomised or non-randomised evidence in children are available, we will consider: Systematic reviews of RCTs which meet our PICOs in adults Randomised control trials in adults</p>
Unit of randomisation	Patient
Crossover study	Not permitted
Minimum duration of study	Not defined
Other inclusions	Babies born at term, children and young people receiving IV fluids in a hospital setting
Other exclusions	Adults aged 16 years or older Babies born prematurely whose corrected age is less than term
Population stratification	Aged 28 days to 16 years Aged 28 days and under Trauma Sepsis Perioperative
Reasons for stratification	Age (neonate < 28 days) have different treatment requirements than over 28 days as they are smaller and are at higher risk
Other stratifications	None
Subgroup analyses if there is heterogeneity	Patients with infectious disease (malaria; dengue fever; sepsis); may respond to treatment differently. Febrile children (febrile; non-febrile); may respond to treatment differently. Patients with traumatic brain injury (traumatic brain injury; no traumatic brain injury); may respond to treatment differently.
Search criteria	Databases: the databases to be searched are Medline, Embase and the

Cochrane Library
Date limits for search: all years
Language: English only

C.1.3 IV fluid therapy for routine maintenance

C.1.3.1 Fluid type for routine maintenance

Table 7: Fluid type for IV fluid maintenance

Review question	What is the most clinically- and cost-effective fluid type for IV fluid maintenance in children?
Guideline condition and its definition	IV fluids in children. Definition: neonates born at term, infants, children and young people up to their 16 th birthday. Receiving routine IV fluid maintenance therapy including following elective surgery, gastroenteritis, pneumonia, meningitis, bronchiolitis
Objectives	To generate recommendations on the most appropriate fluid for routine maintenance in children
Review population	Undefined
	Young people, children and neonates
	Line of therapy not an inclusion criterion
Interventions and comparators: generic/class; specific/drug (All interventions will be compared with each other, unless otherwise stated)	<p>Isotonic crystalloid; 0.9% sodium chloride</p> <p>Isotonic crystalloid; Hartmann's solution</p> <p>Isotonic crystalloid; Ringer's lactate solution</p> <p>Isotonic crystalloid; Plasma-Lyte</p> <p>Isotonic crystalloid + glucose (up to 2.5%, 2.5-5%, 5-10%); 0.9% sodium chloride</p> <p>Isotonic crystalloid + glucose (up to 2.5%, 2.5-5%, 5-10%); Hartmann's solution</p> <p>Isotonic crystalloid + glucose (up to 2.5%, 2.5-5%, 5-10%); Ringer's lactate solution</p> <p>Isotonic crystalloid + glucose (up to 2.5%, 2.5-5%, 5-10%); Plasma-Lyte</p> <p>Isotonic crystalloid solution + glucose (up to 2.5%, 2.6% - 5%, 5.1%-10%) + potassium chloride (20mmol/litre or 40mmol/litre); 0.9% sodium chloride</p> <p>Isotonic crystalloid solution + glucose (up to 2.5%, 2.6% - 5%, 5.1%-10%) + potassium chloride (20mmol/litre or 40mmol/litre); Hartmann's solution</p> <p>Isotonic crystalloid solution + glucose (up to 2.5%, 2.6% - 5%, 5.1%-10%) + potassium chloride (20mmol/litre or 40mmol/litre); Ringer's lactate solution</p> <p>Isotonic crystalloid solution + glucose (up to 2.5%, 2.6% - 5%, 5.1%-10%) + potassium chloride (20mmol/litre or 40mmol/litre); Plasma-Lyte</p> <p>Isotonic crystalloid solution + potassium chloride (20mmol/litre or 40mmol/litre); 0.9% sodium chloride</p> <p>Isotonic crystalloid solution + potassium chloride (20mmol/litre or 40mmol/litre); Hartmann's solution</p> <p>Isotonic crystalloid solution + potassium chloride (20mmol/litre or 40mmol/litre); Ringer's lactate solution</p> <p>Isotonic crystalloid solution + potassium chloride (20mmol/litre or 40mmol/litre); Plasma-Lyte</p> <p>Hypotonic sodium chloride; 0.45% sodium chloride</p> <p>Hypotonic sodium chloride; 0.18 % sodium chloride</p> <p>Hypotonic sodium chloride + glucose (up to 2.5%, 2.5-5%, 5-10%); 0.45% sodium chloride</p> <p>Hypotonic sodium chloride + glucose (up to 2.5%, 2.5-5%, 5-10%); 0.18% sodium chloride</p> <p>Hypotonic sodium chloride + glucose (up to 2.5%, 2.6% - 5%, 5.1%-10%) + potassium chloride (20mmol/litre or 40mmol/litre); 0.45% sodium chloride</p> <p>Hypotonic sodium chloride + glucose (up to 2.5%, 2.6% - 5%, 5.1%-10%) + potassium chloride (20mmol/litre or 40mmol/litre); 0.18% sodium chloride</p>

	Hypotonic sodium chloride + potassium chloride (20mmol/litre or 40mmol/litre); 0.9% sodium chloride Hypotonic sodium chloride + potassium chloride(20mmol/litre or 40mmol/litre); 0.45% sodium chloride 10% dextrose
Outcomes	<p>Critical</p> <ul style="list-style-type: none"> • Mortality at 28 days (dichotomous) • Neurological compromise at define (dichotomous) • Cardiovascular compromise at define (dichotomous) <p>Important</p> <ul style="list-style-type: none"> • Quality of life (continuous) • Length of stay (continuous) • Hyponatraemia (dichotomous) • Hypernatraemia (dichotomous) • Hyperchloraemic acidosis (dichotomous) • Hypoglycaemia (dichotomous)
Study design	RCT Systematic review Non-randomised comparative study
Unit of randomisation	Patient
Crossover study	Not permitted
Minimum duration of study	Not defined
Population stratification	Age (up to 48 hours) Age (48 hours to 28 days) Age (28 days to 16 years) Children in critical care and specialist wards (including cardiac and renal patients)
Reasons for stratification	Children at different gestastional age have different IV fluid needs and children in critical care may have varying fluid requirements
Sensitivity/other analysis	Febrile children Non-osmotic ADH secretion Volaemic status (hypovolaemic, euvolaemic, hypervolaemic) Neurological condition
Subgroup analyses if there is heterogeneity	None specified
Search criteria	Databases: Medline, Embase and the Cochrane Library Date limits for search: all years Language: English

C.1.3.2 Rate of administration for routine maintenance

Table 8: Rate of administration for routine maintenance

Review question	What is the most clinically- and cost-effective rate of administration of IV fluids for routine maintenance?
Guideline condition and its definition	IV fluids in children. Definition: neonates born at term, infants, children and young people up to their 16 th birthday. Receiving routine IV fluid maintenance therapy including following elective surgery, gastroenteritis, pneumonia, meningitis, bronchiolitis
Objectives	To generate recommendations on the most appropriate fluid for routine maintenance in children

Review population	Neonates born at term, infants, children and young people up to their 16 th birthday receiving routine IV fluid maintenance therapy
	Young people, children and neonates
Interventions and comparators: generic/class; specific/drug	Any rate calculation at maintenance or reduced maintenance rate; any sodium-containing IV in the range of 130-154 mmol/litre sodium Any other rate calculation at maintenance or reduced maintenance rate; any sodium-containing IV in the range of 130-154 mmol/litre sodium
Outcomes	<p>Critical</p> <ul style="list-style-type: none"> • Mortality (dichotomous) • Neurological compromise (dichotomous) • Cardiovascular compromise (dichotomous) <p>Important</p> <ul style="list-style-type: none"> • Quality of life (continuous) • Length of stay (continuous) • Hyponatraemia (dichotomous) • Hypernatraemia (dichotomous) • Hyperchloraemic acidosis (dichotomous) • Hypoglycaemia (dichotomous)
Study design	RCT Systematic review Non-randomised comparative study Prospective cohort study
Unit of randomisation	Patient Unit
Population stratification	Age (up to 48 hours) Age (48 hours to 28 days) Age (28 days to 16 years) Children in critical care and specialist wards (including cardiac and renal patients)
Reasons for stratification	Children at different gestational age have different IV fluid needs and children in critical care may have varying fluid requirements
Sensitivity/other analysis	Febrile children Non-osmotic ADH secretion Volaemic status (hypovolaemic, euvolaemic, hypervolaemic) Neurological condition
Subgroup analyses if there is heterogeneity	None specified
Search criteria	Databases: Medline, Embase and the Cochrane Library Date limits for search: all years Language: English

C.1.4 IV fluid therapy for replacement and redistribution

Table 9: Abnormal deficits, excesses and losses

Review question	What fluid types are the most clinically- and cost-effective to address abnormal deficits or excesses, or to replace abnormal losses?
Guideline condition and its definition	IV fluids in neonates born at term, infants, children and young people (up to their 16 th birthday) in hospital.
Objectives	To generate recommendations on the type of IV fluid administration for

	abnormal losses and redistribution in children
Review population	Infants and children (term to 16 years)
	Line of therapy not an inclusion criterion
	Replacement definition: replacement for patients who need IV fluids to address existing deficits or excesses, ongoing abnormal losses, or abnormal fluid distribution including: chest tubes in place, uncontrolled vomiting, continuing diarrhoea, or externalised cerebrospinal fluid shunts
Interventions and comparators: generic/class; specific/drug (All interventions will be compared with each other, unless otherwise stated)	Balanced crystalloid solutions; Hartmann's solution Balanced crystalloid solutions; Ringer's lactate solution Balanced crystalloid solutions; Plasma-Lyte Colloids; 4-5% albumin Isotonic sodium chloride; 0.9% sodium chloride Hypotonic sodium chloride
Outcomes	<p>Critical</p> <ul style="list-style-type: none"> • Mortality at 28 days (dichotomous) • Neurological compromise (dichotomous) • Cardiovascular compromise (dichotomous) • Other organ dysfunction (dichotomous) <p>Important</p> <ul style="list-style-type: none"> • Length of stay (continuous) • Hyperchloraemic acidosis (dichotomous) • Quality of life (continuous) • Hypoglycaemia (dichotomous) • Hypernatraemia (dichotomous) • Hyponatraemia (dichotomous)
Study design	<p>Study design:</p> <p>Order of preference for study designs:</p> <ul style="list-style-type: none"> • Systematic reviews of RCTs which meet our PICOs • Randomised control trials <p>Where no RCTs are available, we will consider:</p> <ul style="list-style-type: none"> • Abstracts on RCTs <p>Where no RCTs or abstracts of RCTs are available, we will consider:</p> <ul style="list-style-type: none"> • Non-randomised trials: prospective or retrospective cohort studies of 50 children or more. • Non-blinded, single + double-blinded trials will be included <p>Where no randomised or non-randomised evidence in children are available, we will consider:</p> <ul style="list-style-type: none"> • Systematic reviews of RCTs which meet our PICOs in adults • Randomised control trials in adults
Unit of randomisation	Patient
Crossover study	Not permitted
Minimum duration of study	Not defined
Population stratification	Isotonic losses Hypotonic losses Age (<28 days) Age (>28 days)

Reasons for stratification	Age (neonate < 28 days) have different treatment requirements than over 28 days as they are smaller and are at higher risk; isotonic and hypotonic losses are considerably different so should be separated
Subgroup analyses if there is heterogeneity	Volaemic status on presentation (hypovolemic; euvolaemic; hypervolaemic); may show differences
Search criteria	Databases: Medline, Embase and the Cochrane Library Date limits for search: all years Language: English language

C.1.5 Managing hypernatraemia and hyponatraemia developing during IV fluid administration

C.1.5.1 Management of hypernatraemia

Table 10: Management of hypernatraemia

Review question	What are the most clinically- and cost-effective methods to address hypernatraemia developing during IV fluid administration?
Guideline condition and its definition	IV fluids in neonates born at term, infants, children and young people (up to their 16 th birthday) in hospital.
Objectives	To generate recommendations on effective types of fluids and the rates of their administration to address symptomatic and non-symptomatic acutely developing hypernatraemia (>145 mmol sodium) developing during intravenous fluid administration in children with different volume statuses.
Review population	Neonates born at term, infants, children and young people up to their 16 th birthday receiving IV fluids in hospital.
Interventions and comparators: generic/class; specific/drug (All interventions will be compared with each other, unless otherwise stated)	<p>Isotonic crystalloid solutions at maintenance rate; Hartmann's solution</p> <p>Isotonic crystalloid solutions at maintenance rate; Ringer's lactate solution</p> <p>Isotonic crystalloid solutions at maintenance rate; 0.9% sodium chloride</p> <p>Isotonic crystalloid solutions at above maintenance rate; Hartmann's solution</p> <p>Isotonic crystalloid solutions at above maintenance rate; 0.9% sodium chloride</p> <p>Isotonic crystalloid solutions at above maintenance rate; Ringer's lactate solution</p> <p>Isotonic crystalloid solutions at below maintenance rate; 0.9% sodium chloride</p> <p>Isotonic crystalloid solutions at below maintenance rate; Ringer's lactate solution</p> <p>Isotonic crystalloid solutions at below maintenance rate; Hartmann's solution</p> <p>Hypotonic crystalloid solutions at maintenance rate; 0.45% sodium chloride</p> <p>Hypotonic crystalloid solutions at maintenance rate; 0.225% sodium chloride</p> <p>Hypotonic crystalloid solutions at maintenance rate; 0.18% sodium chloride</p> <p>Hypotonic crystalloid solutions at maintenance rate; 5% glucose</p> <p>Hypotonic crystalloid solutions at above maintenance rate; 0.45% sodium chloride</p> <p>Hypotonic crystalloid solutions at above maintenance rate; 0.225% sodium chloride</p> <p>Hypotonic crystalloid solutions at above maintenance rate; 0.18% sodium chloride</p> <p>Hypotonic crystalloid solutions at above maintenance rate; 5% glucose</p> <p>Hypotonic crystalloid solutions at below maintenance rate; 0.45% sodium chloride</p> <p>Hypotonic crystalloid solutions at below maintenance rate; 0.225% sodium chloride</p> <p>Hypotonic crystalloid solutions at below maintenance rate; 0.18% sodium chloride</p> <p>Hypotonic crystalloid solutions at below maintenance rate; 5% glucose</p>

	Enteral fluid therapy
Outcomes	<p>Critical</p> <ul style="list-style-type: none"> • Mortality at 28 days (dichotomous) • Rate of return to normal electrolyte levels • Adverse events (for example hypovolaemia, hypervolaemia, neurological compromise, cardiac arrest) (dichotomous) <p>Important</p> <ul style="list-style-type: none"> • Return to normal electrolyte levels (dichotomous) • Length of hospital stay (continuous) • Quality of life (continuous)
Study design	<p>Order of preference for study designs:</p> <ul style="list-style-type: none"> • Systematic reviews of RCTs which meet our PICOs • Randomised control trials <p>Where no RCTs are available, we will consider:</p> <ul style="list-style-type: none"> • Abstracts on RCTs <p>Where no RCTs or abstracts of RCTs are available, we will consider:</p> <ul style="list-style-type: none"> • Non-randomised trials: prospective or retrospective cohort studies of 50 children or more. <p>Non-blinded, single + double-blinded trials will be included</p> <p>Where no randomised or non-randomised evidence in children are available, we will consider:</p> <ul style="list-style-type: none"> • Systematic reviews of RCTs which meet our PICOs in adults • Randomised control trials in adults <p>Where no RCTs in adults are available, we will consider:</p> <ul style="list-style-type: none"> • Abstracts on RCTs in adults
Unit of randomisation	<p>Patient Hospital ward</p>
Crossover study	Not permitted
Minimum duration of study	Not defined
Other exclusions	Pre-mature babies (corrected age less than 40 weeks)
Population stratification	<p>Neonates (less than 28 days) born at term Infants, children and young people (28 days until 16 years old)</p>
Reasons for stratification	Younger children and neonates are more sensitive to the effects of hyponatraemia
Other stratifications	Volume status (hypovolaemia, isovolaemic, hypervolaemia)
Sensitivity/other analysis	High risk of bias
Subgroup analyses if there is heterogeneity	Coexisting medical condition (Diabetes insipidus (including children with a head injury who have developed DI); Congenital adrenal hyperplasia); IV Fluid administration protocols vary with different diseases.
Search criteria	<p>Databases: Medline, Embase and the Cochrane Library Date limits for search: all years Language: English</p>

C.1.5.2 Management of hyponatraemia

Table 11: Management of hyponatraemia

Review question	What are the most clinically- and cost-effective methods to address
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	hyponatraemia developing during IV fluid administration?
Guideline condition and its definition	IV fluids in neonates born at term, infants, children and young people (up to their 16 th birthday) in hospital.
Objectives	To generate recommendations on effective types of fluids and the rates of their administration to address symptomatic and non-symptomatic acutely developing hyponatraemia (< 135 mmol sodium) developing during IV fluid administration in children with different volume statuses
Review population	Neonates born at term, infants, children and young people up to their 16 th birthday receiving IV fluids in hospital
Interventions and comparators: generic/class; specific/drug (All interventions will be compared with each other, unless otherwise stated)	Isotonic crystalloid solutions; 0.9% sodium chloride Isotonic crystalloid solutions; Ringer's lactate solution Isotonic crystalloid solutions; Hartmann's solution Hypertonic sodium chloride; 3% sodium chloride Hypertonic sodium chloride; 5% sodium chloride Rate of isotonic crystalloid solution; rate of administration Rate of hypertonic sodium chloride; rate of administration
Outcomes	Critical <ul style="list-style-type: none"> • Mortality at 28 days (dichotomous) • Rate of return to normal electrolyte levels • Adverse events (for example hypovolaemia, hypervolaemia, neurological compromise, cardiac arrest) (dichotomous) Important <ul style="list-style-type: none"> • Return to normal electrolyte levels (dichotomous) • Length of hospital stay (continuous) • Quality of life (continuous)
Study design	Order of preference for study designs: <ul style="list-style-type: none"> • Systematic reviews of RCTs which meet our PICOs • Randomised control trials Where no RCTs are available, we will consider: <ul style="list-style-type: none"> • Abstracts on RCTs Where no RCTs or abstracts of RCTs are available, we will consider: <ul style="list-style-type: none"> • Non-randomised trials: prospective or retrospective cohort studies of 50 children or more. Non-blinded, single + double-blinded trials will be included Where no randomised or non-randomised evidence in children are available, we will consider: <ul style="list-style-type: none"> • Systematic reviews of RCTs which meet our PICOs in adults • Randomised control trials in adults Where no RCTs in adults are available, we will consider: <ul style="list-style-type: none"> • Abstracts on RCTs in adults
Unit of randomisation	Patient Hospital ward
Crossover study	Not permitted
Minimum duration of study	Not defined
Sample size exclusion criteria	<50 patients for non-randomised trials in any one group (children)
Population stratification	Neonates (less than 28 days) born at term Infants, children and young people (28 days until 16 years old)

Reason for stratification	Younger children and neonates are more sensitive to the effects of hyponatraemia.
Other stratifications	Volume status (hypovolaemia, isovolaemic, hypervolaemia); symptomatic (symptoms of cerebral oedema: headaches, vomiting, seizures) versus non-symptomatic
Sensitivity/other analysis	High risk of bias
Subgroup analyses if there is heterogeneity	Inappropriate fluid administration; SIADH; pseudohyponatremia in diabetes mellitus; congenital adrenal hyperplasia; drug side effect – diuretics; gastrointestinal disorder; salt wasting syndrome
Search criteria	Databases: Medline, Embase and the Cochrane Library Date limits for search: all years Language: English

C.1.6 Training and education of healthcare professionals for management of IV fluid therapy

Table 12: Training and education of healthcare professionals for management of IV fluid therapy

Review question	What skills are needed for the adequate training and education of healthcare professionals involved in prescribing and administering IV fluids?
Guideline condition and its definition	IV fluids in neonates born at term, infants, children and young people (up to their 16 th birthday) in hospital.
Objective	To qualitatively synthesise which components healthcare professionals think they require in training and education in order to administer and prescribe IV fluids to children
Population and setting	All healthcare professionals involved in IV fluid administration and prescription to neonates born at term, infants, children and young people (up to their 16 th birthday) in hospital. Relevant to a NHS setting.
Themes	These will be determined by the qualitative data found. Relevant themes include: <ul style="list-style-type: none"> • Body surface area versus body weight • Recognition and treatment of hyponatraemia • Recognition and treatment of hypoglycaemia • Fluid overload in children Calculation of fluid balance
Exclusions	None
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL, PsychINFO. Studies will be restricted to English language only.
Review strategy	Study designs to be considered: Qualitative studies including questionnaires. Review strategy: We will cross-refer to the NICE clinical guideline 174 for general education and training but will produce a review with a specific focus on issues that are important in children. Studies will be evaluated to assess their relevance to the question asked. Analysis of studies that are most relevant to the review question in terms of population, setting (situation), context and objectives will be carried out. Thematic analysis will be conducted, and common themes across studies will be extracted and reported.

	<p>For observational/surveys/audits, the key findings will be summarised and presented.</p> <p>Setting: The review will start with focusing on studies that are conducted in a setting directly relevant to the NHS setting and the scope of the guideline.</p> <p>Appraisal of methodological quality: The methodological quality of each study will be assessed using NICE checklists and GRADE.</p> <p>Data synthesis: Thematic analysis of the data will be conducted and findings presented.</p>
Key papers	N/A

C.2 Economic evidence reviews

Table 13: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify economic evaluations relevant to the review questions set out above.
Criteria	<p>Populations, interventions and comparators must be as specified in the individual review protocols above.</p> <p>Studies must be of a relevant economic study design (cost–utility analysis, cost–benefit analysis, cost–effectiveness analysis, cost–consequence analysis, comparative cost analysis). Studies must not be an abstract only, a letter, editorial or commentary, or a review of economic evaluations.^a Unpublished reports will not be considered unless submitted as part of a call for evidence.</p> <p>Studies must be in English.</p>
Search strategy	An economic study search will be undertaken using population-specific terms and an economic study filter – see Appendix F.
Review strategy	<p>Each study fulfilling the criteria above will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in Appendix G of the NICE guidelines manual (2012).¹</p> <p>Inclusion and exclusion criteria</p> <p>If a study is rated as both ‘Directly applicable’ and with ‘Minor limitations’ then it will be included in the guideline. An economic evidence table will be completed and it will be included in the economic evidence profile.</p> <p>If a study is rated as either ‘Not applicable’ or with ‘Very serious limitations’ then it will usually be excluded from the guideline. If it is excluded then an economic evidence table will not be completed and it will not be included in the economic evidence profile.</p> <p>If a study is rated as ‘Partially applicable’, with ‘Potentially serious limitations’ or both then there is discretion over whether it should be included.</p> <p>Where there is discretion</p> <p>The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the GDG if required. The ultimate aim is to include studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the GDG if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of</p>

Review question	All questions – health economic evidence
	<p>applicability or methodological limitations will be listed with explanation as excluded economic studies in Appendix I.</p> <p>The health economist will be guided by the following hierarchies.</p> <p>Setting:</p> <ul style="list-style-type: none"> UK NHS OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden) OECD countries with predominantly private health insurance systems (for example, USA, Switzerland) non-OECD settings (always ‘Not applicable’). <p>Economic study type:</p> <ul style="list-style-type: none"> cost–utility analysis other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequence analysis) comparative cost analysis non-comparative cost analyses including cost-of-illness studies (always ‘Not applicable’). <p>Year of analysis:</p> <p>The more recent the study, the more applicable it is.</p> <p>Quality and relevance of effectiveness data used in the economic analysis:</p> <p>The more closely the effectiveness data used in the economic analysis matches with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.</p>

(a) Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.

C.3 References

- 1 National Institute for Health and Clinical Excellence. The guidelines manual. London: National Institute for Health and Clinical Excellence; 2012. Available from: <http://publications.nice.org.uk/the-guidelines-manual-pmg6/>