National Clinical Guideline Centre

IV fluid therapy in adults

Appendices A-Q

Clinical guideline <CG174>

Appendices

December 2013

Commissioned by the National Institute for Health and Care Excellence

Royal College of Physicians
Royal College of Nursing
Royal College of General Practitioners
The Royal College of Surgeons of England
NICE accredited

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Funding
National Institute for Health and Care Excellence

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Appendix A: Scope

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Centre for Clinical Practice

SCOPE

Clinical guideline title: Intravenous fluid therapy in adults in hospital

Quality standard title: Intravenous fluid therapy in adults in hospital

1 Introduction

1.1 Clinical guidelines

Clinical guidelines are recommendations by NICE on the appropriate treatment and care of people with specific diseases and conditions within the NHS. They are based on the best available evidence.

This scope defines what the guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health.

1.2 Quality standards

Quality standards are a set of specific, concise quality statements and measures that act as markers of high-quality, cost-effective patient care, covering the treatment and prevention of different diseases and conditions.

For this topic a NICE quality standard will be produced based on the guideline development recommendations. The clinical guideline and the quality standard will be published at the same time.

This scope defines the areas of care for which specific quality statements and measures will (and will not) be developed.

Intravenous fluid therapy in adults in hospital: final scope Page 1 of 12

The guideline and quality standard development processes are described in detail on the NICE website (see section 8).

2 Need for guidance

2.1 Epidemiology

a) Correct fluid and electrolyte balance is essential to maintain normal physiological function. Hospitalised patients may not be able to eat and drink normally and often have depleted fluid levels and/or an electrolyte imbalance. Intravenous provision of fluid and electrolytes is therefore often needed to maintain or restore balance.

b) Intravenous fluid and electrolyte therapy may also be needed to correct imbalances from losses of red blood cells, plasma, water or electrolytes beyond the normal losses in urine, stool and sweat and maintain in red blood cells, plasma, water or electrolytes. Causes of abnormal losses include blood loss; plasma or fluid loss from burns; fluid loss from diarrhoea, vomiting or surgical drains; and abnormal leakage of fluid from the circulation into the interstitial space.

c) There are many issues to consider when prescribing intravenous fluids and electrolytes. It is imperative that the amount and type is correct for the patient. Inadequate fluid provision can lead to hypovolaemia and poor organ perfusion, and excessive provision can result in hypervolaemia, oedema and heart failure. Under or over provision of electrolytes can also lead to potentially serious disturbances of intracellular or extracellular electrolyte balance, particularly in patients with reduced kidney or liver function.

d) Intravenous fluid therapy spans many medical and surgical disciplines. Inappropriate fluid therapy is rarely documented as being responsible for patient harm, but it is widely accepted that errors in prescribing, leading to insufficient or excessive provision

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of intravenous fluids or electrolytes, are common and have adverse effects on patient morbidity and mortality.

e) These prescribing errors are particularly likely to arise in emergency departments, acute admission units and general ward areas, where initiation and prescription of intravenous fluids may be undertaken by less expert staff. In higher dependency and critical care units more expertise is available and fluid and electrolyte status can be more closely monitored.

f) A report, which summarises lessons learnt from practice in the post operative period (the 1999 UK National Confidential Enquiry into Perioperative Deaths (NCEPOD) emphasised that fluid imbalance leads to serious postoperative morbidity and mortality. The report estimated 20% of patients studied had either poorly documented fluid balance or unrecognised and untreated fluid imbalance. It is likely that similar problems exist in other branches of hospital practice.

2.2 *Current practice*

a) Prescribers are not always aware of the specific constituents of the various intravenous replacements therapies and as such, many fluid prescriptions provide too little or too much fluid or electrolytes to restore and maintain fluid balance. There is little formal training and education in intravenous fluid management to support correct prescribing.

b) There is a wide variation in the type of charts used to record fluid and electrolyte status in practice. Monitoring of patients is often suboptimal, with fluid and electrolyte status not being recorded accurately. Changes to patients' requirements are often not assessed. There is often insufficient attention by clinical staff to ensure that appropriate identification, treatment and monitoring of changes in fluid and electrolyte status is maintained and documented.

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c) There is considerable debate about the efficacy of some specialised intravenous fluids in seriously ill patients, and consequent variation in clinical practice.

d) There is a need for a standardised approach to the clinical assessment of patients' fluid and electrolyte status and the prescription of intravenous fluid therapy in the NHS. This guidance represents a major opportunity to improve patient safety.

3 Clinical guideline

3.1 Population

3.1.1 Groups that will be covered

a) Adults (16 years and older) in hospital.

b) Medical and surgical (pre- and postoperative) patients, including subspecialties not specifically excluded in section 3.1.2.

c) Patients with sepsis.

d) Patients with acute kidney injury who do not need renal replacement therapy.

e) Chronic kidney disease stage 1–3.

f) Specific consideration will be given to the particular needs of:

- older people, who have particular challenges in managing fluid balance
- specific religious groups, in relation to choice of fluid
- any other groups shown to have particular clinical needs.

3.1.2 Groups that will not be covered

a) People younger than 16 years.

b) Pregnant women.

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c) Patients with severe (stage 4 or 5) chronic kidney disease or liver disease (Child-Pugh grade A-C).

d) Patients with diabetes, including those with diabetic ketoacidosis and hyperosmolar states.

e) Patients needing inotropes to support their circulation.

f) Patients with burns.

g) Patients with traumatic brain injury or needing neurosurgery.

3.2 Healthcare settings

a) NHS hospitals.

3.3 Management

3.3.1 Key issues that will be covered

a) Training and education in clinical assessment, prescribing, monitoring, evaluating and documenting intravenous fluid therapy in hospitals.

b) Assessment, monitoring and re-evaluation of fluid and electrolyte status:

- Clinical assessment, including:
  - physical examination
  - fluid intake and output, including measurement of fluids associated with intravenous drug administration and total parenteral nutrition
  - medical history, including current prescriptions of medications that may affect fluid and electrolyte status.
- Laboratory- or ward-based assessment of, for example:
  - plasma or blood
    - ◊ sodium
    - ◊ potassium

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- ◊ chloride
- ◊ urea
- ◊ creatinine
- ◊ pH
- ◊ bicarbonate

– urinary

- ◊ sodium
- ◊ potassium.

c) Appropriate documentation for clinical assessment, prescribing, monitoring and re-evaluation of the patient's fluid and electrolyte status.

d) Types, volume and timing of fluids and electrolytes to restore fluid balance (resuscitation):

- crystalloids compared with other crystalloids
- crystalloids compared with colloids
- colloids compared with other colloids.

e) Types, volume and timing of fluids and electrolytes to maintain fluid balance:

- crystalloids compared with other crystalloids.

f) Types, volume and timing of fluids and electrolytes to replace continuing abnormal fluid losses:

- crystalloids compared with other crystalloids
- crystalloids compared with colloids
- colloids compared with other colloids.

g) Specific considerations related to intravenous fluid therapy in patients who have:

- acute kidney injury, up to the point of renal replacement therapy

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- sepsis
- trauma
- congestive heart failure.

3.3.2 Key issues that will not be covered

a) Route of administration and intravenous catheter-related issues, such as choice of catheter, placement techniques and catheter-related infection.

b) Use of blood and blood products, except albumin.

c) The specific monitoring or prescription of electrolytes, minerals and trace elements other than sodium, potassium and chloride, unless their status directly influences sodium, potassium or chloride provision (for example, low magnesium preventing correction of hypokalaemia).

d) Use of inotropes to support circulatory failure.

e) Invasive monitoring of fluid status, for example in critical care or during surgical anaesthesia.

f) Parenteral nutrition beyond consideration of fluid and electrolyte content.

g) Labelling, preparation and storage of both standard and non-standard intravenous fluids.

h) Ethical issues related to intravenous fluid prescription at the end of life.

3.4 Main outcomes

a) Mortality.

b) Length of stay in hospital.

c) Adverse events relating to fluid and electrolyte imbalance.

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d) Quality of life.

3.5 Economic aspects

Developers will take into account both clinical and cost effectiveness when making recommendations involving a choice between alternative interventions. A review of the economic evidence will be conducted and analyses will be carried out as appropriate. The preferred unit of effectiveness is the quality-adjusted life year (QALY), and the costs considered will usually be only from an NHS and personal social services (PSS) perspective. Further detail on the methods can be found in 'The guidelines manual' (see section 8).

4 Quality standard

Information on the NICE quality standards development process is available on the NICE website, see section 8.

4.1 Areas of care

The areas of care of a patient's journey that will inform the development of the quality statements are set out below (see 4.1.1). The content of the final quality standard statements may differ before and after consultation with stakeholders.

4.1.1 Areas of care that will be considered

a) Training and education.

b) Assessment, monitoring and re-evaluation of fluid and electrolyte status.

c) Documentation.

d) Types, volume and timing of fluids and electrolytes to restore fluid balance (resuscitation).

e) Types, volume and timing of fluids and electrolytes to maintain fluid balance.

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f) Types, volume and timing of fluids and electrolytes to replace continuing abnormal fluid losses.

e) Specific considerations related to intravenous fluid therapy in patients who have:

- acute kidney injury, up to the point of renal replacement therapy
- sepsis
- trauma
- congestive heart failure.

4.1.2 Areas of care that will not be considered

a) Route of administration and intravenous catheter-related issues, such as choice of catheter, placement techniques and catheter-related infection.

b) Use of blood and blood products, except albumin.

c) The specific monitoring or prescription of electrolytes, minerals and trace elements other than sodium, potassium and chloride, unless their status directly influences sodium, potassium or chloride provision (for example, low magnesium preventing correction of hypokalaemia).

d) Use of inotropes to support circulatory failure.

e) Invasive monitoring of fluid status, for example in critical care or during surgical anaesthesia.

f) Prescription of parenteral nutrition.

g) Safe practice in relation to labelling, preparation and storage of intravenous fluids.

h) Ethical issues related to intravenous fluid prescription at the end of life.

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4.2 *Economic aspects*

Developers will take into account both clinical and cost effectiveness when prioritising the quality statements to be included in the quality standard. The economic evidence will be considered, and the cost and commissioning impact of implementing the quality standard will be assessed.

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5 Status

5.1 Scope

This is the final scope.

5.2 Timings

The development of the guideline recommendations and the quality standard will begin in September 2011.

6 Related NICE guidance

6.1 Published

- Medicines adherence. NICE clinical guideline 76 (2009). Available from www.nice.org.uk/guidance/CG76
- Diabetes in pregnancy. NICE clinical guideline 63 (2008). Available from www.nice.org.uk/guidance/CG63
- Acutely ill patients in hospital. NICE clinical guideline 50 (2007). Available from www.nice.org.uk/guidance/CG50
- Nutrition support in adults. NICE clinical guideline 32 (2006). Available from www.nice.org.uk/guidance/CG32
- Type 1 diabetes. NICE clinical guideline 15 (2004). Available from www.nice.org.uk/guidance/CG15
- Pre-hospital initiation of fluid replacement therapy in trauma. NICE technology appraisal guidance 74 (2004). Available from www.nice.org.uk/guidance/TA74

6.2 NICE guidance under development

NICE is currently developing the following related guidance (details available from the NICE website):

- Patient experience in adult NHS services. NICE clinical guideline and quality standard. Publication expected October 2011.
- Prevention and control of healthcare associated infections. NICE public health guidance. Publication expected November 2011.

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- Acute kidney injury. NICE clinical guideline and quality standard. Publication expected August 2013.

7 Further information

Information on the guideline development process is provided in:

- 'How NICE clinical guidelines are developed: an overview for stakeholders the public and the NHS'
- 'The guidelines manual
- 'Developing NICE quality standards: interim process guide'.

These are available from the NICE website (www.nice.org.uk/GuidelinesManual and www.nice.org.uk/aboutnice/qualitystandards). Information on the progress of the guideline and quality standard is also available from the NICE website (www.nice.org.uk).

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Appendix B: Declarations of interest

All members of the GDG were required to make formal declarations of interest at the outset of guideline development and at all meetings during the guideline development process. The following table describes the actions to be taken depending on the type of declaration.

B.1 GDG members declarations of interest

B.1.1 Mike Stroud - Chair

GDG meeting	Declaration of Interests	Action
First GDG meeting [01.09.2011]	Nothing to declare	None
Second GDG meeting [17.10.2011]	Nothing to declare	None
Third GDG meeting [15.12.2011]	Nothing to declare	None
Fourth GDG meeting [18.01.2012]	Nothing to declare	None
Fifth GDG meeting [29.02.2012]	Nothing to declare	None
Sixth GDG meeting [17.04.2012]	Nothing to declare	None
Seventh GDG meeting 07.06.2012	Nothing to declare	None
Eighth GDG meeting [12.07.2012]	Nothing to declare	None
Ninth and tenth GDG meeting [03.10.2012 and 04.10.2012]	Nothing to declare	None
Eleventh GDG meeting [12.12.2012]	Nothing to declare	None
Twelfth GDG meeting [07.01.2013]	Did not attend	
Thirteenth and fourteenth GDG meeting [27.02.2013 and 28.02.2013]	Nothing to declare	None
Fifteenth GDG meeting [03.04.2013]	Nothing to declare	None
Sixteenth GDG meeting [17.07.2013]	Nothing to declare	None

B.1.2 Reem Al-Jayyousi

GDG meeting	Declaration of Interests	Action
First GDG meeting [01.09.2011]	Declared personal non-pecuniary interest: Member of a group of educational leads at the University of Leicester setting guidance for teaching safe intravenous fluid prescribing. I am working on a project to improve intravenous	Declare and participate

GDG meeting	Declaration of Interests	Action
	fluid prescribing amongst foundation doctors and core medical and surgical trainees. I am part of a working group for the renal association issuing guidance on undergraduate curriculum for Nephrology Did not attend.	
Second GDG meeting [17.10.2011]	Nothing to declare	None
Third GDG meeting [15.12.2011]	Nothing to declare	None
Fourth GDG meeting [18.01.2012]	Nothing to declare	None
Fifth GDG meeting [29.02.2012]	Nothing to declare	None
Sixth GDG meeting [17.04.2012]	Nothing to declare	None
Seventh GDG meeting 07.06.2012	Nothing to declare	None
Eighth GDG meeting [12.07.2012]	Nothing to declare	None
Ninth and tenth GDG meeting [03.10.2012 and 04.10.2012]	Did not attend	None
Eleventh GDG meeting [12.12.2012]	Did not attend	None
Twelfth GDG meeting [07.01.2013]	Nothing to declare	None
Thirteenth and fourteenth GDG meeting [27.02.2013 and 28.02.2013]	Nothing to declare	None
Fifteenth GDG meeting [03.04.2013]	Nothing to declare	None
Sixteenth GDG meeting [17.07.2013]	Nothing to declare	None

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B.1.3 Paul Cook

GDG meeting	Declaration of Interests	Action
First GDG meeting [01.09.2011]	Nothing to declare	None
Second GDG meeting [17.10.2011]	Nothing to declare	None
Third GDG meeting [15.12.2011]	Nothing to declare	None
Fourth GDG meeting [18.01.2012]	Did not attend	None
Fifth GDG meeting [29.02.2012]	Nothing to declare	None
Sixth GDG meeting [17.04.2012]	Nothing to declare	None
Seventh GDG meeting 07.06.2012	Did not attend	None
Eighth GDG meeting [12.07.2012]	Nothing to declare	None
Ninth and tenth GDG meeting [03.10.2012 and 04.10.2012]	Nothing to declare	None
Eleventh GDG meeting [12.12.2012]	Nothing to declare	None
Twelfth GDG meeting [07.01.2013]	Did not attend	None
Thirteenth and fourteenth GDG meeting [27.02.2013 and 28.02.2013]	Nothing to declare	None
Fifteenth GDG meeting [03.04.2013]	Did not attend	
Sixteenth GDG meeting [17.07.2013]	Did not attend	

B.1.4 Richard Leach

GDG meeting	Declaration of Interests	Action
First GDG meeting [01.09.2011]	Declared personal non-specific pecuniary interest: I have given four lectures to local GP colleagues and practice nurses on the management of chronic obstructive airways disease. These have been supported by the pharmaceutical industry (Pfizer/ Astra Zeneca) and I received an honorarium of between £300-400/lecture. I have given no lectures and have no personal pecuniary interest relating to intravenous fluid therapy.	Declare and participate
Second GDG meeting [17.10.2011]	Nothing to declare	None

GDG meeting	Declaration of Interests	Action
Third GDG meeting [15.12.2011]	Nothing to declare	None
Fourth GDG meeting [18.01.2012]	Nothing to declare	None
Fifth GDG meeting [29.02.2012]	Nothing to declare	None
Sixth GDG meeting [17.04.2012]	Nothing to declare	None
Seventh GDG meeting 07.06.2012	Nothing to declare	None
Eighth GDG meeting [12.07.2012]	Nothing to declare	None
Ninth and tenth GDG meeting [03.10.2012 and 04.10.2012]	Nothing to declare	None
Eleventh GDG meeting [12.12.2012]	Nothing to declare	None
Twelfth GDG meeting [07.01.2013]	Nothing to declare	None
Thirteenth and fourteenth GDG meeting [27.02.2013 and 28.02.2013]	Nothing to declare	None
Fifteenth GDG meeting [03.04.2013]	Nothing to declare	None
Sixteenth GDG meeting [17.07.2013]	Nothing to declare	None

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2 **B.1.5 Dileep Lobo**

GDG meeting	Declaration of Interests	Action
First GDG meeting [01.09.2011]	Declared non- personal specific pecuniary interest: An unrestricted grant of £60, 000 from Baxter paid to University of Nottingham in 2010 for effects of crystalloid and colloid infusions. The grant closed in February 2011. Non-personal non-specific pecuniary interests: Charitable grant of £18, 000 from AminoUp in 2010 for a study on the effect of antibiotics, prebiotics and probiotics on quorum sensing molecules. Award for £41, 542 from Trent Comprehensive local research network for Research Nurse post. A Northern Norway grant £6, 929 to study muscle gene	Declare and participate

GDG meeting	Declaration of Interests	Action
	and protein expression after carbohydrate loading. The work has been completed and the grant is closed. The grant ran in 2010. CORE grant for £125, 000 to study the effects of carbohydrate loading on muscle gene and protein expression and insulin resistance on obese and non-obese patients after major surgery. It will run for two years from August 2011 Ex-vivo pharmacology centre grant for £2, 969, and 247 from Orthobiotech for 2009-13. This is in vitro research on cells to study mechanisms of tumour metastasis and the role of fibroblasts and mesenchymal cells. This is a programme grant that is due to run over several years. I am a co applicant on this grant.	
Second GDG meeting [17.10.2011]	Nothing to declare	None
Third GDG meeting [15.12.2011]	Nothing to declare	None
Fourth GDG meeting [18.01.2012]	Declared personal specific non-pecuniary interest: Written an editorial on balanced vs. unbalanced crystalloids for Annals of Surgery. Due publication in 2012 Chairing a session on fluid therapy at Association of Surgeons CBI conference (May 2012)	Declare and participate
Fifth GDG meeting [29.02.2012]	Nothing to declare	None
Sixth GDG meeting [17.04.2012]	Declared personal specific pecuniary interest: Unrestricted educational grant (£20, 000 shared between three authors) from B Braun to co-author book on IV fluids.	Declare and participate (Book discussed and agreed to be non-contentious with guideline recommendations)
Seventh GDG meeting 07.06.2012	Nothing to declare	None
Eighth GDG meeting [12.07.2012]	Did not attend	None
Ninth and tenth GDG meeting [03.10.2012 and 04.10.2012]	Did not attend	None
Eleventh GDG meeting [12.12.2012]	Nothing to declare	None
Twelfth GDG meeting [07.01.2013]	Nothing to declare	None
Thirteenth and fourteenth GDG meeting [27.02.2013 and 28.02.2013]	Declared personal specific pecuniary interest: Lectured at CRRT 2013 conference in san Diego. Air travel and accommodation paid by organisers. Lectured at FRACTA 2013; travel and subsistence honorarium paid by Fresenius Kabi.	Declare and participate
Fifteenth GDG	Nothing to declare	None

GDG meeting	Declaration of Interests	Action
meeting [03.04.2013]		
Sixteenth GDG meeting [17.07.2013]	Nothing to declare	None

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2 **B.1.6 Tom McLoughlin-Yip**

GDG meeting	Declaration of Interests	Action
First GDG meeting [01.09.2011]	Nothing to declare	None
Second GDG meeting [17.10.2011]	Nothing to declare	None
Third GDG meeting [15.12.2011]	Nothing to declare	None
Fourth GDG meeting [18.01.2012]	Did not attend	None
Fifth GDG meeting [29.02.2012]	Nothing to declare	None
Sixth GDG meeting [17.04.2012]	Nothing to declare	None
Seventh GDG meeting 07.06.2012	Nothing to declare	None
Eighth GDG meeting [12.07.2012]	Nothing to declare	None
Ninth and tenth GDG meeting [03.10.2012 and 04.10.2012]	Nothing to declare	None
Eleventh GDG meeting [12.12.2012]	Nothing to declare	None
Twelfth GDG meeting [07.01.2013]	Did not attend	None
Thirteenth and fourteenth GDG meeting [27.02.2013 and 28.02.2013]	Nothing to declare	None
Fifteenth GDG meeting [03.04.2013]	Nothing to declare	None
Sixteenth GDG meeting [17.07.2013]	Nothing to declare	None

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4 **B.1.7 Michael Mythen**

GDG meeting	Declaration of Interests	Action
GDG member till October, 2012; expert advisor from October 2012 onwards.		
First GDG meeting [01.09.2011]	Declared personal pecuniary interests: National Clinical lead for the Department of	Declare and participate

GDG meeting	Declaration of Interests	Action
	Health Enhanced Recovery Partnership Director of R and D UCL / UCLH NHS Trust Smiths Medical Professor of Anaesthesia and Critical Care UCL Consultant to AQIX (start-up company with a novel crystalloid solution – pre-clinical). This is at the pre-clinical stage, around a decade before human use. Some monies received. I have received honoraria for speaking / consultation and / or travel expenses from Baxter, Braun, Covidien, Fresenius-kabi, Hospira, LidCo. Director of Medical Defence Technologies LLC – ("Gastrostim" patented) Co-Inventor of "QUENCH" IP being exploited by UCL Business. Member of the Joint RCoA, FPM and FICM Revalidation Speciality Advisory Team Declared non-personal pecuniary interests: Smiths Medical Endow my Chair at the University and thus provide charitable donations on an annual basis. Deltex Medical provide grant funds to my Department I run a number of educational meetings (including the Great Fluid Debate) and these meetings have sponsorship from multiple industry partners declared on a meeting by meeting basis. Run a number of educational meetings (including the Great fluid debate) & these meetings have sponsorship from multiple industry partners declared on a meeting by meeting basis. Declared personal non-pecuniary interests: Council member of the Faculty of Intensive Care Medicine Chairman of the Scientific Advisory Board of the Intensive Care Foundation Council member of the National Institute of Academic Anaesthesia Board member of Society for Perioperative and Quality Improvement Co-Chairman of Evidence Based Perioperative Medicine Co-Director Xtreme Everest Editorial board of Critical Care and British Journal of Anaesthesia Co-Author of the GIFTASUP guidelines	

GDG meeting	Declaration of Interests	Action
	Editor in Chief of Perioperative Medicine Member of the Improving Surgical Outcomes Group	
Second GDG meeting [17.10.2011]	Did not attend	None
Third GDG meeting [15.12.2011]	Nothing to declare	None
Fourth GDG meeting [18.01.2012]	Declared personal non-specific pecuniary Submitted a patent for a novel intravenous fluid pump.	Declare and participate
Fifth GDG meeting [29.02.2012]	Declared personal specific pecuniary interest:	None
Sixth GDG meeting [17.04.2012]	Declared personal specific non-pecuniary interest: Chaired a round table on IV fluids on March 2012	Declare and participate
Seventh GDG meeting 07.06.2012	Did not attend	None
Eighth GDG meeting [12.07.2012]	Declared personal specific pecuniary interests: I have worked with a small group to examine the literature on the use of HES 130/0.4 in the context of major surgery and trauma to look for any signal of harm (coagulation or renal in particular). This was supported by an unrestricted grant from Fresenius-kabi paid to UCL (not to me). It will result in a paper that will be submitted for publication. I am lead author on a consensus statement from the Enhanced Recovery Partnership on fluid management in Elective Surgery.	Declare and withdraw from position as GDG member due to non-avaialblity for further meetings and potential conficts of interest. Continued to provide input group as expert advisor but did not attend further GDG meetings or participate in consensus on recommendations
Ninth and tenth GDG meeting [03.10.2012 and 04.10.2012]	Did not attend further GDG meetings after 3rd October, 2012.	None

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2 **B.1.8 Patrick Nee**

GDG meeting	Declaration of Interests	Action
First GDG meeting [01.09.2011]	Nothing to declare	None
Second GDG meeting [17.10.2011]	Nothing to declare	None
Third GDG meeting [15.12.2011]	Nothing to declare	None
Fourth GDG meeting [18.01.2012]	Did not attend	None
Fifth GDG meeting [29.02.2012]	Did not attend	None
Sixth GDG meeting	Did not attend	None

GDG meeting	Declaration of Interests	Action
[17.04.2012]		
Seventh GDG meeting 07.06.2012	Nothing to declare	None
Eighth GDG meeting [12.07.2012]	Did not attend	None
Ninth and tenth GDG meeting [03.10.2012 and 04.10.2012]	Nothing to declare	None
Eleventh GDG meeting [12.12.2012]	Did not attend	None
Twelfth GDG meeting [07.01.2013]	Nothing to declare	None
Thirteenth and fourteenth GDG meeting [27.02.2013 and 28.02.2013]	Did not attend	None
Fifteenth GDG meeting [03.04.2013]	Nothing to declare	None
Sixteenth GDG meeting [17.07.2013]	Nothing to declare	None

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2 **B.1.9 Fleur North**

GDG meeting	Declaration of Interests	Action
First GDG meeting [01.09.2011]	Nothing to declare	None
Second GDG meeting [17.10.2011]	Nothing to declare	None
Third GDG meeting [15.12.2011]	Nothing to declare	None
Fourth GDG meeting [18.01.2012]	Nothing to declare	None
Fifth GDG meeting [29.02.2012]	Nothing to declare	None
Sixth GDG meeting [17.04.2012]	Nothing to declare	None
Seventh GDG meeting 07.06.2012	Nothing to declare	None
Eighth GDG meeting [12.07.2012]	Nothing to declare	None
Ninth and tenth GDG meeting [03.10.2012 and 04.10.2012]	Nothing to declare	None
Eleventh GDG meeting [12.12.2012]	Did not attend	None
Twelfth GDG meeting [07.01.2013]	Nothing to declare	None

GDG meeting	Declaration of Interests	Action
Thirteenth and fourteenth GDG meeting [27.02.2013 and 28.02.2013]	Nothing to declare	None
Fifteenth GDG meeting [03.04.2013]	Nothing to declare	None
Sixteenth GDG meeting [17.07.2013]	Nothing to declare	None

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2 **B.1.10 Jerry Nolan**

GDG meeting	Declaration of Interests	Action
GDG member from November, 2012.		
Eleventh GDG meeting [12.12.2012]	Declared personal pecuniary interest: Minor shareholder Circle Health Declared personal non-pecuniary interest: I have lectured on the subject of fluid therapy but have never received payment. Did not attend.	Declare and participate
Twelfth GDG meeting [07.01.2013]	Nothing to declare	None
Thirteenth and fourteenth GDG meeting [27.02.2013 and 28.02.2013]	Nothing to declare	None
Fifteenth GDG meeting [03.04.2013]	Nothing to declare	None
Sixteenth GDG meeting [17.07.2013]	Nothing to declare	None

3 **B.1.11 Katie Scales**

GDG meeting	Declaration of Interests	Action
First GDG meeting [01.09.2011]	Nothing to declare	None
Second GDG meeting [17.10.2011]	Nothing to declare	None
Third GDG meeting [15.12.2011]	Nothing to declare	None
Fourth GDG meeting [18.01.2012]	Nothing to declare	None
Fifth GDG meeting [29.02.2012]	Nothing to declare	None
Sixth GDG meeting [17.04.2012]	Nothing to declare	None
Seventh GDG meeting 07.06.2012	Did not attend	None
Eighth GDG meeting	Did not attend	None

GDG meeting	Declaration of Interests	Action
[12.07.2012]		
Ninth and tenth GDG meeting [03.10.2012 and 04.10.2012]	Nothing to declare	None
Eleventh GDG meeting [12.12.2012]	Nothing to declare	None
Twelfth GDG meeting [07.01.2013]	Nothing to declare	None
Thirteenth and fourteenth GDG meeting [27.02.2013 and 28.02.2013]	Nothing to declare	None
Fifteenth GDG meeting [03.04.2013]	Nothing to declare	None
Sixteenth GDG meeting [17.07.2013]	Nothing to declare	None

1 **B.1.12 Rebecca Sherratt**

GDG meeting	Declaration of Interests	Action
First GDG meeting [01.09.2011]	Nothing to declare	None
Second GDG meeting [17.10.2011]	Nothing to declare	None
Third GDG meeting [15.12.2011]	Nothing to declare	None
Fourth GDG meeting [18.01.2012]	Did not attend	None
Fifth GDG meeting [29.02.2012]	Nothing to declare	None
Sixth GDG meeting [17.04.2012]	Nothing to declare	None
Seventh GDG meeting 07.06.2012	Nothing to declare	None
Eighth GDG meeting [12.07.2012]	Nothing to declare	None
Ninth and tenth GDG meeting [03.10.2012 and 04.10.2012]	Nothing to declare	None
Eleventh GDG meeting [12.12.2012]	Did not attend	None
Twelfth GDG meeting [07.01.2013]	Nothing to declare	None
Thirteenth and fourteenth GDG meeting [27.02.2013 and 28.02.2013]	Did not attend on 27th February, 2013.	None
Fifteenth GDG meeting [03.04.2013]	Nothing to declare	None
Sixteenth GDG meeting [17.07.2013]	Nothing to declare	None

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2 **B.1.13 Neil Soni**

GDG meeting	Declaration of Interests	Action
First GDG meeting [01.09.2011]	Declared personal specific pecuniary interest: Expert advisor to Fresenius Kabi on discussion group on balanced solutions. They produced both balanced and unbalanced starches. Subsequently published a paper on the current position. I received expenses and attended a conference to give a lecture. This occurred two years ago. Declared personal non-specific pecuniary interests: Consultancy with Smith industries. No relation to topics covered in the guideline. Declared personal non-pecuniary interests: Wrote an editorial on GIFTASUP guidelines. Have published research and reviews on use of albumin Have published research and reviews on current position with restrictive blood transfusion and given comment on position with other blood products. Given lectures on current position with regard to choosing intravenous fluids.	Declare and participate Declaration more than 12 months old prior to start of guideline (personal specific pecuniary interest)
Second GDG meeting [17.10.2011]	Declared personal specific non-pecuniary interests: Given a talk about the Boldt fluids debate discussing about and consequence. No funding received. Invited to discuss role of albumin in burns at the end of 2012.	Declare and participate
Third GDG meeting [15.12.2011]	Nothing to declare	None
Fourth GDG meeting [18.01.2012]	Nothing to declare	None
Fifth GDG meeting [29.02.2012]	Nothing to declare	None
Sixth GDG meeting [17.04.2012]	Nothing to declare	None
Seventh GDG meeting 07.06.2012	Did not attend	None
Eighth GDG meeting [12.07.2012]	Did not attend	None
Ninth and tenth GDG meeting [03.10.2012 and 04.10.2012]	Did not attend	None
Eleventh GDG meeting [12.12.2012]	Did not attend	None
Twelfth GDG meeting [07.01.2013]	Nothing to declare	None

GDG meeting	Declaration of Interests	Action
Thirteenth and fourteenth GDG meeting [27.02.2013 and 28.02.2013]	Declared personal non-pecuniary interest: Discussed CHEST paper with Fresenius Kabi Talk including IV fluids at WICS.	Declare and participate
Fifteenth GDG meeting [03.04.2013]	Nothing to declare	None
Sixteenth GDG meeting [17.07.2013]	Did not attend	

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2 **B.1.14 Mark Tomlin**

GDG meeting	Declaration of Interests	Action
First GDG meeting [01.09.2011]	Nothing to declare	None
Second GDG meeting [17.10.2011]	Did not attend	None
Third GDG meeting [15.12.2011]	Declared personal non-specific pecuniary interests: Advisory board Mitsubishi pharma (Argatroban) completely unrelated to fluids received a small consultancy fee (21/11/11). Telephone interview Gillian Kenny Associates Ltd on parenteral nutrition unrelated to fluids – received a small fee (21/9/11)	Declare and participate
Fourth GDG meeting [18.01.2012]	Nothing to declare	None
Fifth GDG meeting [29.02.2012]	Nothing to declare	None
Sixth GDG meeting [17.04.2012]	Nothing to declare	None
Seventh GDG meeting 07.06.2012	Nothing to declare	None
Eighth GDG meeting [12.07.2012]	Nothing to declare	None
Ninth and tenth GDG meeting [03.10.2012 and 04.10.2012]	Nothing to declare	None
Eleventh GDG meeting [12.12.2012]	Nothing to declare	None
Twelfth GDG meeting [07.01.2013]	Nothing to declare	None
Thirteenth and fourteenth GDG meeting [27.02.2013 and 28.02.2013]	Nothing to declare	None
Fifteenth GDG meeting [03.04.2013]	Nothing to declare	None
Sixteenth GDG meeting [17.07.2013]	Nothing to declare	None

B.2 Co-opted expert advisor declarations of interest

B.2.1 Andrew Lewington

GDG meeting	Declaration of Interests	Action
Second GDG meeting [17.10.2011]	Nothing to declare	None
Seventh GDG meeting 07.06.2012	Nothing to declare	None
Eighth GDG meeting [12.07.2012]	Nothing to declare	None
Ninth and tenth GDG meeting [03.10.2012 and 04.10.2012]	Nothing to declare	None
Eleventh GDG meeting [12.12.2012]	Nothing to declare	None
Fourteenth GDG meeting [28.02.2013]	Nothing to declare	None
Fifteenth GDG meeting [03.04.2013]	Nothing to declare	None
Sixteenth GDG meeting [17.07.2013]	Nothing to declare	None

B.3 NCGC technical team

GDG meeting	Declaration of Interests of the NCGC members	Actions
First GDG meeting [01.09.2011]	No member of the NCGC knew of personal pecuniary interests, personal family interests, non-personal pecuniary interests or personal non-pecuniary interests in the past 12 months or upcoming months.	None
Second GDG meeting [17.10.2011]	No interests to declare.	None
Third GDG meeting [15.12.2011]	No interests to declare.	None
Fourth GDG meeting [18.01.2012]	No interests to declare.	None
Fifth GDG meeting [29.02.2012]	No interests to declare.	None
Sixth GDG meeting [17.04.2012]	No interests to declare.	None

GDG meeting	Declaration of Interests of the NCGC members	Actions
Seventh GDG meeting 07.06.2012	No interests to declare.	None
Eighth GDG meeting [12.07.2012]	No interests to declare.	None
Ninth and tenth GDG meeting [03.10.2012 and 04.10.2012]	No interests to declare.	None
Eleventh GDG meeting [12.12.2012]	No interests to declare.	None
Twelfth GDG meeting [07.01.2013]	No interests to declare.	None
Thirteenth and fourteenth GDG meeting [27.02.2013 and 28.02.2013]	No interests to declare.	None
Fifteenth GDG meeting [03.04.2013]	No interests to declare.	None
Sixteenth GDG meeting [17.07.2013]	Nothing to declare	None

Appendix C: Review protocols

C.1 Standard principles

Table 1: Review protocol for standard principles

Review question	What is the clinical and cost effectiveness of clinical algorithms or defined protocols for the assessment, monitoring and/or management of intravenous fluid and electrolyte requirement in hospitalised adult patients?
Objectives	To evaluate the effectiveness and impact of implementation of a protocol or algorithm on assessment, monitoring and/or management of intravenous fluid and electrolyte requirement in hospitalised adult patients receiving intravenous fluid therapy. The protocol should include information on appropriate and timely assessment, management, monitoring and documentation of intravenous fluid needs and adverse outcomes.
Population	Adults in hospital and receiving intravenous fluid therapy
Intervention and comparisons	Assessment, monitoring and/or management of hospitalised patients receiving intravenous fluids following clinical algorithms or protocols. These may include algorithms/ protocols on intravenous fluid management which may be specific to a particular hospital or unit, or wider protocols and guidelines for a certain group of patients.
Outcomes	• All-cause mortality within 30 days of hospitalisation • Length of stay in hospital • Length of stay in Intensive care unit • Quality of life • Renal complications

Review question	What is the clinical and cost effectiveness of clinical algorithms or defined protocols for the assessment, monitoring and/or management of intravenous fluid and electrolyte requirement in hospitalised adult patients?
	• Pulmonary oedema • Other health services research based outcomes, potentially including documentation, adherence to the protocol or measures indicating a decrease in error (these may be described narratively)
Study design	Systematic reviews, RCTs. In the absence of RCTs, other designs and settings are considered. Please see review strategy section.
Exclusions	Non-English language studies Abstracts
How the information will be searched	Databases: Medline, Embase, the Cochrane library, CINAHL Date: no date restriction Language: restrict to English language only Study design: Systematic reviews, RCTs
The review strategy	The most appropriate design is likely to be a cluster randomised trial, or randomised controlled trials in adult, hospitalised patients for areas within the scope of the guideline. If no evidence is found in the target population (hospitalised adult patients), evidence from other populations may be reviewed and extrapolated from the populations listed (in descending order of evidence) 1)patients in intensive care units/ high dependency units, 2)burn patients 3)children, 4)intra-operative patients In the absence of systematic reviews and RCTs, the following study designs will be included: 1)Prospective cohort studies conducted in the UK 2)Historical cohorts conducted in the UK (before and after studies) 3)Prospective cohort studies conducted in other resource rich countries 4)Prospective cohort studies conducted in other resource rich countries If data are available, evidence will be grouped according to objectives of intravenous fluid therapy for resuscitation, for replacement of on-going losses or for regular maintenance. Apart from meta-analysis (if appropriate), qualitative observations from the studies included will also be summarised narratively. The following areas will be included in the narrative description: 1) Key components of the protocol i.e. areas in the pathway and whether intravenous fluids were administered for fluid resuscitation, regular maintenance or replacement of ongoing losses. 2)How it was implemented (any education/training/who did it) 3)What was the overall conclusion about the protocol's impact on patient outcomes and clinicians using it 4)What elements were helpful 5)What elements were unhelpful

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C.2 Assessment and monitoring

C.2.1 Review protocol for serial measurement of body weight

Table 2: Review protocol for serial measurement of body weight

Review question	In people in hospital receiving IV fluids, what is the clinical and cost effectiveness for measuring and recording serial body weight?
Objectives	To evaluate the clinical and cost effectiveness of measuring and recording serial body weight on a daily basis in people receiving intravenous fluid therapy.
Population	Adults in hospital who are receiving intravenous fluid therapy for regular maintenance or for replacement of ongoing losses. Subgroups: Chronic renal impairment, congestive heart failure groups Exclusions: Paediatric patients, burns, intra-operative cardiac surgery (CABG, where fluid is used to prime pump).
Intervention and comparisons	Intervention: Protocol to measure and record weight (at least twice a week). Comparison: Any of the following: 1.Usual care, including no protocol to measure and record body weight 2.Fluid balance charts 3.Weight measurement plus fluid balance charts 4. Clinical assessment.
Outcomes	1.All-cause mortality within 30 days of hospitalisation 2.Length of stay in hospital and/or intensive care unit 3.Quality of life 4.Renal complications/Acute Kidney Injury defined as an increase of 50% or more of serum creatinine from baseline 5.Respiratory complications including respiratory failure, chest infection, mechanical ventilation 6.Morbidity – as measure by SOFA (Sepsis-related Organ Failure) Assessment/ Sequential Organ Failure Assessment)score and other scores such as Multiple Organ Dysfunction Score(MODS) 7. Total volume of fluid received (if both groups receive the same type of fluid).
Study design	RCTs, including randomised cluster trials In the absence of randomised trials, prospective cohort studies will be considered
Exclusions	Non-English language studies Abstracts
How the information will be searched	Databases: Medline, Embase, the Cochrane library, CINAHL Date: no date restriction Language: restrict to English language only Study design: systematic reviews, RCTs, observational studies
The review strategy	The most appropriate study design is RCTs in adult, hospitalised patients for areas within the scope of the guideline. However, due to the nature of the intervention, it is likely that studies are conducted as cluster randomised trials. Prospective cohort studies will be included if no evidence is found at RCT level. Analysis will be undertaken based on the study explicitly stating whether measuring and recording of the patient's weight guides the prescription of IV fluids.

Review question	In people in hospital receiving IV fluids, what is the clinical and cost effectiveness for measuring and recording serial body weight?
	Where possible, sensitivity analysis will be carried out on studies with populations of older people if there is heterogeneity.

C.2.2 Review protocol for measurement of urinary output

Table 3: Review protocol for measurement of urinary output

Review question	In people in hospital receiving intravenous fluids, what is the clinical and cost effectiveness of measuring and recording urine output in addition to recording standard parameters stated in NEWS to determine the need for intravenous fluid administration?
Objectives	To evaluate the clinical and cost effectiveness of measuring and recording urinary output in addition to recording standard parameters stated in National Early Warning Score (NEWS)* to inform the clinical need for IV fluid administration in hospitalised patients. *Parameters stated ion NEWS are pulse rate, systolic blood pressure, respiratory rate, temperature, oxygen saturations and level of consciousness
Population	Adults in hospital and receiving intravenous fluid therapy for fluid resuscitation, regular maintenance or replacement of ongoing losses. Subgroups: People with chronic renal impairment, with/ or at risk of acute kidney injury, congestive cardiac failure, older people, peri-operative patients Exclusions: Paediatric patients, burn patients, neurosurgical and brain trauma patients, intra-operative cardiac surgery (CABG, where fluid is used to prime pump), post-operative cardiac bypass patients.
Intervention and comparisons	Intervention: Protocol to measure and record urinary output in addition to other NEWS parameters. Comparison: Any of the following: 1. no protocol to measure and record urinary output 2. weight measurement.
Outcomes	1.All-cause mortality within 30 days of hospitalisation 2.Length of stay in hospital and/or intensive care unit 3.Quality of life 4.Renal complications/Acute Kidney Injury defined as an increase of 50% or more of serum creatinine from baseline 5.Respiratory complications including respiratory failure, chest infection, mechanical ventilation 6.Morbidity – as measure by SOFA (Sepsis-related Organ Failure) Assessment/ Sequential Organ Failure Assessment)score and other scores such as Multiple Organ Dysfunction Score(MODS) Total volume of fluid received (if both groups receive the same type of fluid).
Study design	RCTs, including randomised cluster trials In the absence of randomised trials, prospective cohort studies will be considered
Exclusions	Non-English language studies Abstracts
How the information will be searched	Databases: Medline, Embase, the Cochrane library, CINAHL Date: no date restriction

Review question	In people in hospital receiving intravenous fluids, what is the clinical and cost effectiveness of measuring and recording urine output in addition to recording standard parameters stated in NEWS to determine the need for intravenous fluid administration?
	Language: restrict to English language only Study design: systematic reviews, RCTs, observational studies
The review strategy (The methods that will be used to review the evidence, outlining exceptions and subgroups.)	The most appropriate study design is RCTs in adult, hospitalised patients for areas within the scope of the guideline. However, due to the nature of the intervention, it is likely that studies are conducted as cluster randomised trials. Prospective cohort studies will be included if no evidence is found at RCT level. Although the measurement of parameters according to NEWS is a pre-requisite, the review will include any papers which measure at least pulse, blood pressure and respiratory rate of the patient. Analysis will be undertaken based on the study explicitly stating whether measuring and recording of the patient's urinary output guides the prescription of IV fluids. Where possible, sensitivity analysis will be carried out on studies with populations of older people if there is heterogeneity.

C.2.3 Review protocol for measurement of serum chloride

Table 4: Review protocol for measurement of serum chloride

Review question	In people in hospital who are receiving intravenous fluids, what is the incidence and clinical significance of hyperchloraemia or hypochloraemia?
Objectives	To evaluate the clinical and cost effectiveness of measuring serum chloride concentrations in order to recognise potential problems from hyperchloraemia including hyperchloraemic acidosis or hypochloraemia in people in hospital receiving IV fluids.
Population	Adults in hospital receiving or who have received intravenous fluid therapy for fluid resuscitation, maintenance or ongoing losses. Subgroups: Chronic renal impairment, Acute Kidney Injury (AKI), older people, Congestive heart failure (CHF) Exclusions: paediatric patients, burns, intra-operative cardiac surgery (CABG, where fluid is used to prime pump)
Intervention and comparisons	Section 1.Evaluate incidence of hypo/hyper chloraemia Exposure: Patients in hospital who have received or are receiving intravenous fluids that contain chloride concentrations greater than120 mmol/L. Non-Exposure: Patients in hospital who have received or are receiving any intravenous fluids that contain chloride concentrations up to and including 120 mmol/L. Section 2. Evaluate the clinical significance of hypo/hyper chloraemia Exposure: Patients in hospital with documented hyperchloraemia Non-Exposure: Patients in hospital with documented hypo/normochloraemia
Outcomes	1.All-cause mortality 2.Length of stay in hospital and/or intensive care unit 3.Quality of life 4.Renal complications/Acute Kidney Injury (AKI) defined as an increase of 50% or more of serum creatinine from baseline level 5.Morbidity – as measure by SOFA (Sepsis-related Organ Failure) Assessment/

Review question	In people in hospital who are receiving intravenous fluids, what is the incidence and clinical significance of hyperchloraemia or hypochloraemia?
	Sequential Organ Failure Assessment)score and other scores such as Multiple Organ Dysfunction Score(MODS) 6.Hyperchloraemia 7.Hyperchloraemic acidosis 8.Hypochloraemia.
Study design	Randomised controlled trials Cohort and case control studies
Exclusions	Non-English language studies Abstracts
How the information will be searched	Databases: Medline, Embase, the Cochrane library Date: no date restriction Language: restrict to English language only Study design: no study design restriction
The review strategy (The methods that will be used to review the evidence, outlining exceptions and subgroups.)	The review will be conducted in two sections. The first section will evaluate the development of hyperchloraemia in patients in hospital receiving intravenous fluids. Randomised controlled trials are the most appropriate type of study design for this review. However, it is recognised that the evidence from RCTs will be for short term outcomes. Evidence from cohort studies and case control studies will be extracted for this section only if long term outcomes are not presented in RCTs and the observational studies report these outcomes. The second section will evaluate the clinical significance of abnormal chloride levels. The most appropriate design for this section is cohort or case-control studies in adult, hospitalised patients for areas within the scope of the guideline. Where possible, sensitivity analysis will be carried out on studies with populations of older people if there is heterogeneity.

C.3 Resuscitation

Table 5: Review protocol for types of fluid for resuscitation

Component	Description
Review question	**What is the most clinically and cost effective fluid for intravenous fluid resuscitation of hospitalised patients?**
Objective of review	To evaluate which IV fluid is the most clinically effective, safe and cost effective for patients requiring IV fluid resuscitation.
Population	Adults in hospital who are receiving intravenous fluid therapy for fluid resuscitation. Subgroups: Sepsis patients, AKI patients, congestive heart failure patients, trauma patients, perioperative patients (these groups are included unless fluid was not given for resuscitation) Exclusions: paediatric patients, burns, neurosurgical and brain trauma patients, intraoperative cardiac surgery (CABG, where fluid is used to prime pump).
Interventions & comparisons	The following fluids will be compared with each other: 1.Gelatin 2.Hydroxyethylstarches (Tetrastarches only) 3.Sodum chloride 0.9% 4.Balanced/ Physiological solutions

Component	Description
	5.Albumin •All volumes of intravenous fluids will be considered. •Only isotonic solutions will be considered in the main matrix of comparison, except for albumin where 4% human albumin solution (mildly hypo oncotic to normal plasma) which will be included.
Outcomes	1.All-cause mortality within 30 days of hospitalisation 2.Length of stay in hospital and/or intensive care unit 3.Quality of life 4.Renal complications/Acute Kidney Injury defined as an increase of 50% or more in serum creatinine level from baseline 5.Respiratory complications including pulmonary oedema, respiratory failure, chest infection, mechanical ventilation 6.Morbidity – as measure by SOFA (Sepsis-related Organ Failure Assessement/Sequential Organ Failure Assessment) score and other scores such as Multiple Organ Dysfunction Score (MODS) 7.Volume of IV fluids used (in mL)
Study design	Systematic reviews, RCTs. In the absence of RCTs, other designs and settings are considered. Please see review strategy section.
Exclusions	Non-English studies Abstracts
How the information will be searched	Databases: Medline, Embase, the Cochrane library Date: no date restriction Language: restrict to English language only Study design: systematic reviews, RCTs
The review strategy (The methods that will be used to review the evidence, outlining exceptions and subgroups.)	The most appropriate design is likely to be randomised trials in adult, hospitalised patients for areas within the scope of the guideline. Although the target population is hospitalised adult patients, evidence from other populations will be reviewed and extrapolated from studies on: 1.patients in intensive care units/ high dependency units, 2.emergency services, including patients fluid resuscitation in ambulances and emergency services 3.intra-operative patients (except for normovolaemic hemodilution, cardiac bypass and preload for spinal anaesthesia) Evidence is expected to be found at the RCT level. This review will only consider randomised controlled trials. Specific consideration will be given to areas where there is variation in practice, for example, rate and volume of fluid administration.

Table 6: Review protocol for volumes and timings of fluid administration for resuscitation

Component	Description
Review question	**What is clinical and cost effectiveness of different volumes of fluid administration in patients requiring fluid resuscitation?** **What are the most clinically and cost effective timings and rate of administration of IV fluids in fluid resuscitation?**
Objective of review	To determine what is the clinical and cost effectiveness of different volumes of fluid administration in patients requiring fluid resuscitation
Population	Adults in hospital and receiving intravenous fluid therapy for fluid resuscitation.

Component	Description
	Subgroups: Sepsis patients, AKI patients, chronic heart failure patients, trauma patients. Perioperative patients (only patients requiring fluid resuscitation). Exclusions: Paediatric patients, burns, neurosurgical and brain trauma patient's intra-operative cardiac surgery (CABG, where fluid is used to prime pump), post-operative cardiac bypass patients.
Interventions & comparisons	1.High volume vs. low volume 2.Fast vs. slow rate of administration 3.Early vs. late initiation Studies in the following fluids will be considered: •Hydroxyethylstarches (tetrastarches only) •Gelatin •Sodium chloride 0.9% •Balanced/physiological solutions •Albumin Only studies where both arms use the same class of fluid will be included. Only isotonic solutions will be included.
Outcomes	1.All-cause mortality within 30 days of hospitalisation 2.Length of stay in hospital and/or intensive care unit 3.Quality of life 4.Renal complications/Acute Kidney Injury defined as an increase of 50% or more in serum creatinine level from baseline 5.Respiratory complications including pulmonary oedema, respiratory failure, chest infection, mechanical ventilation 6.Morbidity – as measure by SOFA (Sepsis-related Organ Failure Assessement/Sequential Organ Failure Assessment) score and other scores such as Multiple Organ Dysfunction Score(MODS)
Study design	Systematic reviews, RCTs.
Exclusions	Non-English language studies Abstracts
How the information will be searched	Databases: Medline, Embase, the Cochrane library Date: no date restriction Language: restrict to English language only Study design: systematic reviews, RCTs, observational studies
The review strategy (The methods that will be used to review the evidence, outlining exceptions and subgroups.)	The most appropriate design is likely to be randomised trials in adult, hospitalised patients for areas within the scope of the guideline. Evidence is expected to be found at the RCT level. This review will only consider randomised controlled trials. Evidence from patients undergoing pre-operative fluid loading and post-operative IV fluid therapy will be included in this review. Where possible, sensitivity analysis will be carried out on studies with populations of older people, surgical patients and general medical patients I if there is heterogeneity. Only studies published after 1990 are included.

C.4 Routine maintenance

Table 7: Review protocol for types of fluid for routine maintenance

Review question	What is the most clinically and cost effective fluid to be used for intravenous fluid therapy for routine maintenance in hospitalised patients?
Objectives	To evaluate which intravenous fluid is clinically most effective, safe and cost effective for patients requiring IV fluids for routine maintenance.
Population	Adults in hospital and receiving intravenous fluid therapy for routine maintenance. Subgroups: Perioperative nil-by-mouth patients Exclusions: paediatric patients, burns, neurosurgical and brain trauma patients, intra-operative cardiac surgery (CABG, where fluid is used to prime pump), post-operative cardiac bypass patients.
Intervention and comparisons	The following fluids will be compared with each other: Sodium chloride 0.9% Buffered/physiological solutions Sodium chloride 0.45% in Dextrose 5% Sodium chloride 0.18% in Dextrose 4% Plasmalyte M Dextrose 5%
Outcomes	All-cause mortality within 30 days of hospitalisation Length of stay in hospital and/or intensive care unit Quality of life Renal complications/Acute Kidney Injury defined as an increase of 50% or more in serum creatinine level from baseline Respiratory complications including pulmonary oedema, respiratory failure, chest infection, mechanical ventilation Morbidity – as measure by SOFA (Sepsis-related Organ Failure) Assessment/ Sequential Organ Failure Assessment) score and other scores such as Multiple Organ Dysfunction Score (MODS).
Study design	Systematic reviews, RCTs.
Exclusions	Non-English language studies Abstracts
How the information will be searched	Databases: Medline, Embase, the Cochrane library Date: no date restriction Language: restrict to English language only Study design: systematic reviews, RCTs, observational studies
The review strategy	The most appropriate design is likely to be randomised trials in adult, hospitalised patients for areas within the scope of the guideline. Evidence is expected to be found at the RCT level. This review will only consider randomised controlled trials. Evidence from patients undergoing pre-operative fluid loading and post-operative IV fluid therapy will be included in this review. All volumes of intravenous fluids will be considered. Where possible, sensitivity analysis will be carried out on studies with populations of older people if there is heterogeneity. Specific consideration will be given to areas where there is variation in practice, for example, rate and volume of fluid administration.
Key papers	

Table 8: Review protocol for volumes and timings of fluid administration for routine maintenance

Review question	What is clinical and cost effectiveness of different volumes of fluid administration in patients requiring intravenous fluids for routine maintenance? What are the most clinically and cost effective timings of administration of intravenous fluids in patients requiring intravenous fluids for routine maintenance?
Objectives	To determine what is the clinical and cost effectiveness of different volumes and timing of fluid administration in patients requiring intravenous fluids for routine maintenance. The aim was to determine whether factors such as when intravenous fluid therapy is initiated, rate of administration (ml/kg/hour), total volume (ml/kg/day) of fluid administered and giving fluids continuously over 24 hours (versus intermittently), would affect the safety and efficacy of maintenance.
Population	Adults in hospital and receiving intravenous fluid therapy for routine maintenance. Patients within the 24 hour post- surgery period (except patients undergoing transplant surgery or neurosurgery) will be included. Subgroups: Peri-operative Nil-by-mouth patients Exclusions: paediatric patients, burns, neurosurgical and brain trauma patients, intraoperative patients, cirrhosis/paracentesis patients, transplant patients
Intervention and comparisons	Studies comparing different volumes, rate of administration and timing of administration between the intervention and comparison arms will be included. Studies using the following fluids will be considered: Sodium chloride 0.9% Buffered/ physiological solutions (e.g. Lactated Ringer's solution, Plasmalyte M) Sodium chloride 0.45% in Dextrose 5% Sodium chloride 0.18% in Dextrose 4% Dextrose 5% Ideally only studies where both arms use the same type of fluid will be included. In the absence of evidence, studies where the fluids used contain the same type of components will be included.
Outcomes	All-cause mortality within 30 days of hospitalisation Length of stay in hospital and/or intensive care unit Quality of life Renal complications/Acute Kidney Injury defined as an increase of 50% or more in serum creatinine level from baseline Respiratory complications including pulmonary oedema, respiratory failure, chest infection and mechanical ventilation Morbidity – as measure by SOFA (Sepsis-related Organ Failure) Assessment/ Sequential Organ Failure Assessment)score and other scores such as Multiple Organ Dysfunction Score(MODS)
Study design	Systematic reviews, RCTs.
Exclusions	Non-English language studies Abstracts
How the information will be searched	Databases: Medline, Embase, the Cochrane library Date: no date restriction Language: restrict to English language only

Review question	**What is clinical and cost effectiveness of different volumes of fluid administration in patients requiring intravenous fluids for routine maintenance?** **What are the most clinically and cost effective timings of administration of intravenous fluids in patients requiring intravenous fluids for routine maintenance?**
	Study design: systematic reviews, RCTs
The review strategy	The most appropriate design is randomised controlled trials in adult, hospitalised patients for areas within the scope of the guideline. Evidence is expected to be found at the RCT level. This review will only consider randomised controlled trials. Evidence from patients undergoing post-operative intravenous fluid therapy (within and after 24 hours post- surgery) will be included in this review. Where possible, sensitivity analysis will be carried out on studies with populations of older people, surgical patients and orthopaedic patients if there is heterogeneity.
Key papers	

C.5 Replacement and redistribution

Table 9: Review protocol for fluid type for replacement of ongoing losses

Review question	**What is the most clinically and cost effective fluid to be used for intravenous fluid therapy for replacement of ongoing losses in hospitalised patients?**
Objectives	To evaluate which IV fluid is clinically most effective, safe and cost effective for patients requiring IV fluid to replace ongoing losses.
Population	Adults in hospital receiving intravenous fluid therapy for replacement of ongoing losses The following patients with ongoing losses will be included: 1.Patients with gastrointestinal tract losses For upper GI losses, this includes: •Vomiting •Nasogastric aspirates •Small bowel obstruction (malignancy) •Jejunostomy loss •High intestinal fistula loss •Post-operative drains. For mid GI losses, this includes: •Ileostomy loss •Mid intestinal (small bowel)fistula loss •Post- operative drains. For lower GI losses, this includes: •Diarrhoea 2. Excessive urinary loss •Recovery (diuresis/polyuric) stage of AKI, or •urinary obstruction •Diabetes insipidus patients will be considered only in the absence of any evidence for diuresis patients. Excluded populations: Paediatric patients, burns patients, neurosurgical and brain trauma patients, all intraoperative patients, cirrhosis/paracentesis patients, transplant patients Excessive urinary losses due to drug interventions (e.g.) furosemide.
Interventions &	The following fluids will be compared with each other:

Review question	What is the most clinically and cost effective fluid to be used for intravenous fluid therapy for replacement of ongoing losses in hospitalised patients?
comparisons	Sodium chloride 0.9% Balanced/ physiological solutions Sodium chloride 0.45% in Dextrose 5% Sodium chloride 0.18% in Dextrose 4% Plasmalyte M Dextrose 5%
Outcomes	1.All-cause mortality within 30 days of hospitalisation 2.Length of stay in hospital and/or intensive care unit 3.Quality of life 4.Renal complications/AKI – this is defined as an increase of 50% or more of serum creatinine from baseline 5.Respiratory complications including pulmonary oedema, respiratory failure, chest infection and use of mechanical ventilation 6.Morbidity – as measure by SOFA (Sepsis-related Organ Failure) Assessment/ Sequential Organ Failure Assessment)score and other scores such as Multiple Organ Dysfunction Score(MODS) 7. Electrolyte abnormalities (Na+, K+, Mg+2, Ca+2, PO4-3, Cl-), such as hyponatraemia in the upper GI losses.
Study design	•Systematic reviews, RCTs. •Cohort studies*
Exclusions	Non-English language studies Abstracts
How the information will be searched	Databases: Medline, Embase, the Cochrane library Date: no date restriction Language: restrict to English language only Study design: systematic reviews, RCTs, observational studies
The review strategy (The methods that will be used to review the evidence, outlining exceptions and subgroups.)	The most appropriate design is likely to be randomised trials in adult, hospitalised patients for areas within the scope of the guideline. * Evidence is expected to be found at the RCT level. If no evidence is found at RCT level then evidence from large (n>1000), well designed prospective parallel cohort studies will be considered. Where possible, sensitivity analysis will be carried out on studies with populations of older people if there is heterogeneity. Results from upper/lower/mid gastrointestinal losses will not be pooled. Urinary losses population is considered as a separate population and will not be pooled together with GI losses.

Table 10: Review protocol for fluid volume and timing of administration for replacement of ongoing losses

Review questions	What is clinical and cost effectiveness of different volumes of fluid administration in patients requiring intravenous fluids for replacement for ongoing losses? What are the most clinically and cost effective timings for the administration of intravenous fluids for replacement for ongoing losses?
Objectives	To determine what is the clinical and cost effectiveness of different volumes and timing of fluid administration in patients requiring fluid replacement for ongoing losses. The objective was to ascertain whether factors such as timing of initiation of intravenous fluid therapy, rate of administration (ml/kg/hour), total volume

Review questions	What is clinical and cost effectiveness of different volumes of fluid administration in patients requiring intravenous fluids for replacement for ongoing losses? What are the most clinically and cost effective timings for the administration of intravenous fluids for replacement for ongoing losses?
	administered (ml/kg/day), continuous administration of intravenous fluids over 24 hours compared to intermittent administration would affect the safety and efficacy of fluid replacement for ongoing losses.
Population	Adults in hospital receiving intravenous fluid therapy for replacement of ongoing losses The following patients with ongoing losses will be included: 1.Patients with gastrointestinal tract losses For upper GI losses, this includes: •Vomiting •Nasogastric aspirates •Small bowel obstruction (malignancy) •Jejunostomy loss •High intestinal fistula loss •Post-operative drains. For mid GI losses, this includes: •Ileostomy loss •Mid intestinal (small bowel)fistula loss •Post- operative drains. For lower GI losses, this includes: •Diarrhoea 2. Excessive urinary loss •Recovery (diuresis/polyuric) stage of AKI, or •urinary obstruction •Diabetes insipidus patients will be considered only in the absence of any evidence for diuresis patients. Excluded populations: Paediatric patients, burns patients, neurosurgical and brain trauma patients, all intraoperative patients, cirrhosis/paracentesis patients, transplant patients Excessive urinary losses due to drug interventions (e.g.) furosemide.
Interventions & comparisons	Studies comparing different volumes, rates of administration and timing of administration between the intervention and comparison arms will be included. The following fluids will be compared with each other. 1.Sodium chloride 0.9% 2.Balanced/ physiological solutions 3.Sodium chloride 0.45% in Dextrose 5% 4.Sodium chloride 0.18% in Dextrose 4% 5.Plasmalyte M 6.Dextrose 5%
Outcomes	1.All-cause mortality within 30 days of hospitalisation 2.Length of stay in hospital and/or intensive care unit 3.Quality of life 4.Renal complications/AKI – this is defined as an increase of 50% or more of serum creatinine from baseline 5.Respiratory complications including pulmonary oedema, respiratory failure, chest infection and use of mechanical ventilation 6.Morbidity – as measure by SOFA (Sepsis-related Organ Failure) Assessment/ Sequential Organ Failure Assessment)score and other scores such as Multiple Organ

Review questions	**What is clinical and cost effectiveness of different volumes of fluid administration in patients requiring intravenous fluids for replacement for ongoing losses?** **What are the most clinically and cost effective timings for the administration of intravenous fluids for replacement for ongoing losses?**
	Dysfunction Score(MODS) 7. Electrolyte abnormalities (Na+, K+, Mg+2, Ca+2, PO4-3, Cl-), such as hyponatraemia in the upper GI losses.
Study design	•Systematic reviews, RCTs. •Cohort studies*
Exclusions	Non-English language studies Abstracts
How the information will be searched	Databases: Medline, Embase, the Cochrane library Date: no date restriction Language: restrict to English language only Study design: systematic reviews, RCTs, observational studies
The review strategy (The methods that will be used to review the evidence, outlining exceptions and subgroups.)	The most appropriate design is likely to be randomised trials in adult, hospitalised patients for areas within the scope of the guideline. * Evidence is expected to be found at the RCT level. If no evidence is found at RCT level then evidence from large (n>1000), well designed prospective parallel cohort studies will be considered. Where possible, sensitivity analysis will be carried out on studies with populations of older people if there is heterogeneity. Results from upper/lower/mid gastrointestinal losses will not be pooled. Urinary losses population is considered as a separate population and will not be pooled together with GI losses.

C.6 Training and education

Table 11: Review protocol for training and education

Review question	**What are the barriers faced by healthcare professionals in the effective prescription and monitoring of intravenous fluids in hospital settings?**
Objectives	Main objective: To provide a systematic narrative review of the relevant literature that will aid the GDG towards consensus recommendations. Background: The issues relating to training and education are as follows: 1.Training, education and assessment of healthcare professionals involved in IV fluids management on: •When to give IV fluids •What to give •What type and effects of the solution •The effects of fluids in patients with normal physiology and during illness •Understanding the patient groups i.e. high risk patients •Assessment of competence •Skills and responsibilities for evaluation and fluid input/output •Identifying who should receive what monitoring and when •Are monitored data correctly evaluated •Who is responsible 2.Communication with patients of key issues including why the patient is receiving

Review question	What are the barriers faced by healthcare professionals in the effective prescription and monitoring of intravenous fluids in hospital settings?
	IV fluid, how long or prerequisites for stopping and patient safety issues. •It is unclear whether patients currently receive information about the treatment when IV fluid therapy is started. This is considered to be an important element to patient experience and satisfaction which is often missed. •This issue will be covered by the NICE Patient Experience Guideline.
Settings (or situations)	Inclusions: •Hospital based care including wards, medical, surgical and emergency departments. •Only studies published after 1990 will be included. Exclusions: Out of hospital care and critical care settings.
Population	All health care professionals involved in IV fluid prescription and management.
Intervention	Prescription and management of intravenous fluids
Evaluation	Cohort (high quality prospective and retrospective cohorts), quasi-experimental, RCT if available - knowledge of prescription and monitoring of intravenous fluids, including factors which encourage or prevent effective prescription and monitoring of intravenous fluids.
How the information will be searched	Databases: Medline, Embase, the Cochrane library, CINAHL, PsycINFO Date: post 1990 data Language: restrict to English language only Study design: systematic reviews, RCTs, observational studies
The review strategy	Studies will be evaluated to assess their relevance to the question asked. The review will start with focusing on studies which are conducted in a setting directly relevant to the NHS setting and the scope of the guideline. 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. The review will be considered as complete when no new themes are found within the area (theme saturation reached). For observational/surveys/audits, the key findings will be summarised and presented.

C.7 Appended economic protocol

Table 12: Appended economic review protocol for intravenous fluid therapy

Review question	All questions – health economic evidence
Objectives	To identify economic studies relevant to the review questions set out above.
Criteria	Populations, interventions and comparators as specified in the individual review protocols above. Must be a relevant economic study design (cost-utility analysis, cost-benefit analysis, cost-effectiveness analysis, cost-consequence analysis, comparative cost analysis).
Search strategy	An economic study search was undertaken using population specific terms and an economic study filter – see Appendix D.
Review strategy	Each study is assessed using the NICE economic evaluation checklist – NICE (2009) Guidelines Manual. Inclusion/exclusion criteria •If a study is rated as both 'Directly applicable' and 'Minor limitations' (using the

Review question	All questions – health economic evidence
	NICE economic evaluation checklist) then it should be included in the guideline. An evidence table should be completed and it should be included in the economic profile. •If a study is rated as either 'Not applicable' or 'Very serious limitations' then it should be excluded from the guideline. It should not be included in the economic profile and there is no need to include an evidence table. •If a study is rated as 'Partially applicable' and/or 'Potentially serious limitations' then there is discretion over whether it should be included. The health economist should 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 being to include studies that are helpful for decision making in the context of the guideline and current NHS setting. Where exclusions occur on this basis, this should be noted in the relevant section of the guideline with references. Also exclude: •unpublished reports unless submitted as part of a call for evidence •abstract-only studies •letters •editorials •reviews of economic evaluations. •foreign language articles Where there is discretion The health economist should be guided by the following hierarchies. Setting: •UK NHS •OECD countries with predominantly public health insurance systems (e.g. France, Germany, Sweden) •OECD countries with predominantly private health insurance systems (e.g. USA, Switzerland) •Non-OECD settings (always 'Not applicable') Economic study type: •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') Year of analysis: •The more recent the study, the more applicable it is Quality and relevance of effectiveness data used in the economic analysis: •The more closely the effectiveness data used in the economic analysis matches with the studies included for the clinical review the more useful the analysis will be to decision making for the guideline.

1

Appendix D: Literature search strategies

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D.4.2	Quality of life search

Search strategies used for the IV fluid therapy guideline are outlined below and were run in accordance with the methodology in the NICE Guidelines Manual 2009.[275] All searches were run up to 12 March 2013 unless otherwise stated. Any studies added to the databases after this date were not included unless specifically stated in the text. Where possible searches were limited to retrieve material published in English.

Searches for the **clinical reviews** were run in Medline (OVID), Embase (OVID) and the Cochrane Library (Wiley). Additional searches were run in CINAHL (EBSCOHost) and PsychInfo (Ovid) for some questions. Usually, searches were constructed in the following way:

- A PICO format was used for **intervention** searches where population (P) terms were combined with intervention (I) and sometimes comparison (C) terms. An intervention can be a drug, a procedure or a diagnostic test. Outcomes (O) are rarely used in search strategies for interventions. Search filters were also added to the search where appropriate.

- A PEO format was used for **prognosis** searches where population (P) terms were combined with exposure (E) terms and sometimes outcomes (O). Search filters were added to the search where appropriate.

Searches for the **health economic reviews** were run in Medline (Ovid), Embase (Ovid), the NHS Economic Evaluations Database (NHS EED), the Health Technology Assessment (HTA) database and the Health Economic Evaluation Database (HEED). HTA and NHS EED searches were carried out via the Centre for Reviews and Dissemination (CRD) interface. Searches in NHS EED and HEED were constructed only using population terms. For Medline and Embase an economic filter (instead of a study type filter) was added to the same clinical search strategy.

D.1 Population search strategies

Due to the broad scope of this guideline four different search populations were used, as appropriate to the focus of each question. The search strategies for the populations used are given below. In the section on searches for specific questions the population used is specified for each question.

D.1.1 Fluid therapy population

Medline search terms

1	fluid therapy/
2	*water-electrolyte balance/
3	((fluid* or electrolyte*) adj3 (balance* or imbalance* or manag* or maint* or loss* or status or monit* or assess* or reassess* or evaluat* or re-evaluat* or reevaluat* or prescri* or document* or chart* or strateg* or regimen* or load* or require* or need*)).ti,ab.
4	((fluid* or volum* or electrolyte*) adj3 (therap* or intravenous* or iv or infusion* or drip or drips or administrat*)).ti,ab.
5	((fluid* or volume) adj2 overload*).ti,ab.
6	((fluid* or volum*) adj3 (restor* or resuscita* or replac* or deplet* or deficien*)).ti,ab.
7	(fluid* adj3 (challenge or bolus)).ti,ab.
8	or/1-7

Embase search terms

1	fluid therapy/
2	fluid balance/
3	((fluid* or electrolyte*) adj3 (balance* or imbalance* or manag* or maint* or loss* or status or monit* or assess* or reassess* or evaluat* or re-evaluat* or reevaluat* or prescri* or document* or chart* or strateg* or regimen* or load* or require* or need*)).ti,ab.
4	((fluid* or volum* or electrolyte*) adj3 (therap* or intravenous* or iv or infusion* or drip or drips or administrat*)).ti,ab.
5	*electrolyte balance/
6	fluid resuscitation/
7	((fluid* or volum*) adj3 (restor* or resuscita* or replac* or deplet* or deficien*)).ti,ab.
8	(fluid* adj3 (challenge or bolus)).ti,ab.
9	or/1-8

Cochrane search terms

#1	MeSH descriptor Fluid Therapy, this term only
#2	MeSH descriptor Water-Electrolyte Balance, this term only
#3	((fluid* or electrolyte*) NEAR/3 (balance* or imbalance* or manag* or maint* or loss* or status or monit* or assess* or reassess* or evaluat* or re-evaluat* or reevaluat* or prescri* or

	document* or chart* or strateg* or regimen* or load* or require* or need*)):ti,ab
#4	((fluid* or volum* or electrolyte*) NEAR/3 (therap* or intravenous* or iv or infusion* or drip or drips or administrat*)):ti,ab
#5	((fluid* or volum*) NEAR/3 (restor* or resuscita* or replac* or deplet* or deficien*)):ti,ab
#6	(fluid* NEAR/3 (challenge or bolus)):ti,ab
#7	((fluid* or volume) NEAR/2 overload*):ti,ab
#8	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)

CINAHL search terms

S1	(MH "Fluid Therapy") OR (MH "Fluid Resuscitation") OR (MH "Intravenous Therapy")
S2	((fluid* or electrolyte*) n3 (therap* or substitut* or replac* or intravenous* or iv or infusion* or drip or drips or administrat*))
S3	((fluid* or blood) n1 volume)
S4	((fluid* or electrolyte*) n3 (balance* or imbalance* or manag* or maint* or loss* or status or monit* or assess* or reassess* or evaluat* or re-evaluat* or reevaluat* or prescri* or document* or chart* or strateg* or regimen* or load*))
S5	((fluid* or volum*) n3 (restor* or resuscita* or defici* or deplet* or challenge*))
S6	(MH "Fluid-Electrolyte Balance+")
S7	S1 or S2 or S3 or S4 or S5 or S6

PsychInfo search terms

1	((fluid* or electrolyte*) adj3 (therap* or substitut* or replac* or intravenous* or iv or infusion* or drip or drips or administrat*)).ti,ab.
2	((fluid* or blood) adj volume).ti,ab.
3	((fluid* or electrolyte*) adj3 (balance* or imbalance* or manag* or maint* or loss* or status or monit* or assess* or reassess* or evaluat* or re-evaluat* or reevaluat* or prescri* or document* or chart* or strateg* or regimen* or load*)).ti,ab.
4	((fluid* or volum*) adj3 (restor* or resuscita* or defici* or deplet* or challenge*)).ti,ab.
5	or/1-4

D.1.2 Routine maintenance population

Medline search terms

1	fluid therapy/
2	((fluid* or volum* or electrolyte*) adj3 (therap* or intravenous* or iv or infusion* or drip or drips or administrat*)).ti,ab.
3	((fluid* or electrolyte*) adj3 (balance* or imbalance* or manag* or maint* or loss* or status or monit* or assess* or evaluat* or re-evaluat* or reevaluat* or require* or need*)).ti,ab.
4	*water-electrolyte balance/
5	(euvol?emi* or normovol?emi*).ti,ab.
6	(((nil or nothing) adj2 mouth) or nil-by-mouth).ti,ab.
7	insensible loss*.ti,ab.
8	((swallow* or drink*) adj2 (difficult* or problem* or unable)).ti,ab.
9	or/1-8

Embase search terms

1	fluid therapy/
2	fluid balance/
3	((fluid* or volum* or electrolyte*) adj3 (therap* or intravenous* or iv or infusion* or drip or drips or administrat*)).ti,ab.

4	((fluid* or electrolyte*) adj3 (balance* or imbalance* or manag* or maint* or loss* or status or monit* or assess* or evaluat* or re-evaluat* or reevaluat* or require* or need*)).ti,ab.
5	exp *electrolyte balance/
6	(euvol?emi* or normovol?emi*).ti,ab.
7	(((nil or nothing) adj2 mouth) or nil-by-mouth).ti,ab.
8	insensible loss*.ti,ab.
9	((swallow* or drink*) adj2 (difficult* or problem* or unable)).ti,ab.
10	or/1-9

Cochrane search terms

#1	MeSH descriptor Fluid Therapy explode all trees
#2	((fluid* or volum* or electrolyte*) NEAR/3 (therap* or intravenous* or iv or infusion* or drip or drips or administrat*)):ti,ab
#3	((fluid* or electrolyte*) NEAR/3 (balance* or imbalance* or manag* or maint* or loss* or status or monit* or assess* or evaluat* or re-evaluat* or reevaluat* or require* or need*)):ti,ab
#4	MeSH descriptor Water-Electrolyte Balance explode all trees
#5	(euvol*emi* or normovol*emi*):ti,ab
#6	(((nil or nothing) NEAR/2 mouth) or nil-by-mouth):ti,ab
#7	insensible loss*:ti,ab
#8	((swallow* or drink*) NEAR/2 (difficult* or problem* or unable)):ti,ab
#9	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8)

CINAHL search terms

S1	(MH "Fluid Therapy") OR (MH "Intravenous Therapy") OR (MH "Fluid-Electrolyte Balance+")
S2	((fluid* or electrolyte*) n3 (balance* or imbalance* or manag* or maint* or loss* or status or monit* or assess* or reassess* or evaluat* or re-evaluat* or reevaluat* or prescri* or document* or chart* or strateg* or regimen* or load* or require* or need*))
S3	((fluid* or volum* or electrolyte*) n3 (therap* or intravenous* or iv or infusion* or drip or drips or administrat*))
S4	euvolaemi* OR euvolemi* OR normovolaemi* OR normovolemi*
S5	(((nil or nothing) n2 mouth) or nil-by-mouth)
S6	insensible loss*
S7	((swallow* or drink*) n2 (difficult* or problem* or unable))
S8	((fluid* or volume) n2 overload*)
S9	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8

D.1.3 Resuscitation population

Medline search terms

1	exp shock/
2	hypovolemia/
3	hypotension/
4	dehydration/
5	*fluid therapy/
6	((fluid* or volum*) adj3 (restor* or resuscita* or replac* or deplet* or deficien*)).ti,ab.
7	(fluid* adj3 (challenge or bolus)).ti,ab.
8	(hypotens* adj2 resuscit*).ti,ab.

9	((shock or resuscit* or hypotens* or dehydrate*) and fluid*).ti,ab.
10	(hypovol?emi* or sepsis syndrome* or circulatory failure*).ti,ab.
11	((circulatory or h?emodynamic) adj2 (failure* or insufficien* or abnormalit* or instability*)).ti,ab.
12	(shock or resuscit* or hypotens* or dehydrate*).ti.
13	exp perioperative care/
14	exp perioperative period/
15	((perioperativ* or intraoperativ* or postoperativ*) adj3 fluid*).ti,ab.
16	(volume adj2 (expand* or expansion* or substitut*)).ti,ab.
17	or/1-16

1 **Embase search terms**

1	exp *shock/
2	exp *hypovolemia/
3	exp *hypotension/
4	*dehydration/
5	fluid resuscitation/
6	*fluid therapy/
7	*fluid balance/
8	((fluid* or volum*) adj3 (restor* or resuscita* or replac* or deplet* or deficien*)).ti,ab.
9	(fluid* adj3 (challenge or bolus)).ti,ab.
10	(hypotens* adj2 resuscit*).ti,ab.
11	((shock or resuscit* or hypotens* or dehydrate*) and fluid*).ti,ab.
12	(hypovol?emi* or sepsis syndrome* or circulatory failure*).ti,ab.
13	((circulatory or h?emodynamic) adj2 (failure* or insufficien* or abnormalit* or instability*)).ti,ab.
14	(shock or resuscit* or hypotens* or dehydrate*).ti.
15	intraoperative period/ or perioperative period/ or postoperative period/ or preoperative period/
16	((perioperativ* or intraoperativ* or postoperativ*) adj3 fluid*).ti,ab.
17	(volume adj2 (expand* or expansion* or substitut*)).ti,ab.
18	or/1-17

2 **Cochrane search terms**

#1	MeSH descriptor Shock explode all trees
#2	MeSH descriptor Hypovolemia, this term only
#3	MeSH descriptor Hypotension, this term only
#4	MeSH descriptor Dehydration, this term only
#5	MeSH descriptor Fluid Therapy, this term only
#6	((fluid* or volum*) NEAR/3 (restor* or resuscita* or replac* or deplet* or deficien*)):ti,ab
#7	(fluid* NEAR/3 (challenge or bolus)):ti,ab
#8	(hypotens* NEAR/2 resuscit*):ti,ab
#9	((shock or resuscit* or hypotens* or dehydrate*) and fluid*):ti,ab
#10	(hypovol*emi* or sepsis syndrome* or circulatory failure*):ti,ab
#11	((circulatory or h*modynamic) NEAR/2 (failure* or insufficien* or abnormalit* or instability*)):ti,ab
#12	(shock or resuscit* or hypotens* or dehydrate*):ti

#13	MeSH descriptor Perioperative Care explode all trees
#14	MeSH descriptor Perioperative Period explode all trees
#15	((perioperativ* or intraoperativ* or postoperativ*) NEAR/3 fluid*):ti,ab
#16	(volume NEAR/2 (expand* or expansion* or substitut*)):ti,ab
#17	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16)

1 **CINAHL search terms**

S1	(MH "Shock+") OR (MH "Fluid Resuscitation") OR (MH "Hypervolemia Management (Iowa NIC)") OR (MH "Hypovolemia Management (Iowa NIC)") OR (MH "Hypotension") OR (MH "Altered Fluid Volume (NANDA) (Non-Cinahl)+") OR (MH "Dehydration")
S2	((fluid* or volum*) n3 (restor* or resuscita* or replac* or deplet* or deficien*))
S3	(fluid* n3 (challenge or bolus))
S4	(hypotens* n2 resuscit*)
S5	((shock or resuscit* or hypotens* or dehydrate*) and fluid*)
S6	(hypovolemi* or hypovolaemi* or sepsis syndrome* or circulatory failure*)
S7	((circulatory or hemodynamic or haemodynamic) n2 (failure* or insufficien* or abnormalit* or instability*))
S8	TI shock OR TI resuscit* OR TI hypotens* OR TI dehydrate*
S9	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8

2 ### D.1.4 Replacement population

3 **Medline search terms**

1	((fluid* or electrolyte*) adj2 loss*).ti,ab.
2	vomiting/
3	((vomit* or emesis) and (replace* or loss* or fluid* or electrolyte*)).ti,ab.
4	intubation, gastrointestinal/
5	(nasogastric adj2 (aspirat* or intubat*)).ti,ab.
6	exp intestinal obstruction/
7	((obstruct* or block*) adj3 (bowel* or intestin* or duoden* or jejun* or ileu* or ileal)).ti,ab.
8	duodenal neoplasms/ or ileal neoplasms/ or jejunal neoplasms/
9	((neoplasm* or cancer* or malignan*) adj3 (duoden* or jejun* or ileu* or ileal or (small adj (bowel* or intestin*)))).ti,ab.
10	jejunostomy/
11	jejunostom*.ti,ab.
12	intestinal fistula/
13	(fistula adj2 (intestin* or cholecystoduoden* or colovesical or enterocutaneous)).ti,ab.
14	drainage/
15	(drain* adj2 (postoperativ* or surgical)).ti,ab.
16	ileostomy/
17	ileostom*.ti,ab.
18	diarrhea/
19	(diarrhoea* or diarrhea*).ti,ab.
20	ureteral obstruction/
21	exp urethral obstruction/
22	polyuria/

23	exp diuresis/
24	((obstruct* or block*) adj3 (urin* or ureter* or urethr*)).ti,ab.
25	(polyuria* or hyperures* or diures* or natriures* or (urin* adj2 (excess* or loss*))).ti,ab.
26	or/1-25

1 **Embase search terms**

1	*vomiting/
2	((vomit* or emesis) and (replace* or loss* or fluid* or electrolyte*)).ti,ab.
3	gastric suction/
4	stomach intubation/
5	(nasogastric adj2 (aspirat* or intubat*)).ti,ab.
6	small intestine obstruction/
7	((obstruct* or block*) adj3 (bowel* or intestin* or duoden* or jejun* or ileu* or ileal)).ti,ab.
8	exp small intestine cancer/
9	((neoplasm* or cancer* or malignan*) adj3 (duoden* or jejun* or ileu* or ileal or (small adj (bowel* or intestin*)))).ti,ab.
10	*ileostomy/ or *jejunostomy/
11	jejunostom*.ti,ab.
12	Ileostom*.ti,ab.
13	intestine fistula/
14	(fistula adj2 (intestin* or cholecystoduoden* or colovesical or enterocutaneous)).ti,ab.
15	exp *surgical drainage/
16	(drain* adj2 (postoperativ* or surgical)).ti,ab.
17	exp *diarrhea/
18	(diarrhoea* or diarrhea*).ti,ab.
19	exp *urinary tract obstruction/
20	((obstruct* or block*) adj3 (urin* or ureter* or urethr*)).ti,ab.
21	polyuria/
22	exp *diuresis/
23	(polyuria* or hyperures* or diures* or natriures* or (urin* adj2 (excess* or loss*))).ti,ab.
24	((fluid* or electrolyte*) adj2 loss*).ti,ab.
25	or/1-24

2 **Cochrane search terms**

#1	MeSH descriptor Vomiting, this term only
#2	((vomit* or emesis) and (replace* or loss* or fluid* or electrolyte*)):ti,ab
#3	MeSH descriptor Intubation, Gastrointestinal, this term only
#4	(nasogastric NEAR/2 (aspirat* or intubat*)):ti,ab
#5	MeSH descriptor Intestinal Obstruction explode all trees
#6	((obstruct* or block*) NEAR/3 (bowel* or intestin* or duoden* or jejun* or ileu* or ileal)):ti,ab
#7	MeSH descriptor Duodenal Neoplasms, this term only
#8	MeSH descriptor Ileal Neoplasms, this term only
#9	MeSH descriptor Jejunal Neoplasms, this term only
#10	((neoplasm* or cancer* or malignan*) NEAR/3 (duoden* or jejun* or ileu* or ileal or (small NEXT (bowel* or intestin*)))):ti,ab
#11	MeSH descriptor Jejunostomy, this term only

#12	MeSH descriptor Ileostomy, this term only
#13	jejunostom*:ti,ab
#14	Ileostom*:ti,ab
#15	MeSH descriptor Intestinal Fistula, this term only
#16	(fistula NEAR/2 (intestin* or cholecystoduoden* or colovesical or enterocutaneous)):ti,ab
#17	MeSH descriptor Drainage, this term only
#18	(drain* NEAR/2 (postoperativ* or surgical)):ti,ab
#19	MeSH descriptor Diarrhea, this term only
#20	(diarrhoea* or diarrhea*):ti,ab
#21	MeSH descriptor Ureteral Obstruction, this term only
#22	MeSH descriptor Urethral Obstruction explode all trees
#23	MeSH descriptor Polyuria, this term only
#24	MeSH descriptor Diuresis explode all trees
#25	((obstruct* or block*) NEAR/3 (urin* or ureter* or urethr*)):ti,ab
#26	(polyuria* or hyperures* or diures* or natriures* or (urin* NEAR/2 (excess* or loss*))):ti,ab
#27	((fluid* or electrolyte*) NEAR/2 loss*):ti,ab
#28	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27)

D.2 Study filter search terms

D.2.1 Systematic review search terms

Medline search terms

1	meta-analysis/
2	meta-analysis as topic/
3	(meta analy* or metanaly* or metaanaly*).ti,ab.
4	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
5	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7	(search* adj4 literature).ab.
8	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9	cochrane.jw.
10	((indirect or mixed) adj2 comparison*).ti,ab.
11	or/1-10

Embase search terms

1	systematic review/
2	meta-analysis/
3	(meta analy* or metanaly* or metaanaly*).ti,ab.
4	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
5	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6	(search strategy or search criteria or systematic search or study selection or data extraction).ab.

7	(search* adj4 literature).ab.
8	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9	((pool* or combined) adj2 (data or trials or studies or results)).ab.
10	cochrane.jw.
11	((indirect or mixed) adj2 comparison*).ti,ab.
12	or/1-11

D.2.2 Randomised controlled studies (RCTs) search terms

Medline search terms

1	randomized controlled trial.pt.
2	controlled clinical trial.pt.
3	randomi#ed.ab.
4	placebo.ab.
5	randomly.ab.
6	Clinical Trials as topic.sh.
7	trial.ti.
8	or/1-7

Embase search terms

1	random*.ti,ab.
2	factorial*.ti,ab.
3	(crossover* or cross over*).ti,ab.
4	((doubl* or singl*) adj blind*).ti,ab.
5	(assign* or allocat* or volunteer* or placebo*).ti,ab.
6	crossover procedure/
7	single blind procedure/
8	randomized controlled trial/
9	double blind procedure/
10	or/1-9

D.2.3 Observational studies search terms

Medline search terms

1	epidemiologic studies/
2	exp case control studies/
3	exp cohort studies/
4	cross-sectional studies/
5	case control.ti,ab.
6	(cohort adj (study or studies or analys*)).ti,ab.
7	((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab.
8	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab.
9	or/1-8

Embase search terms

1	clinical study/
2	exp case control study/
3	family study/
4	longitudinal study/
5	retrospective study/
6	prospective study/
7	cross-sectional study/
8	cohort analysis/
9	follow-up/
10	cohort*.ti,ab.
11	9 and 10
12	case control.ti,ab.
13	(cohort adj (study or studies or analys*)).ti,ab.
14	((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab.
15	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab.
16	or/1-8,11-15

D.2.4 Health economic search terms

Medline search terms

1	economics/
2	value of life/
3	exp "costs and cost analysis"/
4	exp economics, hospital/
5	exp economics, medical/
6	economics, nursing/
7	economics, pharmaceutical/
8	exp "fees and charges"/
9	exp budgets/
10	budget*.ti,ab.
11	cost*.ti.
12	(economic* or pharmaco?economic*).ti.
13	(price* or pricing*).ti,ab.
14	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
15	(financ* or fee or fees).ti,ab.
16	(value adj2 (money or monetary)).ti,ab.
17	or/1-16

Embase search terms

1	*health economics/
2	exp *economic evaluation/
3	exp *health care cost/
4	exp *fee/
5	budget/
6	funding/

7	budget*.ti,ab.
8	cost*.ti.
9	(economic* or pharmaco?economic*).ti.
10	(price* or pricing*).ti,ab.
11	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
12	(financ* or fee or fees).ti,ab.
13	(value adj2 (money or monetary)).ti,ab.
14	or/1-13

D.2.5 Quality of life search terms

Medline search terms

1	quality-adjusted life years/
2	sickness impact profile/
3	(quality adj2 (wellbeing or well being)).ti,ab.
4	sickness impact profile.ti,ab.
5	disability adjusted life.ti,ab.
6	(qal* or qtime* or qwb* or daly*).ti,ab.
7	(euroqol* or eq5d* or eq 5*).ti,ab.
8	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
9	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
10	(hui or hui1 or hui2 or hui3).ti,ab.
11	(health* year* equivalent* or hye or hyes).ti,ab.
12	discrete choice*.ti,ab.
13	rosser.ti,ab.
14	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
15	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
16	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
17	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
18	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
19	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
20	or/1-19

Embase search terms

1	quality adjusted life year/
2	"quality of life index"/
3	short form 12/ or short form 20/ or short form 36/ or short form 8/
4	sickness impact profile/
5	(quality adj2 (wellbeing or well being)).ti,ab.
6	sickness impact profile.ti,ab.
7	disability adjusted life.ti,ab.
8	(qal* or qtime* or qwb* or daly*).ti,ab.
9	(euroqol* or eq5d* or eq 5*).ti,ab.
10	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
11	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
12	(hui or hui1 or hui2 or hui3).ti,ab.

13	(health* year* equivalent* or hye or hyes).ti,ab.
14	discrete choice*.ti,ab.
15	rosser.ti,ab.
16	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
17	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
18	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
19	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
20	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
21	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
22	or/1-21

D.2.6 Excluded study designs and publication types

The following study designs and publication types were removed from retrieved results using the NOT operator.

Medline search terms

1	letter/
2	editorial/
3	news/
4	exp historical article/
5	anecdotes as topic/
6	comment/
7	case report/
8	(letter or comment*).ti.
9	or/1-8
10	randomized controlled trial/ or random*.ti,ab.
11	9 not 10
12	animals/ not humans/
13	animals, laboratory/
14	exp animal experiment/
15	exp animal model/
16	exp rodentia/
17	(rat or rats or mouse or mice).ti.
18	or/11-17

Embase search terms

1	letter.pt. or letter/
2	note.pt.
3	editorial.pt.
4	case report/ or case study/
5	(letter or comment*).ti.
6	or/1-5
7	randomized controlled trial/ or random*.ti,ab.
8	6 not 7
9	animal/ not human/
10	nonhuman/

11	exp animal experiment/
12	exp experimental animal/
13	animal model/
14	exp rodent/
15	(rat or rats or mouse or mice).ti.
16	or/8-15

Cinahl search terms

S1	PT anecdote or PT audiovisual or PT bibliography or PT biography or PT book or PT book review or PT brief item or PT cartoon or PT commentary or PT computer program or PT editorial or PT games or PT glossary or PT historical material or PT interview or PT letter or PT listservs or PT masters thesis or PT obituary or PT pamphlet or PT pamphlet chapter or PT pictorial or PT poetry or PT proceedings or PT "questions and answers" or PT response or PT software or PT teaching materials or PT website

D.3 Searches by specific questions

D.3.1 Algorithms

What is the clinical and cost effectiveness of clinical algorithms or defined protocols for the assessment, monitoring and/or management of intravenous fluid and electrolyte requirement in hospitalised adult patients?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Fluid therapy	Algorithms		Exclusions SRs RCTs	No date restriction. Search run up to 12 March 2013.

Algorithms search terms

Medline search terms

1	algorithms/
2	clinical protocols/
3	critical pathways/
4	algorithm*.ti,ab.
5	((protocol* or path* or plan*) adj3 (patient* or treat* or clinical* or fluid* or critical*)).ti,ab.
6	(goal* adj1 direct*).ti,ab.
7	or/1-6

Embase search terms

1	exp algorithm/
2	clinical protocol/
3	clinical pathway/
4	algorithm*.ti,ab.
5	((protocol* or path* or plan*) adj3 (patient* or treat* or clinical* or fluid* or critical*)).ti,ab.
6	(goal* adj1 direct*).ti,ab.
7	or/1-6

Cochrane search terms

#1	MeSH descriptor Algorithms, this term only
#2	MeSH descriptor Clinical Protocols, this term only
#3	MeSH descriptor Critical Pathways, this term only
#4	algorithm*:ti,ab
#5	((protocol* or path* or plan*) NEAR/3 (patient* or treat* or clinical* or fluid* or critical*)):ti,ab
#6	(goal* NEAR direct*):ti,ab
#7	(#1 OR #2 OR #3 OR #4 OR #5 OR #6)

CINAHL search terms

S1	(MH "Algorithms") OR (MH "Decision Trees")
S2	(MH "Protocols+")
S3	algorithm* OR protocol* n3 patient* OR protocol* n3 treat* OR protocol* n3 clinical* OR protocol* n3 fluid* OR protocol* n3 critical* OR path* n3 patient* OR path* n3 treat* OR path* n3 clinical* OR path* n3 fluid* OR path* n3 critical* OR goal* n1 direct*
S4	S1 or S2 or S3

D.3.2 Body weight

In people in hospital receiving IV fluids, what is the clinical and cost effectiveness for measuring and recording serial body weight?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Fluid therapy OR renal insufficiency, heart failure	Body weight		Exclusions SRs RCTs Observational	No date restriction. Search run up to 12 March 2013.

Renal insufficiency, heart failure search terms

Medline search terms

1	exp renal insufficiency/
2	((kidney or renal) adj (failure* or injur* or insufficien* or dysfunction* or impair*)).ti,ab.
3	exp heart failure/
4	((heart or myocardial) adj2 (failure* or decompensat*)).ti,ab.
5	or/1-4
6	(water* or fluid* or volume or hydrat*).ti,ab.
7	5 and 6

Embase search terms

1	*kidney failure/ or *chronic kidney failure/
2	((kidney or renal) adj (failure* or injur* or insufficien* or dysfunction* or impair*)).ti,ab.
3	exp *heart failure/
4	((heart or myocardial) adj2 (failure* or decompensat*)).ti,ab.
5	or/1-4
6	(water* or fluid* or volume or hydrat*).ti,ab.
7	5 and 6

1 **Cochrane search terms**

#1	MeSH descriptor Renal Insufficiency explode all trees
#2	((kidney or renal) NEAR (failure* or injur* or insufficien* or dysfunction* or impair*)):ti,ab
#3	MeSH descriptor Heart Failure explode all trees
#4	((heart or myocardial) NEAR/2 (failure* or decompensat*)):ti,ab
#5	(#1 OR #2 OR #3 OR #4)
#6	(water* or fluid* or volume or hydrat*):ti,ab
#7	(#5 AND #6)

2 **CINAHL search terms**

S1	(MH "Renal Insufficiency+")
S2	((kidney or renal) n1 (failure* or injur* or insufficien* or dysfunction* or impair*))
S3	(MH "Heart Failure+")
S4	((heart or myocardial) n2 (failure* or decompensat*))
S5	S1 or S2 or S3 or S4
S6	(water* or fluid* or volume or hydrat*)
S7	S5 and S6

3 **Body weight search terms**

4 **Medline search terms**

1	body weight/
2	body weight changes/
3	(weigh* adj3 (body or measure* or daily or lean or change* or week* or day or serial)).ti,ab.
4	or/1-3

5 **Embase search terms**

1	*body weight/ or *lean body weight/ or *weight change/ or *weight fluctuation/ or *weight gain/ or *weight reduction/
2	(weigh* adj3 (body or measure* or daily or lean or change* or week* or day or serial)).ti,ab.
3	or/1-2

6 **Cochrane search terms**

#1	MeSH descriptor Body Weight, this term only
#2	MeSH descriptor Body Weight Changes explode all trees
#3	(weigh* NEAR/3 (body or measure* or daily or lean or change* or week* or day or serial)):ti,ab
#4	(#1 OR #2 OR #3)

7 **CINAHL search terms**

S1	(MH "Body Weight") OR (MH "Weight Gain") OR (MH "Weight Loss") OR (MH "Body Weights and Measures+")
S2	(MH "Body Weight Changes")
S3	(weigh* n3 (body or measure* or daily or lean or change* or week* or day or serial))
S4	S1 or S2 or S3

D.3.3 Urinary output

In people in hospital receiving intravenous fluids, what is the clinical and cost effectiveness of measuring and recording urine output in addition to recording standard parameters stated in NEWS to determine the need for intravenous fluid administration?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Resuscitation OR routine maintenance	Urinary output		Exclusions SRs RCTs Observational	No date restriction. Search run up to 12 March 2013.

Urinary output search terms

Medline search terms

1	*urodynamics/
2	*urination/
3	*urine/
4	(urin* adj3 (output* or volume* or record* or measur* or level* or amount* or monit* or protocol*)).ti,ab.
5	or/1-4

Embase search terms

1	urine volume/
2	*micturition/
3	(urin* adj3 (output* or volume* or record* or measur* or level* or amount* or monit* or protocol*)).ti,ab.
4	or/1-3

Cochrane search terms

#1	MeSH descriptor Urodynamics, this term only
#2	MeSH descriptor Urination, this term only
#3	MeSH descriptor Urine, this term only
#4	(urin* NEAR/3 (output* or volume* or record* or measur* or level* or amount* or monit* or protocol*)):ti,ab
#5	(#1 OR #2 OR #3 OR #4)

CINAHL search terms

S1	(MH "24-hour Urine Collection") OR (MH "Fluid Intake-Output Measures") OR (MM "Urination") OR (MM "Urine")
S2	(urin* n3 (output* or volume* or record* or measur* or level* or amount* or monit* or protocol*))
S3	S1 or S2

D.3.4 Serum chloride

In people in hospital who are receiving intravenous fluids, what is the incidence and clinical significance of hyperchloraemia or hypochloraemia?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Fluid therapy OR fluids	Hyperchloraemia/ hypochloraemia		Exclusions	No date restriction. Search run up to 12 March 2013.

1 **Fluids search terms**

2 **Medline search terms**

1	albumins/ or exp serum albumin/
2	hetastarch/
3	colloids/
4	dextrans/
5	exp hypertonic solutions/
6	exp plasma substitutes/
7	sodium bicarbonate/
8	potassium chloride/ or sodium chloride/
9	isotonic solutions/ or rehydration solutions/
10	(sodium or salin* or hartman* or ringer* or glucose or lactate* or acetate*).ti,ab.
11	(crystalloid* or isotonic).ti,ab.
12	(dextrose or potassium or bicarbonate).ti,ab.
13	(dextran or rescueflow).ti,ab.
14	(colloid* or hemaccel* or haemaccel* or hydrocolloid*).ti,ab.
15	(hypertonic or hyperhaes or hypotonic).ti,ab.
16	(albumin* or albumen* or albunorm or octalbin or zenalb or flexbumin).ti,ab.
17	((balanced or physiologic*) adj (fluid* or solution*)).ti,ab.
18	(gelatin* or gelofusin* or geloplasma or geloflex or gelo or isoplex or volplex).ti,ab.
19	(starch* or hetastarch* or pentastarch* or pentaspan* or haes-steril or hemohes or hespan or elohaes or hexastarch* or tetrastarch* or tetraspan or venofundin or volulyte or voluven).ti,ab.
20	(plasmalyte or albutein or (plasma adj1 substitut*)).ti,ab.
21	or/1-20

3 **Embase search terms**

1	albumin/
2	exp albuminoid/
3	plasma substitute/ or dextran/ or dextran 40/ or dextran 60/ or dextran 70/ or gelatin succinate/ or gelatinol/ or hetastarch/
4	exp colloid/
5	hypertonic solution/
6	bicarbonate/
7	sodium chloride/
8	potassium chloride/
9	isotonic solution/
10	crystalloid/
11	(sodium or salin* or hartman* or ringer* or glucose or lactate* or acetate*).ti,ab.
12	(crystalloid* or isotonic).ti,ab.

13	(dextrose or potassium or bicarbonate).ti,ab.
14	(dextran or rescueflow).ti,ab.
15	(colloid* or hemaccel* or haemaccel* or hydrocolloid*).ti,ab.
16	(hypertonic or hyperhaes or hypotonic).ti,ab.
17	((balanced or physiologic*) adj (fluid* or solution*)).ti,ab.
18	(albumin* or albumen* or albunorm or octalbin or zenalb or flexbumin).ti,ab.
19	(plasmalyte or albutein or (plasma adj1 substitut*)).ti,ab.
20	(gelatin* or gelofusin* or geloplasma or geloflex or gelo or isoplex or volplex).ti,ab.
21	(starch* or hetastarch* or pentastarch* or pentaspan* or haes-steril or hemohes or hespan or elohaes or hexastarch* or tetrastarch* or tetraspan or venofundin or volulyte or voluven).ti,ab.
22	or/1-21

Cochrane search terms

#1	MeSH descriptor Albumins, this term only
#2	MeSH descriptor Serum Albumin explode all trees
#3	MeSH descriptor Hetastarch, this term only
#4	MeSH descriptor Colloids, this term only
#5	MeSH descriptor Dextrans, this term only
#6	MeSH descriptor Hypertonic Solutions explode all trees
#7	MeSH descriptor Plasma Substitutes explode all trees
#8	MeSH descriptor Sodium Bicarbonate, this term only
#9	MeSH descriptor Potassium Chloride, this term only
#10	MeSH descriptor Sodium Chloride, this term only
#11	MeSH descriptor Isotonic Solutions, this term only
#12	MeSH descriptor Rehydration Solutions, this term only
#13	(sodium or salin* or hartman* or ringer* or glucose or lactate* or acetate*):ti,ab
#14	(crystalloid* or isotonic):ti,ab
#15	(dextrose or potassium or bicarbonate):ti,ab
#16	(dextran or rescueflow):ti,ab
#17	(colloid* or hemaccel* or haemaccel* or hydrocolloid*):ti,ab
#18	(hypertonic or hyperhaes or hypotonic):ti,ab
#19	(albumin* or albumen* or albunorm or octalbin or zenalb or flexbumin):ti,ab
#20	((balanced or physiologic*) NEAR (fluid* or solution*)):ti,ab
#21	(gelatin* or gelofusin* or geloplasma or geloflex or gelo or isoplex or volplex):ti,ab
#22	(starch* or hetastarch* or pentastarch* or pentaspan* or haes-steril or hemohes or hespan or elohaes or hexastarch* or tetrastarch* or tetraspan or venofundin or volulyte or voluven):ti,ab
#23	(plasmalyte or albutein or (plasma NEAR substitut*)):ti,ab
#24	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23)

<u>Hyperchloraemia/hypochloraemia search terms</u>

Medline search terms

1	(hyperchlor?emi* or hypochlor?emi*).ti,ab.

Embase search terms

1	(hyperchlor?emi* or hypochlor?emi*).ti,ab.

2	hyperchloremia/
3	hypochloremia/
4	or/1-3

Cochrane search terms

#1	(hyperchlor*mi* or hypochlor*mi*):ti,ab

D.3.5 Routine maintenance: fluid type

What is the most clinical and cost effective fluid to be used for intravenous fluid therapy for routine maintenance in hospitalised patients?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Routine maintenance	Maintenance fluids		Exclusions SRs RCTs Observational	No date restriction. Search run up to 12 March 2013.

Maintenance fluids search terms

Medline search terms

1	dextrans/
2	exp hypertonic solutions/
3	sodium bicarbonate/
4	sodium chloride/
5	isotonic solutions/ or rehydration solutions/
6	(sodium or salin* or hartman* or ringer* or lactate* or acetate* or plasmalyte).ti,ab.
7	(crystalloid* or isotonic).ti,ab.
8	(dextrose or bicarbonate).ti,ab.
9	(dextran or rescueflow).ti,ab.
10	(hypertonic or hypotonic).ti,ab.
11	((balanced or physiologic*) adj (fluid* or solution*)).ti,ab.
12	or/1-11

Embase search terms

1	hypertonic solution/
2	*bicarbonate/
3	*sodium chloride/
4	isotonic solution/
5	crystalloid/
6	(sodium or salin* or hartman* or ringer* or lactate* or acetate* or plasmalyte).ti,ab.
7	(crystalloid* or isotonic).ti,ab.
8	(dextrose or bicarbonate).ti,ab.
9	(dextran or rescueflow).ti,ab.
10	(hypertonic or hypotonic).ti,ab.
11	((balanced or physiologic*) adj (fluid* or solution*)).ti,ab.
12	or/1-11

Cochrane search terms

#1	MeSH descriptor Dextrans, this term only
#2	MeSH descriptor Hypertonic Solutions explode all trees
#3	MeSH descriptor Sodium Bicarbonate, this term only
#4	MeSH descriptor Sodium Chloride, this term only
#5	MeSH descriptor Isotonic Solutions, this term only
#6	MeSH descriptor Rehydration Solutions, this term only
#7	(sodium or salin* or hartman* or ringer* or lactate* or acetate* or plasmalyte):ti,ab
#8	(crystalloid* or isotonic):ti,ab
#9	(dextrose or bicarbonate):ti,ab
#10	(dextran or rescueflow):ti,ab
#11	(hypertonic or hypotonic):ti,ab
#12	((balanced or physiologic*) NEXT (fluid* or solution*)):ti,ab
#13	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12)

D.3.6 Fluid volume and timing

Searches for the following four questions were run as one search:

What is clinical and cost effectiveness of different volumes of fluid administration in patients requiring intravenous fluids for routine maintenance?

What are the most clinical and cost effective timings of administration of intravenous fluids in patients requiring intravenous fluids for routine maintenance?

What is clinical and cost effectiveness of different volumes of fluid administration in patients requiring fluid resuscitation?

What are the most clinically and cost effective timings and rate of administration of IV fluids in fluid resuscitation?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Resuscitation OR routine maintenance	Volume, timing		Exclusions SRs RCTs Observational (Observational filter used with resuscitation population only)	No date restriction. Search run up to 12 March 2013.

<u>Volume, timing search terms</u>

Medline search terms

1	time factors/
2	((rapid or fast* or slow*) adj3 (infus* or administ* or fluid* or volume)).ti,ab.
3	((small* or large* or high* or low*) adj3 volume).ti,ab.
4	((restrict* or conservativ* or liberal*) adj2 (fluid* or regime* or protocol* or intake*)).ti,ab.
5	((timing or delayed or intermediate or early or selective or rapid or immediate*) adj3 (fluid* or therap* or intravenous* or iv)).ti,ab.

6	or/1-5

Embase search terms

1	*time factors/
2	infusion rate/
3	((rapid or fast* or slow*) adj3 (infus* or administ* or fluid* or volume)).ti,ab.
4	((small* or large* or high* or low*) adj3 volume).ti,ab.
5	((restrict* or conservativ* or liberal*) adj2 (fluid* or regime* or protocol* or intake*)).ti,ab.
6	((timing or delayed or intermediate or early or selective or rapid or immediate*) adj3 (fluid* or therap* or intravenous* or iv)).ti,ab.
7	or/1-6

Cochrane search terms

#1	MeSH descriptor Time Factors, this term only
#2	((rapid or fast* or slow*) NEAR/3 (infus* or administ* or fluid* or volume)):ti,ab
#3	((small* or large* or high* or low*) NEAR/3 volume):ti,ab
#4	((restrict* or conservativ* or liberal*) NEAR/2 (fluid* or regime* or protocol* or intake*)):ti,ab
#5	((timing or delayed or intermediate or early or selective or rapid or immediate*) NEAR/3 (fluid* or therap* or intravenous* or iv)):ti,ab
#6	(#1 OR #2 OR #3 OR #4 OR #5)

D.3.7 Resuscitation: fluid type

What is the most clinically and cost effective fluid for intravenous fluid resuscitation of hospitalised patients?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Resuscitation	Resuscitation fluids		Exclusions SRs RCTs	No date restriction. Search run up to 12 March 2013.

Resuscitation fluids search terms

Medline search terms

1	albumins/ or exp serum albumin/
2	hetastarch/
3	colloids/
4	dextrans/
5	exp hypertonic solutions/
6	exp plasma substitutes/
7	sodium bicarbonate/
8	potassium chloride/ or sodium chloride/
9	isotonic solutions/ or rehydration solutions/
10	(sodium or salin* or hartman* or ringer* or glucose or lactate* or acetate*).ti,ab.
11	(crystalloid* or isotonic).ti,ab.
12	(dextrose or potassium or bicarbonate).ti,ab.
13	(albumin* or albumen* or albunorm or octalbin or zenalb or flexbumin).ti,ab.

14	(dextran or rescueflow).ti,ab.
15	(gelatin* or gelofusin* or geloplasma or geloflex or gelo or isoplex or volplex).ti,ab.
16	(starch* or hetastarch* or pentastarch* or pentaspan* or haes-steril or hemohes or hespan or elohaes or hexastarch* or tetrastarch* or tetraspan or venofundin or volulyte or voluven).ti,ab.
17	(colloid* or hemaccel* or haemaccel* or hydrocolloid*).ti,ab.
18	(hypertonic or hyperhaes or hypotonic).ti,ab.
19	((balanced or physiologic*) adj (fluid* or solution*)).ti,ab.
20	(plasmalyte or albutein or (plasma adj1 substitut*)).ti,ab.
21	or/1-20

1 **Embase search terms**

1	albumin/
2	exp albuminoid/
3	plasma substitute/ or dextran/ or dextran 40/ or dextran 60/ or dextran 70/ or gelatin succinate/ or gelatinol/ or hetastarch/
4	exp colloid/
5	hypertonic solution/
6	bicarbonate/
7	sodium chloride/
8	potassium chloride/
9	isotonic solution/
10	crystalloid/
11	(sodium or salin* or hartman* or ringer* or glucose or lactate* or acetate*).ti,ab.
12	(crystalloid* or isotonic).ti,ab.
13	(dextrose or potassium or bicarbonate).ti,ab.
14	(albumin* or albumen* or albunorm or octalbin or zenalb or flexbumin).ti,ab.
15	(dextran or rescueflow).ti,ab.
16	(gelatin* or gelofusin* or geloplasma or geloflex or gelo or isoplex or volplex).ti,ab.
17	(starch* or hetastarch* or pentastarch* or pentaspan* or haes-steril or hemohes or hespan or elohaes or hexastarch* or tetrastarch* or tetraspan or venofundin or volulyte or voluven).ti,ab.
18	(colloid* or hemaccel* or haemaccel* or hydrocolloid*).ti,ab.
19	(hypertonic or hyperhaes or hypotonic).ti,ab.
20	((balanced or physiologic*) adj (fluid* or solution*)).ti,ab.
21	(plasmalyte or albutein or (plasma adj1 substitut*)).ti,ab.
22	or/1-21

2 **Cochrane search terms**

#1	MeSH descriptor Albumins, this term only
#2	MeSH descriptor Serum Albumin explode all trees
#3	MeSH descriptor Hetastarch, this term only
#4	MeSH descriptor Colloids, this term only
#5	MeSH descriptor Dextrans, this term only
#6	MeSH descriptor Hypertonic Solutions explode all trees
#7	MeSH descriptor Plasma Substitutes explode all trees
#8	MeSH descriptor Sodium Bicarbonate, this term only

#9	MeSH descriptor Potassium Chloride, this term only
#10	MeSH descriptor Sodium Chloride, this term only
#11	MeSH descriptor Isotonic Solutions, this term only
#12	MeSH descriptor Rehydration Solutions, this term only
#13	(sodium or salin* or hartman* or ringer* or glucose or lactate* or acetate*):ti,ab
#14	(crystalloid* or isotonic):ti,ab
#15	(dextrose or potassium or bicarbonate):ti,ab
#16	(albumin* or albumen* or albunorm or octalbin or zenalb or flexbumin):ti,ab
#17	(dextran or rescueflow):ti,ab
#18	(gelatin* or gelofusin* or geloplasma or geloflex or gelo or isoplex or volplex):ti,ab
#19	(starch* or hetastarch* or pentastarch* or pentaspan* or haes-steril or hemohes or hespan or elohaes or hexastarch* or tetrastarch* or tetraspan or venofundin or volulyte or voluven):ti,ab
#20	(colloid* or hemaccel* or haemaccel* or hydrocolloid*):ti,ab
#21	(hypertonic or hyperhaes or hypotonic):ti,ab
#22	((balanced or physiologic*) NEAR (fluid* or solution*)):ti,ab
#23	(plasmalyte or albutein or (plasma NEAR substitut*)):ti,ab
#24	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23)

D.3.8 Replacement: fluid type

What is the most clinical and cost effective fluid for intravenous fluid replacement in hospitalised patients?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Replacement	Replacement fluids		Exclusions SRs RCTs Observational	No date restriction. Search run up to 12 March 2013.

Replacement fluids search terms

Medline search terms

1	dextrans/
2	exp hypertonic solutions/
3	sodium chloride/
4	isotonic solutions/ or rehydration solutions/
5	(sodium chloride or salin* or hartman* or ringer* or lactate* or acetate* or plasmalyte).ti,ab.
6	(crystalloid* or isotonic).ti,ab.
7	(dextran or dextrose or rescueflow).ti,ab.
8	(hypertonic or hypotonic).ti,ab.
9	((balanced or physiologic*) adj (fluid* or solution*)).ti,ab.
10	or/1-9
11	exp *analgesics/ or exp *anesthesia/ or exp *anesthetics/
12	10 not 11

Embase search terms

1	hypertonic solution/
2	*sodium chloride/
3	isotonic solution/
4	crystalloid/
5	(sodium chloride or salin* or hartman* or ringer* or lactate* or acetate* or plasmalyte).ti,ab.
6	(crystalloid* or isotonic).ti,ab.
7	(dextran or dextrose or RescueFlow).ti,ab.
8	(hypertonic or hypotonic).ti,ab.
9	((balanced or physiologic*) adj (fluid* or solution*)).ti,ab.
10	or/1-9
11	exp *analgesic agent/
12	exp *anesthetic agent/
13	exp *anesthesia/
14	or/11-13
15	10 not 14

Cochrane search terms

#1	MeSH descriptor Dextrans, this term only
#2	MeSH descriptor Hypertonic Solutions explode all trees
#3	MeSH descriptor Sodium Chloride, this term only
#4	MeSH descriptor Isotonic Solutions, this term only
#5	MeSH descriptor Rehydration Solutions, this term only
#6	(sodium chloride or salin* or hartman* or ringer* or lactate* or acetate* or plasmalyte):ti,ab
#7	(crystalloid* or isotonic):ti,ab
#8	(dextran or dextrose or RescueFlow):ti,ab
#9	(hypertonic or hypotonic):ti,ab
#10	((balanced or physiologic*) NEAR (fluid* or solution*)):ti,ab
#11	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10)

D.3.9 Replacement: volume and timing

Searches for the following two questions were run as one search:

What is clinical and cost effectiveness of different volumes of fluid administration in patients requiring fluid replacement for ongoing losses?

What are the most clinical and cost effective timings for the administration of IV fluid replacement for ongoing losses?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Replacement	Volume, timing		Exclusions SRs RCTs Observational	No date restriction. Search run up to 12 March 2013.

Volume, timing search terms

Medline search terms

1	time factors/
2	fluid therapy/
3	1 and 2
4	((rapid or fast* or slow*) adj3 (infus* or administ* or fluid* or volume)).ti,ab.
5	((small* or large* or high* or low*) adj3 volume).ti,ab.
6	((restrict* or conservativ* or liberal*) adj2 (fluid* or regime* or protocol* or intake*)).ti,ab.
7	((timing or delayed or intermediate or early or selective or rapid or immediate*) adj3 (fluid* or therap* or intravenous* or iv)).ti,ab.
8	or/3-7

Embase search terms

1	fluid therapy/
2	fluid balance/
3	or/1-2
4	time factors/
5	3 and 4
6	infusion rate/
7	((rapid or fast* or slow*) adj3 (infus* or administ* or fluid* or volume)).ti,ab.
8	((small* or large* or high* or low*) adj3 volume).ti,ab.
9	((restrict* or conservativ* or liberal*) adj2 (fluid* or regime* or protocol* or intake*)).ti,ab.
10	((timing or delayed or intermediate or early or selective or rapid or immediate*) adj3 (fluid* or therap* or intravenous* or iv)).ti,ab.
11	or/5-10

Cochrane search terms

#1	MeSH descriptor Time Factors, this term only
#2	MeSH descriptor Fluid Therapy, this term only
#3	(#1 AND #2)
#4	((rapid or fast* or slow*) NEAR/3 (infus* or administ* or fluid* or volume)):ti,ab
#5	((small* or large* or high* or low*) NEAR/3 volume):ti,ab
#6	((restrict* or conservativ* or liberal*) NEAR/2 (fluid* or regime* or protocol* or intake*)):ti,ab
#7	((timing or delayed or intermediate or early or selective or rapid or immediate*) NEAR/3 (fluid* or therap* or intravenous* or iv)):ti,ab
#8	(#3 OR #4 OR #5 OR #6 OR #7)

D.3.10 Training and education

What are the barriers faced by healthcare professionals in the effective prescription and monitoring of intravenous fluids in hospital settings?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Fluid therapy	Training		Exclusions SRs RCTs Observational	No date restriction. Search run up to 12 March 2013.

1 **Training search terms**

2 **Medline search terms**

1	clinical competence/
2	exp *education/
3	health knowledge, attitudes, practice/
4	physician's practice patterns/
5	ed.fs.
6	professional practice/
7	*medication errors/
8	*medical staff, hospital/
9	(train* or educat* or teach*).ti,ab.
10	(profession* adj2 develop*).ti,ab.
11	(barrier* or knowledge or attitude*).ti,ab.
12	(perception* or opinion* or ignoran* or unaware or responsibilit*).ti,ab.
13	((core or clinical) adj2 skill*).ti,ab.
14	(prescri* adj2 (protocol* or practice*)).ti,ab.
15	staff.ti,ab.
16	audit*.ti,ab.
17	or/1-16

3 **Embase search terms**

1	competence/ or clinical competence/ or professional competence/
2	exp *education/
3	*clinical practice/
4	exp *professional practice/
5	*medication error/
6	*medical staff/
7	(train* or educat* or teach*).ti,ab.
8	(profession* adj2 develop*).ti,ab.
9	(barrier* or knowledge or attitude*).ti,ab.
10	(perception* or opinion* or ignoran* or unaware or responsibilit*).ti,ab.
11	((core or clinical) adj2 skill*).ti,ab.
12	(prescri* adj2 (protocol* or practice*)).ti,ab.
13	staff.ti,ab.
14	audit*.ti,ab.
15	or/1-14

4 **Cochrane search terms**

#1	MeSH descriptor Clinical Competence, this term only
#2	MeSH descriptor Education explode all trees
#3	MeSH descriptor Health Knowledge, Attitudes, Practice, this term only
#4	MeSH descriptor Physician's Practice Patterns, this term only
#5	Any MeSH descriptor with qualifier: ED
#6	MeSH descriptor Professional Practice, this term only
#7	MeSH descriptor Medication Errors, this term only
#8	MeSH descriptor Medical Staff, Hospital, this term only

#9	(train* or educat* or teach*):ti,ab
#10	(profession* NEAR/2 develop*):ti,ab
#11	(barrier* or knowledge or attitude*):ti,ab
#12	(perception* or opinion* or ignoran* or unaware or responsibilit*):ti,ab
#13	((core or clinical) NEAR/2 skill*):ti,ab
#14	(prescri* NEAR/2 (protocol* or practice*)):ti,ab
#15	staff:ti,ab
#16	audit*:ti,ab
#17	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16)

CINAHL search terms

S1	(MM "Education+") OR (MH "Professional Competence") OR (MH "Clinical Competence") OR (MM "Health Knowledge and Behavior (Iowa NOC) (Non-Cinahl)+") OR (MM "Practice Patterns") OR (MM "Professional Practice")
S2	MW ed
S3	(MH "Medication Errors") OR (MM "Medical Staff, Hospital")
S4	train* OR educat* OR teach*
S5	profession* n2 develop* OR barrier* OR knowledge OR attitude*
S6	perception* OR opinion* OR ignoran* OR unaware OR responsibilit*
S7	core n2 skill* OR clinical n2 skill* OR prescri* n2 protocol* OR prescri* n2 practice* OR TI staff OR AB staff OR audit
S8	S1 or S2 or S3 or S4 or S5 or S6 or S7

PsychInfo search terms

1	exp competence/
2	exp *education/
3	*health knowledge/
4	*clinical practice/
5	exp *medical personnel/
6	(train* or educat* or teach*).ti,ab.
7	(profession* adj2 develop*).ti,ab.
8	(barrier* or knowledge or attitude*).ti,ab.
9	(perception* or opinion* or ignoran* or unaware or responsibilit*).ti,ab.
10	((core or clinical) adj2 skill*).ti,ab.
11	(prescri* adj2 (protocol* or practice*)).ti,ab.
12	Staff.ti,ab.
13	Audit*.ti,ab.
14	or/1-13

D.4 Economics search

D.4.1 Economic searches

Economic searches were conducted in Medline, Embase, HEED and CRD for NHS EED and HTA.

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Fluid therapy			Economic	No date

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
				restriction. Search run up to 12 March 2013.

1 **CRD search terms**

#1	MeSH Fluid Therapy EXPLODE 1
#2	MeSH Isotonic Solutions
#3	MeSH Rehydration Solutions
#4	MeSH Water-Electrolyte Balance
#5	MeSH Water-Electrolyte Imbalance EXPLODE 1
#6	(water NEAR balance*) OR (water NEAR imbalance*) OR (electrolyte* NEAR balance*) OR (electrolyte* NEAR imbalance*) OR osmoregulation*
#7	(fluid* NEAR replace*) OR (fluid* NEAR therap*) OR (fluid* NEAR substitut*) OR (fluid* NEAR restorat*) OR (fluid* NEAR resuscitat*)
#8	(fluid* NEAR perfusion) OR (fluid* NEAR volume) OR (fluid* NEAR balance*) OR (fluid* NEAR imbalance*)
#9	rehydrat*
#10	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9

2 **HEED search terms**

1	AX=fluid* AND (replace* OR therap* OR substitut* OR restorat* OR resuscitat* OR perfusion OR volume OR prescri* OR load* OR overload* OR monit* OR assess* OR document* OR chart* OR challenge)
2	AX=(water or electrolyte* or fluid*) AND (balance* or imbalance*)
3	AX=osmoregulation* OR rehydrat* OR isotonic*
4	CS=1 OR 2 OR 3

3 Economic searches were conducted in Medline, Embase, HEED and CRD for NHS EED and HTA.

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Resuscitation			Economic	No date restriction. Search run up to 12 March 2013.

4 **CRD search terms**

#1	MeSH DESCRIPTOR shock EXPLODE ALL TREES WITH QUALIFIER undefined
#2	MeSH DESCRIPTOR Hypovolemia WITH QUALIFIER undefined
#3	MeSH DESCRIPTOR Hypotension WITH QUALIFIER undefined
#4	MeSH DESCRIPTOR Dehydration WITH QUALIFIER undefined
#5	MeSH DESCRIPTOR fluid therapy WITH QUALIFIER undefined
#6	(fluid* NEAR restor*) OR (fluid* NEAR resuscita*) OR (fluid* NEAR replac*):AU OR (fluid* NEAR deplet*) OR (fluid* NEAR deficien*)
#7	(volume* NEAR restor*) OR (volume* NEAR resuscita*) OR (volume* NEAR replac*):AU OR (volume* NEAR deplet*) OR (volume* NEAR deficien*)
#8	(fluid* NEAR challenge) OR (fluid* NEAR bolus) OR (hypotens* NEAR resuscit*):AU OR (hypovol?emi* or sepsis syndrome* or circulatory failure*)
#9	(shock or resuscit* or hypotens* or dehydrate*) AND (fluid*)

#10	(circulatory NEAR failure*) OR (circulatory NEAR insufficien*) OR (circulatory NEAR abnormalit*):AU OR (circulatory NEAR instability*)
#11	(h?emodynamic NEAR failure*) OR (h?emodynamic NEAR insufficien*) OR (h?emodynamic NEAR abnormalit*):AU OR (h?emodynamic NEAR instability*)
#12	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11

HEED search terms

1	AX=(fluid* OR volume*) AND (restor* OR resuscita* OR replac* OR deplet* OR deficien*)
2	AX=fluid* AND (challenge or bolus)
3	AX=hypotens* AND resuscit*
4	AX=fluid* AND (shock OR resuscit* OR hypotens* OR dehydrate*)
5	AX=hypovolemi* OR hypovolaemi* OR 'sepsis syndrome' OR 'circulatory failure'
6	AX=(circulatory OR hemodynamic OR haemodynamic) AND (failure* OR insufficien* OR abnormalit* OR instability*)
7	CS=1 OR 2 OR 3 OR 4 OR 5 OR 6

D.4.2 Quality of life searches

Quality of life searches were conducted in Medline and Embase.

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Fluid therapy			Quality of life	No date restriction. Search run up to 12 March 2013.

Appendix E: Clinical evidence tables

E.1 Principles and protocols for intravenous fluid therapy

Study details	Patients	Interventions	Outcomes	Effect Sizes	Comments
Benes et al. 2010 [24] **Comparison:** Protocol using monitoring of patients fluid status vs no protocol **Country of study:** Czech republic **Setting:** Department of anaesthiology and intensive care medicine. **Study**	**Patient group:** High risk patients scheduled for major abdominal surgery **Inclusion criteria:** One of: - anticipated operation time of >120 minutes, - presumed blood loss of >1000 mL, opened peritoneal cavity. And one of: -ischaemic heart disease of severe heart dysfunction -COPD ->70 -ASA3 or more for other reasons (VKD, diabetes etc.) **Exclusion criteria:**	**Group 1- Protocol** Group assigned to intraoperative monitoring with Vigileo/FLoTrac- continuous monitoring of patients haemodynamic status using online analysis of arterial waveform. Examining the effect of stroke volume variation (SVV) guided therapy in perioperative care. Protocol covers-assessment, treatment, and monitoring. - Protocol designed around the monitoring of SVV and cardiac index during the peri-operative period. Obtain baseline physiological variables. Measure SVV and CI→give colloid bolus (3 ml/kg) if SVV rose above 10% from previous measurement, or repeat monitoring if SVV	**All cause mortality** (state the definition used in study)	Group 1: 1 (1.67%) Group 2: 2 (3.33%) P value: not significant	**Funding:** Research grant from Czech ministry of education. **Limitations:** • Single centre study • >10% dropouts • Partially blinded • Study undertaken in perioperative population • Study undertaken in people with heart failure, largely an older population. • Inclusion of a mixture of
			Length of stay (hospitalisation)	Group 1: 9 (8-11.5) Group 2: 10 (8-16) P value: 0.0937	
			Morbidity (patients with complications) (day 30)	Group 1:18 Group 2:35 P value: 0.0033	
			Complications	Group 1: 34 Group 2: 77 P value: 0.0066	
			Severe complications (these include, pneumonia, sepsis, intra-abdominal infection, catheter related bloodstream infection, arrhythmias, heart failure, pulmonary oedema, acute myocardial infarction, PE, ALI/ARDS, new onset of ventilator support, renal failure with dialysis, stroke (including TIA), pancreatitis, hepatic dysfunction.	Group 1: 13 Group 2: 41 P value: 0.0132	
			Sepsis	Group 1: 1 Group 2: 8 P value: NR	
			Renal complications (AKI without dialysis)	Group 1: 2 Group 2: 4	

Study details	Patients	Interventions	Outcomes	Effect Sizes	Comments
design: Prospective RCT **Duration of follow-up/ or period of time when study was conducted** Day 30 after operation.	Irregular heart rhythm, body weight <55kg or >140 kg, <18 years. **All patients** N: 120 Age (mean): NR Drop outs: 15 **Group 1** N: 60 Age (mean): 66.73 (7.88) Drop outs: 9 m/f: 50/10 APACHE II score: 6.59 (3.04) SOFA score: 1 (1-2) **Group 2** N: 60 Age (mean): 66.32 (8.38) Drop outs: 6 m/f: 47/13 APACHE II score: 6.76 (2.61) SOFA score: 1 (0-2)	normal. Dobutamine infused to maintain CI 2.5/4 L/min/m2 under low cardiac output conditions after appropriate fluid administration. Ephedrine or norepinephrine allowed in addition to colloid infusion to treat fall in systolic arterial pressure below 90 mmHg or MAP below 65 mmHg. **Group 2- no protocol** Anaesthologist free to give additional fluids (crystalloid or colloid) or use vasoactive substances to maintain blood pressure, dieresis and CVP in normal ranges (MAP >65mmHg, heart rate >100 bpm, CVP 8-15mmHg, urine output >0.5 ml/kg/hr). For all patients: Intraoperative basal fluid replacement with continuous infusion of 8 mL/kg/hr crystalloid solution.		P value: NR	surgical procedures could have influenced the results **Other outcomes:** • Baseline biochemical tests • -number of hypotensive periods intraoperatively, • amount of fluid given intraoperatively • SOFA • APACHE II **Notes:** Randomisation using opaque sealed envelopes. Anaesthetist aware of group assignment, all other members of healthcare team were not.
			Renal complications (Renal failure with dialysis)	Group 1: 1 Group 2: 1 P value: NR	
			How was this protocol designed? Rationale/process To incorporate the used of a specific piece of equipment for intraoperative monitoring of patients undergoing surgery.		
			Was the protocol considered helpful (authors conclusions)? Optimisation using SVV in high risk patients associated with improved haemodynamic stability and reduced serum lactate concentration at the end of surgery. GDT using SVV as an end point was associated with reduced post-operative complication rates.		
			What elements have been identified as helpful/contribute to better outcomes? -Mean lactate measurement (difference in lactate measurements in those patients with and without complications) -ScvO2 levels		
			What elements have been identified as not useful/did not contribute to better outcomes? (this can be a what went wrong/lessons learned section in discussion) -may be better in more homogenous population --further evaluation of dynamic variables is needed -results from protocols based on variations only should be assessed with caution. -influence of systemic vascular resistance alteration on accuracy of Vigileo monitor is of note and may be a source of bias		
			Adherence to protocol (was the protocol followed)? NR, but states that different protocols used in post- operative care (i.e. ICU and ward protocols). Discharge criteria were not pre-defined, this can lead to people being over-treated and therefore explain the lack of difference between groups (authors explanation).		

Abbreviations: ASA= American society of anaesthesiologist, CAD=: Coronary artery disease, CVP= central venous pressure, HES= hydroxyethyl starch, HR=hazard ratio, HR= Heart rate, ITT=Intention to treat analysis, ISS=Injury severity score, ITBVI= intrathoracic blood volume index, MAP= Mean arterial pressure, M/F=male/female, mL= millilitres, mEq= millieqivalent, N=total number of patients randomised, NISS=New injury severity score, NS= Not significant, RIFLE= Risk, Injury, Failure, Loss and End-stage serum creatinine criteria, SD= standard deviation, SE=Standard Error, SICU= Surgical ICU, SOFA= Sequential Organ Failure Assessment, $ScvO_2$= Central venous oxygen saturation

Study details	Patients	Interventions	Outcomes	Effect sizes	Comments
Gan 2002 [134] **Comparison:** Protocol vs standard intraoperative care **Country of study:** USA **Setting:** surgical **Study design:** RCT **List who was masked to interventi**	**Patient group:** Patients undergoing major elective surgery **Inclusion criteria:** Patients undergoing major elective general, urologic, gynaecological with an anticipated blood loss of >500mL. **Exclusion criteria:** Patients <18 years, emergency surgery, preoperative bowel obstruction, coagulopathy, significant renal and hepatic dysfunction, CHF, oesophageal pathology, or on antiemetic medication within 3 days of surgery. **<u>All patients</u>** **N:** 100 **Age (mean):** **Drop outs:** **<u>Group 1</u>** **N:** 50 **Age (mean):** 56(13) **Drop outs:** **m/f:** 31/19 **ASA physical status:** **I:** 3 **II:** 36 **III:** 11	**Group 1 Protocol** Boluses of fluid were administered, guided by algorithm depending on the Doppler estimations of stroke volume and FTc. • FTc<0.35s- 200mL of 6% HES in saline given • If SV maintained or increased by fluid challenge and FTc remained<0.35s fluid challenge was repeated. • If SV increased by >10% and FTc >0.35s fluid challenge repeated until no further increase in SV occurred. • FTc >0.40s and no change in SV- no further fluid administered until SV decreased by 10% of last value. Procedure started immediately after probe placement and every 15 mins until max SV and target FTc reached. • Further aliquots of fluid given to maintain FTc, patients also received fluid equivalent to that judged to be lost from surgical haemorrhage. When 20mL/kg of 6% HES given, Ringer's lactate used for fluid boluses as required (institution criteria) Crystalloid used in 3:1 ratio for replacement of surgical blood loss. Haemodynamic variables triggering fluid	**All cause mortality** (state the definition used in study)	**NR**	**Funding:** NR **Limitations:** • unable to blind anaesthiologists. • Mortality NR, but length of follow up stated as to discharge or death. • Setting is intraoperative and includes invasive monitoring- both outside of scope. • Differences between outcomes in groups could be due to differences in the types of fluids
			Length of stay(hospitalisation)	**Group 1:**5 (3) **Group 2:** 7 (3) **P value:** 0.03	
			Acute renal dysfunction (urine output <500mL)	**Group 1:** 4/50 (8) **Group 2:** 2/50 (4) RR (95% CI): **P value:** not significant	
			Respiratory support for >24 hours	**Group 1:** 1/50 (2) **Group 2:** 3/50 (6) **P value:** NR	
			Cardiovascular (hypotension, pulmonary oedema, arrhythmia)	**Group 1:** 1/50 (2) **Group 2:** 1/50 (4) **P value:** NR	
			How was this protocol designed? Rationale/process NR		

Study details	Patients	Interventions	Outcomes	Effect sizes	Comments
ons: Research personnel. States it was an unblended study. **Duration of follow-up/ or period of time when study was conducted** To discharge or death	**Surgery type:** **-general:** 16 **-gynaecologic:** 13 **-urologic:** 21 **Patients with CVP:** 43 **Use of vasoactive drugs:** 8 **Duration of surgery (mean, SD):** 250 (115) **<u>Group 2</u>** **N:** 50 **Age (mean):** 59 (12) **Drop outs:** **m/f:** 26:24 **ASA physical status:** **I:** 8 **II:** 32 **III:** 10 **Surgery type:** **-general:** 15 **-gynaecologic:** 19 **-urologic:** 16 **Patients with CVP:** 45 **Use of vasoactive drugs:** 13 **Duration of surgery:** 218 (90)	administration include: • Urine output <0.5ml/kg/hr • Increase in heart rate>20% above baseline or >110 bpm • Decrease in mean systolic bp<20% below baseline or <90mmHg • CVP <20% baseline Boluses of 200mL fluid were administered until the above target was restored. Anaemia and hypocoagulation treated with blood products **Group 2- standard care/ control** **For all patients:** Before anaesthesia, given iv bolus of 5mL/kg Ringers lactate, followed by iv infusion at rate of 5mL/kg/hr continued for duration of surgery. Had oesophageal Doppler probe (EDM) inserted to monitor blood flow velocity waveform in order to calculate corrected flow time (FTc).	**Was the protocol considered helpful (authors conclusions)?** "proactive intraoperative fluid administration can improve postoperative recovery in patients undergoing moderate to high risk surgery" **What elements have been identified as helpful/contribute to better outcomes?** -Usefulness of measuring SV and CO. can use other relatively non-invasive devices e.g. carbon dioxide rebreathing, Fick indicator technique, thoracic impedance. **What elements have been identified as not useful/did not contribute to better outcomes?** Routinely measured standard cardiovascular variables such as bp, hr, oxygen saturation were unreliable indicators of hypovolaemia. **Adherence to protocol (was the protocol followed)?** NR		administered. • States aggressive fluid resuscitation may reduce mortality, however this was not a reported outcome in this study. **Notes:** • Randomised using random number generator in sealed envelopes • Patients in protocol group received significantly more 6% HES than control group

Abbreviations: ASA= American society of anaesthesiologist, CAD=: Coronary artery disease, CVP= central venous pressure, HES= hydroxyethyl starch, HR=hazard ratio, HR= Heart rate, ITT=Intention to treat analysis, ISS=Injury severity score, ITBVI= intrathoracic blood volume index, MAP= Mean arterial pressure, M/F=male/female, mL= millilitres, mEq= millieqivalent, N=total number of patients randomised, NISS=New injury severity score, NS= Not significant, RIFLE= Risk, Injury, Failure, Loss and End-stage serum creatinine criteria, SD= standard deviation, SE=Standard Error, SICU= Surgical ICU, SOFA= Sequential Organ Failure Assessment, ScvO2= Central venous oxygen saturation

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Study details	Patients	Interventions	Outcomes	Effect sizes	Comments
Hopkins 1983[182] **Comparison:** Protocol vs no protocol **Country of study:** USA **Setting**: Surgical section of an ED **Study design:** RCT List who was masked to interventions: **Duration of follow-up/ or period of time when study was conducted** -Follow up NR	**Patient group:** Hypotensive adults seen in adult surgical ED **Inclusion criteria:** Adults with an emergency condition with a mean arterial pressure of <80mmHg **Exclusion criteria:** mean arterial pressure of <80mmHg as usual day-to-day pre-illness BP **All patients** N: 603 Age (mean): Drop outs: **Group 1** N: 212 Age (mean): 35 (15-95) Drop outs: m/f: 154 (72)/ satisfactory compliance (%): 179 (84)	**Group 1-Protocol service** Patients included were resuscitated according to the protocol. Protocol was for initial (1st hour) resuscitation of emergency admissions. Residents on the Protocol service were given the algorithm and a 20-30 minute instruction on how to follow it. - **what the protocol covers (assessment/diagnostic/treatment/monitoring/documentation/others)** **- who is the protocol targeted to (used by nurses/doctors) and which patient group?** <u>Components of protocol</u> -Use of protocol if patient's Map is >20mmHg – 60mmHg. -History, physical exam and laboratory assessment (not detailed) - measurement of MAP, CVP and haematocrit to guide treatment -Administration of 5% dextrose in ringer's lactate, PPF or colloid at different points in the algorithm/ or for subset of patients (e.g. <45	**All cause Mortality**	Group1: 39/212 Group 2: 75/391 p value: Not sig	**Funding:** Note down name of grant provider, it maybe helpful to highlight potential conflict of interest here: eg "GSK (manufacturer for LMWH)" **Limitations:** • resuscitation of patients in protocol group not always in compliance with algorithm • * numbers of patients adhering to protocol do not add up. • analysis carried out on different numbers of patients- not all ITT. • does not state length of follow up. **Additional outcomes** • Days on ventilator • Numbers of patients on ventilator • MAP time deficit • compares patients with deviation from protocol (n=18) vs satisfactory adherence
			Length of stay(hospitalisation) **Hospital days** **Survivors only included**	Group1: 16 (6) n=173 Group 2: 17 (26) n=316 p value: Not sig	
			Quality of life	Group 1: Group 2: RR (95% CI): P value: (no need to state this if 95% CI available)	
			Resuscitation time **Time from MAP <80mmHg to first MAP >80mmHg** **minutes**	Group1: 169 (262) n=197 Group 2: 239 (421) n=353 p value: 0.001	
			ICU days **Survivors only included**	Group1: 4 (9) n=173 Group 2: 4 (11) n=316 p value: Not sig	
			Complication s related to shock and resuscitation Patients who entered with cardiopulmonary arrest or arrested in ED excluded because they did not live long enough to develop complications	Group1: 13/192 Group 2: 35/353 p value: Not sig	
			Was the protocol considered helpful (authors conclusions)? This algorithm provided criteria for expeditious therapeutic, diagnostic and monitoring decisions in the resuscitation of emergency patients. A feasible way to present the clinical management concepts of acute problems as a rational		

Study details	Patients	Interventions	Outcomes	Effect sizes	Comments
	severely ill (%): 101 (48) **Group 2** N: 391 Age (mean): 35 (16-95) Drop outs: m/f: 259 (66%) satisfactory compliance (%): 306 (78) severely ill (%): 164 (42)	years without history of cardiac problems) -Assessment of patient MAP <60mmHg -signposting to other protocols at appropriate nodes. **Group 2- No protocol** Patients included were resuscitated, but not following the protocol. The protocol/ no protocol service was rotated by a pre-arranged schedule to each of the 3"on call" services that covered the surgical ED **For all patients:** (state any VTE related treatments here)	systematic process. Self educational tools that are well accepted by physicians Particularly applicable to teaching principles of management of emergency victims, where routine activities should be reflex **What elements have been identified as helpful/contribute to better outcomes?** Greatest usefulness in patients with severe associated illnesses- delay or disorganisation of therapy also led to shock-related complications. **What elements have been identified as not useful/did not contribute to better outcomes?** Outcome of patients with head injury did not improve, outcome determined by degree of neurological damage at time of injury, excess fluid may be contraindicated in these patients. **Adherence to protocol (was the protocol followed)?** Satisfactory compliance: n=57 Deviation: n=18 Paper states high rate of satisfactory compliance- willingness of residents to use this algorithm. Initially reluctant to use, but most found it useful in organising care and determining therapeutic priorities.		to protocol (n=57)*see limitations

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Study details	Patients	Interventions	Outcomes	Effect sizes	Comments
Lin 2006 [221] **Comparison:**	**Patient group:** Adult ICU patients	**Group 1- goal directed therapy (GDT)** - **what the protocol**	**All cause mortality (ICU mortality rate for the whole cohort)**	Group 1: 54/108 Group 2: 78/116	**Funding:** NR **Limitations:**

Study details	Patients	Interventions	Outcomes	Effect sizes	Comments
GDT protocol vs non GDT (no protocol **Country of study:** Taiwan **Setting:** ICU (referred from ED and medical wards) **Study design:** RCT	**Inclusion criteria:** Patients from emergency and medical wards, transferred to ICU once sepsis with organ failure was found, and when shock developed during their stay in ICU. Patients with septic shock in the ED or medical wards were included if they were transferred to the medical ICU within 4 hours. Fulfil criteria for septic shock: Known origin of infection At least 2 of the criteria for SIRS Bp not >90 mmHg (after fluid challenge) **Exclusion criteria:** <18 year, Pregnancy Cardiovascular problems, Active GI haemorrhage, seizure, drug overdose, burn injury, requirement for immediate surgery, trauma, active cancer, immunosuppression, DNR status. **All patients** N: 224 Age (mean): Drop outs: 17 Transferred from ED: 86/224 **Group 1** N: 108 Age (mean): 67.2 (15) Drop outs: NR F: 44 (40.7) APACHE III score: 66.35 (16.9) GCS: 9.2 (3.9) CVP (mmHg): 5.6 (4.7) Chronic co-existing conditions: -diabetes: 30 (27.8)	**covers (assessment/diagnostic/treatment/monitoring/documentation/others)** - protocol targeted to doctors - 500mL bolus of crystalloid (Ringers lactate or 0.9% saline) given every 30 mins to achieve CVP of 8-12mmHg. If MAP still <65mmHg after reaching right CVP, vasopressors given to maintain MAP of at least 65mmHg. 50mg hydrocortisone administered iv every 6h for 7 days if relative adrenal insufficiency was diagnosed. -urine output should be >0.5mL/kg/hr. If urine output persistently low Swan-Ganz catheter introduced to determine cardiac index- if decreased dobutamine given.		P value: 0.009	• Unblinded design • Mortality rate for whole cohort higher than in other EGDT studies • Indirect population • Protocol included invasive monitoring- outside of scope **Notes:** • Randomisation in computer generated blocks of 2- 8. In sealed opaque randomly assorted envelopes. • Levels of clinicians in both groups similar- senior residents (3rd or 4th year residents) and attending physicians).
			Length of stay(hospitalisation)	Group 1: 36.6 (22.9) Group 2: 33.8 (23.1) P value: not significant	
			Quality of life	NR	
			Length of ICU stay (days)	Group 1: 14.3 (11.7) Group 2: 20.3 (16.6) P value: 0.003	
			Duration of mechanical ventilation (days)	Group 1: 12.9 (11.5) Group 2: 18.8 (17.1) P value: 0.003	
			Sepsis associated renal failure	Group 1: 42 (38.9) Group 2: 64 (55.2) P value: 0.015	
			How was this protocol designed? NR **Was the protocol considered helpful (authors conclusions)?** "Large fluid deficits exist in patients with septic shock. Volume repletion in these patients produces significant improvement in cardiac function and systemic oxygen delivery, thereby		

Study details	Patients	Interventions	Outcomes	Effect sizes	Comments
	-cardiorespiratory: 105 -renal insufficiency: 14 (13) -neurological disease: 13 (12) History of malignancy: 14 (13) Pneumonia as primary origin of sepsis: 65 (60.2) Transferred from ED: 40 (37) **Group 2** N: 116 Age (mean): Drop outs: NR F: 50 (43.1) APACHE III score: 64.9 (14.4) GCS: 8.9 (3.9) CVP: 6.5 (4.5) Chronic co-existing conditions: -diabetes: 38 (32.8) -cardiorespiratory: 140 -renal insufficiency: 18 (15.5) -neurological disease: 17 (14.7) History of malignancy: 12 (10.3) Pneumonia as primary origin of sepsis: 69 (58.5) Transferred from ED: 46 (39.7)	**Group 2- non GDT** Standard therapy adjusted by a physician without a fixed protocol.	increasing tissue perfusion and decreasing mortality" "Rapid haemodynamic optimisation caused by aggressive fluid resuscitation and less delayed vasopressor administration in GDT group may prevent the development of major organ dysfunction" "the protective effects against organ failure by GDT may contribute to the reduction in mortality rate and in improvement in clinical outcomes amongst patients with septic shock" **What elements have been identified as helpful/contribute to better outcomes?** Targeting CVP, MAP and urine output in GDT **What elements have been identified as not useful/did not contribute to better outcomes?** NR **Adherence to protocol (was the protocol followed)?** NR		• States there was higher mortality than in similar studies, which could be due to higher % transferred from medical wards rather than EDs • High percentage of patients with pneumonia in the study

Abbreviations: ASA= American society of anaesthesiologist, CAD=: Coronary artery disease, CVP= central venous pressure, HES= hydroxyethyl starch, HR=hazard ratio, HR= Heart rate, ITT=Intention to treat analysis, ISS=Injury severity score, ITBVI= intrathoracic blood volume index, MAP= Mean arterial pressure, M/F=male/female, mL= millilitres, mEq= millieqivalent, N=total number of patients randomised, NISS=New injury severity score, NS= Not significant, RIFLE= Risk, Injury, Failure, Loss and End-stage serum creatinine criteria, SD= standard deviation, SE=Standard Error, SICU= Surgical ICU, SOFA= Sequential Organ Failure Assessment, $ScvO_2$= Central venous oxygen saturation, UFH= unfractionated heparin

	Patients	Interventions	Study details	Effect sizes	Comments
NOBLETT 2006[284]	**Patient group:**	**Both groups:**	**Mortality**	Group 1: 0 (0%)	**Funding:** Royal

	Patients	Interventions	Study details	Effect sizes	Comments
Comparison: Protocolized oesophageal Doppler guided fluid administration v non-protocolized administration **Country of study:** United Kingdom **Setting:** Surgical wards (Intraoperative and post-operative care) **Study design:** RCT **List who was masked to interventions:** Anaethestists, surgeon and researcher	Patients undergoing elective colorectal resection **Exclusion criteria:** Severe oesophageal disease, recent oesophageal or upper airway surgery, systemic steroid medication, moderate or severe aortic valve disease, bleeding diathesis, patient choice. **All patients** N: 108 (randomised) Drop outs: 5 **Group 1** N: 54 (randomised), 50 (received intervention), 3(withdrawn by anaesthetist's choice, 1(did not receive intervention), 51 (completed trial) Age (mean): 62.3±14.0 years Baseline characteristics: Colonic: Rectal resection= 30:24 POSSUM scores: Physiological score: 16.0±3.5 Operative score: 15.4±4.2 Predictive morbidity: 40.7±20.4 **Group 2** N: 54 (randomised), 51(received intervention), 1(withdrawn by anaesthetist's choice), 1(withdrawn by patient choice), 1(anaesthetist unblinded), 52(completed trial) Age (mean): 67.6±15.2 years Baseline characteristics: Colonic:Rectal resection= 25:29 POSSUM scores:	All patients had Doppler probe insertion and monitoring Patients received a standard volatile based general anaesthetic. Routine perioperative monitoring included electrocardiography, pulse oximetry, end-tidal carbon dioxide monitoring and non-invasive or invasive blood pressure monitoring. All patients had continuous oesophageal Doppler monitoring (Cardio-Q, Deltex medical) Crystalloid, colloid or blood products were administered by the anaesthetist based on intraoperative losses and standard haemodynamic parameters ***Above was the regimen for Group 2** **Group 1** In addition to above, patients received additional colloid boluses to maintain a descending aortic corrected flow time (FTc) of more than 0.35s and further boluses were given to optimize the stroke volume (SV). Once achieved, further fluid boluses were given only if the SV altered more than 10 percent or the FTc fell below 0.35s. Haemodynamic parameters were recorded every 10 minutes.		Group 2: 1(2%) P value: 0.990	College of Surgeons Research Fellowship Scheme **Limitations:** • Unclear randomisation and allocation concealment • Blinding was breached for one of the participants **Notes:** Indirect population (intraoperative protocol, invasive monitoring)
			Total post-operative stay (days)[median, IQR]	Group 1:7 (3-35) Group 2: 9 (4-45) P value:0.005	
			Post- operative complications requiring pharmacological management	Group 1: 6(12%) Group 2:7(13%) P value:0.767	
			Post- operative complications requiring surgical, endoscopic or radiological intervention	Group 1:1(2%) Group 2:2(4%) P value:0.558	
			Life threatening complication requiring HDU or ICU care	Group 1:0(0%) Group 2:4(8%) P value:0.242	
			Was the protocol considered helpful (authors conclusions)? Yes, protocolized fluid administration reduced morbidity, allowed earlier tolerance of diet and reduced postoperative hospital stay.		

	Patients	Interventions	Study details	Effect sizes	Comments
	Physiological score: 16.4±3.6 Operative score: 16.1±3.7 Predictive morbidity: 44.6±19.8				

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Study details	Patients	Interventions	Outcomes	Effect sizes	Comments
Rivers 2001 [311] **Comparison:** Country of study: USA **Setting:** Emergency department **Study design:** RCT **List who was masked to interventions:** Critical care clinicians **Duration of follow-up:** At least 6 hours after the start of therapy, up to death or discharge	**Patient group:** Adult patients presenting to ED with severe sepsis, septic shock or sepsis syndrome. **Inclusion criteria:** Fulfilment of 2 of the 4 criteria for the systemic inflammatory response syndrome and a systolic bp no higher than 90mmHg. (after a crystalloid fluid challenge) or a blood lactate of 4mmol/L or more **Exclusion criteria:** <18 years, Pregnancy, Cardiovascular problems, Active GI haemorrhage, seizure, drug overdose, burn injury, requirement for immediate surgery, trauma, active cancer, immunosuppression, DNR status. **All patients** N: 263 Age (mean): Drop outs: 27 **Group 1- GDT**	**Group 1- Early goal directed therapy** Protocol aimed at critical care clinicians treating the patients (intensivists, fellows, residents). Received a central venous catheter capable of measuring central venous oxygen saturation, connected to a computerised spectrophotometer for continuous monitoring Treated for at least 6 hours according to protocol the transferred to first available inpatient beds. <u>Details of protocol:</u> -500mL bolus crystalloid given every 30 minutes to achieve CVP of 8-12 mmHg -If MAP was <65mmHg, vasopressors given until it was	**All cause mortality (in hospital mortality)**	Group 1: 38 (30.5) Group 2: 59 (46.5) RR (95% CI): 0.58 (0.38-0.87)	**Funding:** Supported by the Henry Ford Health Systems Fund for research, Weatherby Healthcare Resuscitation Fellowship, Edwards lifesciences (produce oximetry equipment and catheters) Nova biomedical (provided equipment for laboratory assays). **Limitations:** • >10% dropout • Follow up
			28 day mortality	Group 1: 40 (33.3) Group 2: 61 (49.2) RR (95% CI): 0.58 (0.39-0.87) P value: 0.01	
			60 day mortality	Group 1: 50 (44.3) Group 2: 70 (56.9) RR (95% CI): 0.67 (0.46-0.96) P value: 0.03	
			Length of stay(hospitalisation)	Group 1: Group 2: RR (95% CI): P value: (no need to state this if 95% CI available)	
			Mean duration of	Group 1:9 (13.1)	

Study details	Patients	Interventions	Outcomes	Effect sizes	Comments
(unclear)	N: 130 Age (mean): 67.1 (17.4) Drop outs: 13 m/f: 50.8/49.2 Time from arrival at ED to enrolment(hr): 1.3 (1.5) chronic coexisting conditions: -alcohol use: 38.5 -Cardiorespiratory disorders (mean of 4 domains): 37.4 -diabetes: 30.8 -HIV: 4.3 -Liver disease: 23.1 -history of cancer: 12.8 - neurologic disease: 34.2 -renal insufficiency: 21.4 -smoking: 29.9 **Group 2 –standard care** N: 133 Age (mean): 64.4 (17.1 Drop outs: 14 m/f: 50.4/49.6 time from arrival at ED to enrolment: 1.5 (1.7) chronic coexisting conditions: -alcohol use: 38.7 -Cardiorespiratory disorders (mean of 4 domains): 33.4 -diabetes: 31.9 -HIV: 1.7 -Liver disease: 23.5 -history of cancer: 10.1	90mmHg or below. -If central venous oxygen saturation was <70% red cells were transfused to achieve a haematocrit of at least 30% -If CVP, MAP and haematocrit were optimised, if central venous oxygen saturation was <70% dobutamine administration was commenced. Until central venous oxygen saturation was 70% or higher until a maximal dose of 20 ug/kg/min was given. To decrease oxygen consumption, patients in whom haemodynamic optimisation could not be achieved received mechanical ventilation and sedatives The protocol covers assessment, treatment and monitoring. **Group 2- standard therapy** no further information given	**mechanical ventilation** **Length of stay of those patients that survived to hospital discharge** **How was this protocol designed?** NR **Was the protocol considered helpful (authors conclusions)?** "Significant benefits with respect to outcome when goal directed therapy was applied at an earlier stage of disease" GDT provided at the earliest stages of severe sepsis and septic shock has significant short and long term benefits. Benefits arise from early identification of patients at risk of cardiovascular collapse and from early therapeutic intervention to restore a balance between oxygen delivery and oxygen demand. **What elements have been identified as helpful/contribute to better outcomes?** Aspects helpful in identifying need for therapy: decreased mixed venous oxygen saturation and increased lactate concentration. Quality and timing of the resuscitation is important and should be studied. **What elements have been identified as not useful/did not contribute to better outcomes?** "no benefit in terms of outcome with respect to normal and supranormal haemodynamic end points, as well as those guided by mixed venous oxygen saturation" **Adherence to protocol (was the protocol**	Group 2: 9 (11.4) P value: 0.38 Group 1: 14.6 (14.5) Group 2: 18.4 (15) P value: 0.04	unclear • Patients in the standard therapy group may have received some sort of GDT, reducing the treatment effect. **Notes:** • Randomisation by computer generated blocks of 2- 8. Assignments placed in sealed opaque, randomly assorted envelopes. • Majority of baseline data given as %, n calculated by NCGC.

Study details	Patients	Interventions	Outcomes	Effect sizes	Comments
	- neurologic disease: 31.9 -renal insufficiency: 21.9 -smoking: 31.1		**followed)?** NR, but stated that patients in the non-protocol group may have inadvertently had some sort of GDT, reducing the treatment effects		

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E.2 Assessment and monitoring

E.2.1 Measurement of serum chloride

In people in hospital who require IV fluids, what is the incidence and clinical significance of hyperchloraemia or hypochloraemia in people receiving any IV fluid?

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author and year: **Scheingraber et al. 1999** [321] **Study design:** RCT **Comparison:** 0.9% sodium chloride v Lactated ringer's solution **Randomisation:** Unclear; details	**Patient group:** Females scheduled for elective lower abdominal gynaecologic surgery. **Inclusion criteria:** Women undergoing elective lower abdominal gynaecologic surgery; had no apparent cardiac, pulmonary or renal diseases (classified as American Society of Anaesthesiologists physical status I or II) **Exclusion criteria:** Not reported **All patients** N: 24	**Group 1- 0.9% sodium chloride** Patients received 0.9% sodium chloride solution at an infusion rate of approximately 35 ml/kg/hour. Sodium chloride solution contained 154 mmol sodium and 154 mmol chloride. **Group 2- Lactated Ringer's solution** Patients received lactated Ringer's solution at an infusion rate of approximately 35 ml/kg/hour. Lactated Ringer's solution contained 130 mmol sodium, 5.4 mmol	**Acidosis (pH levels) after 120 minutes of infusion**	**Group 1:** 7.28 **Group 2:** 7.41	**Funding:** Research budget of Ludwig-Maximilians-University, Munich, Germany. **Additional limitations:** Small sample size **Additional outcomes:** Measurement of bicarbonate, anion gap and strong ion difference. **Notes:** • Study aimed to compare the changes
			Chloride levels (mean) after 120 minutes of infusion	**Group 1:** 115mmol **Group 2:** 106mmol	
			Observation: 'Hyperchloraemic acidosis caused by large 0.9% sodium chloride seems to be benign ,		

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
of randomisation not reported. **Allocation concealment:** Unclear; details not reported, unclear if carried out at all **Blinding:** Unclear; details not reported, unclear if study was blinded. **Setting:** Intra-operative; Surgical unit, Germany.	**Group 1- 0.9% sodium chloride** N: 12 Age in years (mean ± SD): 46 ± 14 Baseline chloride value (mean): 104mmol Time of infusion in minutes (mean ± SD): 135 ± 23 Crystalloid infusion after 120 min in ml/kg (mean ± SD): 71 ±14 Patients requiring potassium supplementation during surgery: 8 **Group 2- Lactated Ringer's solution** N: 12 Age in years (mean ± SD): 53 ± 5 Baseline chloride value (mean): 104mmol Time of infusion in minutes (mean ± SD): 138 ± 20 Crystalloid infusion after 120 min in ml/kg (mean ± SD): 67 ±18 Patients requiring potassium supplementation during surgery: 2	potassium, 1.8mmol calcium, 112 mmol chloride and 27 mmol lactate. • During the study no patient received colloids, plasma products or blood transfusions. • Infusion of intravenous fluids were started after baseline arterial blood tests for PaO2, serum sodium, serum potassium, serum chloride, and serum lactate were conducted during stable anaesthetic conditions and at the time of surgical incision. • Every 30 minutes, new blood samples were taken, urine production and temperature were measured and blood loss was estimated. • If potassium was less than 3.3mmol/L, then 20 mmol potassium chloride solution was infused with next infusion bottle.	unless it is confused with hypoperfusion; Nevertheless, it should be treated to to provide a bases excess close to zero at the end of surgery, (or alternately, lactated Ringers' solution should be used)'		in serum bicarbonate concentration as calculated by Henderson-Hasselbach equation and the Stewart equations to assess the influence of crystalloid infusion on acid-base changes

Abbreviations: ASA= American society of anaesthesiologist, CAD=: Coronary artery disease, CVP= central venous pressure, HES= hydroxyethyl starch, HR=hazard ratio, HR= Heart rate, ITT=Intention to treat analysis, ISS=Injury severity score, ITBVI= intrathoracic blood volume index, MAP= Mean arterial pressure, M/F=male/female, mL= millilitres, mEq= millieqivalent, N=total number of patients randomised, NISS=New injury severity score, NS= Not significant, RIFLE= Risk, Injury, Failure, Loss and End-stage serum creatinine criteria, SD= standard deviation, SE=Standard Error, SICU= Surgical ICU, SOFA= Sequential Organ Failure Assessment, $ScvO_2$= Central venous oxygen saturation, UFH= unfractionated heparin

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Shaw et al. 2012[330]	**Patient group:** Patients undergoing major open abdominal surgery **Inclusion criteria:** Age≥18 years, hospitalised	**Group 1- Balanced crystalloid therapy (Plasmalyte)**	**Mortality**	Group 1(n): 27 Group 2(n): 93 OR: 0.769 (0.484,	**Funding:** Baxter Healthcare Inc., Deerfield, Illinois, USA.

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Study design: Retrospective cohort study **Comparison:** 0.9% sodium chloride v Plasmalyte **Randomisation:** Non – randomised observational study **Setting:** Intra-operative setting; Information obtained from the Premier perspective comparative database, a US automated hospital claims database covering 600 Us acute care hospitals.	patients who received intravenous crystalloid replacement therapy during an elective or emergency open (not laparoscopic) general surgical operation between Jnauary 1, 2005 and December 31, 2009; Included only if had received exclusively 0.9% saline or a calcium free isotonic balanced crystalloid solution (Plasma-Lyte A or Plasma-Lyte 148) on the day of surgery. **Exclusion criteria:** Patients undergoing major abdominal operations for traumatic injuries; patients who received calcium containing crystalloids such as Ringer's lactate; patients receiving dextrose based crystalloids or combinations of crystalloid solutions. **All patients (Propensity score, matched cohort 3:1)** N: 3704 **Group 1- Balanced crystalloid therapy (Plasmalyte)** N: 926 Age (51-80 years): 62% of total participants Female: 52.8% Admission type, emergency: 26.0% Primary payer, Medicare:42.2% Primary payer, Medicaid:9.7% Admitted to teaching hospital:52.2% Comorbidities*: Valvular disease:6.4% Diabetes (no chronic complications):16.5% Hypothyroidism:9.7% Liver disease:5.1%	Patients were assigned to this group if they received exclusively balanced crystalloid solution **Group 2- 0.9% sodium chloride** Patients were assigned to this group if they received exclusively 0.9% saline on the day of surgery. • For both fluids only doses of 500 ml and 1000 ml were included to differentiate volume replacement from fluid being used as a drug diluent.		1.220)	**Limitations:** • Non- randomised study • Observational retrospective study from database; codes used to identify outcomes which may not be accurate • Large differences in baseline characteristics between groups (co-morbidities, socio-economic status)- unresolved by matching, therefore residual bias present • Unclear when balanced crystalloid solution was exclusively given (only for surgery?) **Notes:** • Three outcome models were constructed: ordinary logistic regression, ordinary logistic regression including propensity score (observed probability of receiving each type of fluid) as a model predictor, and ordinary logistic regression on a sample of patients matched by propensity score 3:1, 0.9% sodium chloride to balanced crystalloid • Results presented for the standard logistic regression 3:1 matched sample • Primary outcome was major
			Morbidity (Major complicatio n index)	Group 1(n): 213 Group 2(n): 714 OR:0.798 (0.656, 0.970)	
			Acute renal failure	Group 1(n): 5 Group 2(n): 23 OR: 0.451 (0.160, 1.273)	
			Electrolyte disturbance s	Group 1(n): 82 Group 2(n): 297 OR: 0.753 (0.571, 0.994)	
			Length of stay in days, mean (SD)	Group 1(n): 6.4 (4.8) Group 2(n): 5.9 (4.4) P<0.001	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Metastatic cancer:9.0% Deficiency anemias:17.2% Depression:8.3% **Group 2- 0.9% sodium chloride** N: 2778 Age(51-80 years):61.2% of participants Female: 51.7% Admission type, emergency: 29.4% Primary payer, Medicare:47.0% Primary payer, Medicaid:7.1% Admitted to teaching hospital:30.4% Comorbidities*: Valvular disease:5.1% Diabetes (no chronic complications):14.0% Hypothyroidism:7.8% Liver disease:4.1% Metastatic cancer:7.4% Deficiency anemias:14.5% Depression:6.2%				morbidity which was defined as a composite of one or more major complications; complications were included if they occurred on post-operative day 1 or later • Potential confounding risk factors for morbidity and mortality considered in the analysis included age, gender, geographic region, hospital characteristics and patient co-morbidities. • Study does not report hyper/hypo chloraemia as an outcome. *Comorbidities reported where difference in baseline groups was significant or approached significance.

Abbreviations: ASA= American society of anaesthesiologist, CAD=: Coronary artery disease, CVP= central venous pressure, HES= hydroxyethyl starch, HR=hazard ratio, HR= Heart rate, ITT=Intention to treat analysis, ISS=Injury severity score, ITBVI= intrathoracic blood volume index, MAP= Mean arterial pressure, M/F=male/female, mL= millilitres, mEq= millieqivalent, N=total number of patients randomised, NISS=New injury severity score, NS= Not significant, RIFLE= Risk, Injury, Failure, Loss and End-stage serum creatinine criteria, SD= standard deviation, SE=Standard Error, SICU= Surgical ICU, SOFA= Sequential Organ Failure Assessment, $ScvO_2$= Central venous oxygen saturation, UFH= unfractionated heparin

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Waters et al. 2001[390]	**Patient group:** Patients undergoing aortic reconstructive surgery.	**Group 1- 0.9% sodium chloride solution for resuscitation** Volume of fluid given in ml, median(25th, 75th percentiles): 7000(5000, 8500)	**pH (acidosis) mean (SD)**	**Group 1:** Pre-op: 7.43(0.06) SICU:	**Funding:** Grant sponsored by the I.H. Page Center for Health Outcomes

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Study design: RCT **Comparison:** 0.9% sodium chloride v Lactated ringer's solution **Randomisation:** Adequate; Computerised random number generator **Allocation concealment:** Not reported **Blinding:** Adequate; labels of crystalloid solutions covered **Setting:** Intra- operative followed by ICU	**Inclusion criteria:** Patients undergoing open aortic aneurysm repair **Exclusion criteria:** Patients with history of abnormal renal function; Patients with abnormal serum blood urea nitrogen, abnormal creatinine levels, abnormal chloride levels, pre-existing acid-base abnormalities as assessed by base excess (>2 oe <-2 mEq/L). **All patients** **N: 66** **Group 1- 0.9% sodium chloride solution** N: 33 Age in years, mean(SD): 69.8(8.7) Average ASA class, mean(SD): 3.1(0.3) CAD (%of patients): 82% Hypertension (%of patients): 85% Diabetes (%of patients): 18% **Group 2- Lactated Ringer's solution** N: 33 Age in years, mean(SD): 69.9(7.8) Average ASA class, mean(SD): 3.1(0.3) CAD (%of patients):70% Hypertension (%of patients): 58% Diabetes (%of patients): 6%	**Group 2- Lactated Ringer's solution for resuscitation** Volume of fluid given in ml, median(25th, 75th percentiles): 6871 (5700, 7900) • Patients on 0.9% saline received, on average, 500 ml larger volumes of crystalloid solution and 1500 ml more total fluid. • Patients were randomised to receive 0.9% saline or lactate Ringer's solution as predominant resuscitation fluid • Study solution administration started in the operating room and ended on arrival in the ICU • All patients had standardized anaesthetic management • All patients received mannitol 12.5 gms before aortic cross clamping along with dopamine 2µg/kg/min • All patients were monitored via arterial and central venous catheters		7.35(0.09) **Group 2:** Pre-op: 7.42 (0.07) SICU: 7.4 (0.07)	Research **Additional limitations:** Small sample size Solutions not given exclusively; patients received intra-operative albumin at discretion of anaesthesiologist **Notes:** Study conducted a multivariate analysis in addition to determine which of the independent variables were related to the outcome measures of ventilation time, surgical ICU stay and hospital stay.
			Chloride level (mmmol/L) mean (SD)	**Group 1:** Pre-op: 105(3) SICU: 114(6) **Group 2 :** Pre-op: 105(3) SICU: 107(4)	
			Renal insufficiency n(%)	Group 1: 5/33 (12%) Group 2 : 4/33 (15%)	
			Mortality n(%)	Group 1: 1/33 (3%) Group 2: 1/33 (3%)	
			Multivariate analysis showed no relationship between ICU length of stay and hospital length of stay and type of crystalloid used.		

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
McFarlane et al. 1994 [253] **Study design:** RCT **Comparison:** 0.9% sodium chloride v Plasmalyte **Randomisation:** Unclear if adequate, details not reported **Allocation concealment:** NR **Blinding:** NR **Setting:** Intra-operative	**Patient group:** Patients scheduled to undergo elective major hepatobiliary or pancreatic surgery **Inclusion criteria:** As above **Exclusion criteria:** Patients receiving diuretic therapy or having a pre-operative bowel washout; patients with abnormal electrolyte status **All patients** N: 30 **Group 1- 0.9% sodium chloride** N: 15 Age in years , mean(SD): 54(14) Chloride at baseline, mmol/l: 105(4.1) Fluid infused, ml/kg/hour: 14.6(4.1) **Group 2- Plasmalyte 148** N: 15 Age in years , mean(SD):57(8.8) Chloride at baseline, mmol/l: 103(3.4) Fluid infused, ml/kg/hour: 15.1(3.5)	**Group 1- 0.9% sodium chloride** **Group 2- Plasmalyte 148** • Blood was transfused when losses exceeded 20% of estimated circulating volume. • A maintenance rate of 15ml/kg/hour was administered by the anaesthetist, which could be altered depending on the clinical state of the patient.	**Chloride (change from pre-operative value) in mmol/l, mean(SD); Time : end of surgery**	Group 1: +6.9(2.3) Group 2: +0.6(1.2)	**Funding:** NR **Additional limitations:** Small sample size **Additional outcomes:** • Bicarbonate concentrations • Base excess **Notes:** All patients were ASA level 1 or 2.
			Chloride (change from pre-operative value) in mmol/l, mean(SD); Time : 24 hours after surgery	Group 1: +1.5(2.3) Group 2 :-1.3(2.4)	
			'The use of 0.9% saline produces a tendency to metabolic acidosis, with reduced bicarbonate concentration and increased base deficit'		

Abbreviations: ASA= American society of anaesthesiologist, CAD=: Coronary artery disease, CVP= central venous pressure, HES= hydroxyethyl starch, HR=hazard ratio, HR= Heart rate, ITT=Intention to treat analysis, ISS=Injury severity score, ITBVI= intrathoracic blood volume index, MAP= Mean arterial pressure, M/F=male/female, mL= millilitres, mEq= millieqivalent, N=total number of patients randomised, NISS=New injury severity score, NS= Not significant, RIFLE= Risk, Injury, Failure, Loss and End-stage serum creatinine criteria, SD= standard deviation, SE=Standard Error, SICU= Surgical ICU, SOFA= Sequential Organ Failure Assessment, $ScvO_2$= Central venous oxygen saturation, UFH= unfractionated heparin

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Takil et al. 2002[345] **Study design:** RCT **Comparison:** 0.9% sodium chloride v lactated Ringer's solution **Randomisation:** Unclear, details not reported **Allocation concealment:** Adequate, sealed envelopes used for concealing allocation **Blinding:** NR **Setting:** Intraoperative	**Patient group:** Patients undergoing major spine surgery **Inclusion criteria:** As above; patients aged 18-70 years and were classified as ASA physical status I and II. **Exclusion criteria:** NR **All patients** **N:** 30 **Group 1- 0.9% sodium chloride solution** N: 15 Age in years, mean(SD): 45(19) Duration of surgery in minutes, mean(SD): 295(52) ASA classification, mean(SD): 1.2(0.4) **Group 2- Lactated Ringer's solution** N: 15 Age in years, mean(SD): 37(20**)** Duration of **s**urgery in minutes, mean(SD): 291(98**)**	**Group 1- 0.9% sodium chloride solution** **Group 2- Lactated Ringer's solution** • Both groups received study solutions at rate of 20 ml/kg/hr intraoperatively • Patients with greater than 20% blood loss received blood transfusions • For the first 500 ml of blood loss, 500 ml of colloid solution (Gelofusine) was administered • Post- operatively, same solutions were administered at the rate of 2.5ml/kg/hour for 12 hours • Electrolytes (Na+, K+, and Cl-) and arterial blood gases were measured pre-operatively, every hour intraoperatively and at 1st, 2nd 4th, 6th and 12th hours postoperatively.	**Acidosis (pH), mean(SD)**	**Group 1:** Pre-op: 7.38(0.02) Intra-op(4 hrs): 7.28(0.04) Post-op(12 hrs):7.35(0.03) **Group 2:** Pre-op: 7.39(0.02) Intra-op(4 hrs): 7.37(0.04) Post-op(12 hrs):7.36(0.03)	**Funding:** NR **Additional limitations:** Small sample size **Notes:** Study aimed to compare the intra-operative and post-operative effects (and their duration) of large volume infusion of 0.9% sodium chloride and lactated Ringer's solution.
			Chloride levels in mEq/l, mean(SD)	**Group 1:** Pre-op: 107(4) Intra-op(4 hrs): 122(4) Post-op(12 hrs):115(5) **Group 2 :** Pre-op: 108(2) Intra-op(4 hrs): 114(4) Post-op(12 hrs):109(7)	
			Length of stay in ICU in hours, mean(SD)	Group 1:42(18) Group 2: 47(23)	
			Length of stay in hospital in days, mean(SD)	Group 1:10(2) Group 2:11(2)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	ASA classification, mean(SD): 1.1(0.3)				

Abbreviations: ASA= American society of anaesthesiologist, CAD=: Coronary artery disease, CVP= central venous pressure, HES= hydroxyethyl starch, HR=hazard ratio, HR= Heart rate, ITT=Intention to treat analysis, ISS=Injury severity score, ITBVI= intrathoracic blood volume index, MAP= Mean arterial pressure, M/F=male/female, mL= millilitres, mEq= millieqivalent, N=total number of patients randomised, NISS=New injury severity score, NS= Not significant, RIFLE= Risk, Injury, Failure, Loss and End-stage serum creatinine criteria, SD= standard deviation, SE=Standard Error, SICU= Surgical ICU, SOFA= Sequential Organ Failure Assessment, $ScvO_2$= Central venous oxygen saturation, UFH= unfractionated heparin

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Boniatti et al. 2011[41] **Study design:** Prospective cohort study **Comparison:** Patients with hyperchloraemia v Patients with hypo/normochloraemia **Setting:** ICU setting, University hospital, Porto Alegre, Brazil.	**Patient group:** Patients with hyperchloraemia **Inclusion criteria:** All patients admitted to ICU between February 2007 and May 2007. **Exclusion criteria:** Patients were excluded if they did not have all the laboratory variables needed for the acid- base evaluation proposed and/or remained in the ICU for less than 24 hours. **All patients** N: 212	**Group 1-** Patients with hyperchloraemia **Group 2-** Patients with hypochloraemia/normochloraemia	**Mortality** (patients with hyperchloraemia vs patients with hypo/ normochloraemia)	OR: 1.065 (95% CI 1.015, 1.118)	**Funding:** NR **Limitations:** • Non-randomised observational study • Small sample size • Unclear if all patients actually received intravenous fluids, therefore even if hyperchloraemia occurred, it may not be related to iv fluid therapy **Notes:** Study actually presents co-relation of chloride levels with survivors and non- survivors.
			Chloride level was independently associated with mortality in the multiple regression model.		
			There was no correlation between chloride level and the severity of disease according to the APACHE II score.		

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Silva et al. 2009[333] **Study design:** Prospective cohort study **Comparison**: Patients with hyperchloraemia vs patients with hyperchloraemia **Setting:** Intra-operative an post-surgical (ICU), Sao Paulo.	**Patient group:** Patients undergoing surgery and then admitted to ICU **Inclusion criteria:** Aged> 18 years; underwent surgery and then admitted to ICU post-operatively **Exclusion criteria:** Terminal patients, diabetics, patients with chronic renal failure. **All patients** **N: 393** **Group 1- Patients with hyperchloraemia** N: 124 **Group 2- Patients without hyperchloraemia** N: 269	**Group 1-** Patients with hyperchloraemia at the end of surgery **Group 2-** Patients without hyperchloraemia at the end of surgery.	**Mortality:**	Group 1: 19.3%(Group 2: 7.4%(Risk ratio (95% CI): 2.60(1.50, 4.53)	**Funding: NR** **Limitations:** • Non-randomised observational study • Does not report fluid type or volume administered; assumption that since underwent surgery, have received intravenous fluids.
			Length of stay in ICU	Group 1:2.0 (1.0-3.0) Group 2: 2.0 (1.0-3.0)	
			Length of stay in hospital (median, 25th-75th percentiles)	Group 1:13.0(9.0-19.5) Group 2: 10.0(6.0- 18.0)	

Abbreviations: ASA= American society of anaesthesiologist, CAD=: Coronary artery disease, CVP= central venous pressure, HES= hydroxyethyl starch, HR=hazard ratio, HR= Heart rate, ITT=Intention to treat analysis, ISS=Injury severity score, ITBVI= intrathoracic blood volume index, MAP= Mean arterial pressure, M/F=male/female, mL= millilitres, mEq= millieqivalent, N=total number of patients randomised, NISS=New injury severity score, NS= Not significant, RIFLE= Risk, Injury, Failure, Loss and End-stage serum creatinine criteria, SD= standard deviation, SE=Standard Error, SICU= Surgical ICU, SOFA= Sequential Organ Failure Assessment, $ScvO_2$= Central venous oxygen saturation, UFH= unfractionated heparin

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Tani et al. 2012[348] **Study design:** Retrospective study	**Patient group:** Critically ill patients in medical and surgical intensive care units. **Inclusion criteria:**	**Group 1-** Patients with hyperchloraemia(Chloride level > 106mmol/L)	**Hospital mortality, n (%)**	Group 1:3/81 (3.7%) Group 2: 14/364(3.8%) Group 3:	**Funding: NR** **Limitations:** • Non-randomised

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Comparison: Hyperchloraemia vs Normochloraemia vs Hyperchloraemia **Setting:** ICU setting, University hospital, Japan.	Patients admitted to ICU between January and December 2009; Older than 16 years; stayed in ICU for longer than 24 hours; had their arterial blood gas and biochemistry checked at least once **Exclusion criteria:** NR **All patients** N: 488 Age in years, mean(SD): 61.8(16.2) Type of admission: Surgical: 443 Medical:45 **Group 1- Hyperchloraemia** N: 81 **Group 2- Normochloraemia** N: 364 **Group 3-Hypochloraemia** N: 43	**Group 2-** Patients with normochloraemia (Chloride level 98-106mmol/L) **Group 3-** Patients with hypochloraemia (Chloride level < 98mmol/L)		10/43(23.3%)	observational study • Does not report if patients received intravenous fluids (indirect population and intervention) **Notes:** Data collected during routine practice used in study.
			Length of stay in ICU in days, mean(SD)	Group 1: 4.4(2.5) Group 2:7.3(9.6) Group 3:14.3(13.3)	
			Length of stay in hospital in days, mean(SD)	Group 1: 28.4(19.5) Group 2:41.4(37.3) Group 3:70.5(65.7)	
			Chloride levels showed significant co-relation with APACHE II score in the study population (r^2=0.085, P< 0.0001) showing that chloride level was associated with the severity of the medical condition. Specifically, the severity of the conditions was greater in hypochloraemic patients in a critical care setting.		

Abbreviations: ASA= American society of anaesthesiologist, CAD=: Coronary artery disease, CVP= central venous pressure, HES= hydroxyethyl starch, HR=hazard ratio, HR= Heart rate, ITT=Intention to treat analysis, ISS=Injury severity score, ITBVI= intrathoracic blood volume index, MAP= Mean arterial pressure, M/F=male/female, mL= millilitres, mEq= millieqivalent, N=total number of patients randomised, NISS=New injury severity score, NS= Not significant, RIFLE= Risk, Injury, Failure, Loss and End-stage serum creatinine criteria, SD= standard deviation, SE=Standard Error, SICU= Surgical ICU, SOFA= Sequential Organ Failure Assessment, $ScvO_2$= Central venous oxygen saturation, UFH= unfractionated heparin

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Yunos et al. 2012[415]	**Patient group:** Patients admitted to intensive care units. **Inclusion criteria:**	**Group 1- Chloride liberal intravenous strategy (Control phase):** Patients were admitted consecutively over 6	**Incidence of AKI** **RIFLE class: Risk +Injury**	Group 1: 176/760 (23%) Group 2: 122/773(16%)	**Funding:** University grant **Limitations:**

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Study design: Prospective open label before and after study **Comparison:** Chloride liberal vs Chloride restrictive intravenous fluid strategy. **Setting:** Intensive care unit, Austin Hospital, Melbourne, Australia	All patients admitted to ICU and receiving intravenous fluids. **Exclusion criteria:** NR **All patients** N: 1533 **Group 1- Chloride liberal intravenous strategy** N:760 Age in years(mean, 95% CI): 60(59.0-61.6) Baseline creatinine level, mean(95%CI): 90(69-125) **Group 2- Chloride restrictive intravenous strategy** N:773 Age in years(mean, 95% CI): 60.5(59.2-61.8**)** Baseline creatinine level, mean(95%CI): 86(67-121**)**	months and were given intravenous fluids according to clinician preferences with free use of chloride rich fluids. Chloride rich fluids included: 0.9% saline (Chloride concentration 150mmol/L- Baxter Pty Ltd), 4% succinylated gelatin solution (Chloride concentration: 120mmol/L- Gelofusine, BBraun) and 4% albumin in sodium chloride (chloride concentration: 128mmol/L- 4% Albumex, CSL Bioplasma). **Group 2- Chloride restrictive intravenous strategy (Intervention phase)** Patients admitted consecutively over 6 months after a washout period of 6 months following the control phase. In this phase, chloride rich fluids were only made available on prescription of the attending specialist for specific conditions (eg, hyponatremia, traumatic brain injury, and cerebral edema). In place of chloride rich fluids, the following fluids were used: Hartmann solution (chloride concentration: 109mmmol/L), Plasmalyte 148(chloride concentration; 98mmol/L) and a 20% albumin solution (chloride concentration: 19mmol/L).	**+Failure** **Hospital Mortality** **Length of stay in ICU in hours (median, IQR)** **Length of stay in hospital in days (median, IQR)**	Group 1: 112/760(15%) Group 2: 102/773(13%) Group 1: 42.9(21.1-88.6) Group 2: 42.8(21.8-90.5) Group 1: 11(7-21) Group 2:11(7-22)	• Non- randomised open label study. • Study in both groups conducted over two different time periods • Data on pre-admission baseline renal risk was not available for some patients and was achieved using MDRD equation. • Some patients w ere still prescribed chloride rich fluids in the chloride restrictive period at discretion of specialist- results for this group not reported separately.

Abbreviations: ASA= American society of anaesthesiologist, CAD=: Coronary artery disease, CVP= central venous pressure, HES= hydroxyethyl starch, HR=hazard ratio, HR= Heart rate, ITT=Intention to treat analysis, ISS=Injury severity score, ITBVI= intrathoracic blood volume index, MAP= Mean arterial pressure, M/F=male/female, mL= millilitres, mEq= millieqivalent, N=total number of patients randomised, NISS=New injury severity score, NS= Not significant, RIFLE= Risk, Injury, Failure, Loss and End-stage serum creatinine criteria, SD= standard deviation, SE=Standard Error, SICU= Surgical ICU, SOFA= Sequential Organ Failure Assessment, $ScvO_2$= Central venous oxygen saturation, UFH= unfractionated heparin

E.3 Resuscitation

E.3.1 Gelatin

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
INNERHOFER 2002/ FRIES 2004[128,187] **Study design:** RCT **Setting:** Orthopaedic and anaesthesia and critical care departments, Innsbruck, Austria. **Duration of follow-up:** 2 hours post-surgically **Funding:** Supported in part by Fresenius GmbH Austria and B Braun, Germany	**Patient group:** Patients undergoing primary knee replacement surgery with tourniquet technique. **Inclusion criteria:** ASA physical status I-III, age <80 yr. **Exclusion criteria:** Contraindications for regional anaesthesia, and puncture of the radial artery, any known allergies, primary or secondary haemostatic disorders (preoperative coagulation abnormalities, renal and liver dysfunction or intake of aspirin or other platelet aggregation inhibitors). **All patients** **N:** 60 **Age (mean):** NR **Drop outs:** NR **Group 1- Gelatin (4% Gelofusine, Braun) + RL** N: 20 Age (mean ± SD): 68 (7) Drop outs: NR Tourniquet time (min): 72 (16) Duration of surgery (min): 133 (21) Intraoperative blood loss (mL): 360 (167) Total blood loss (mL): 611 (270) **Group 2- Ringer's lactate (Fresenius, Pharma**	**Group 1- Gelatin (4% Gelofusine, Braun) + RL** Intraoperatively received: 4mL/kg/hr Compensation for blood loss after tourniquet release: 1:1.3 blood loss: fluid ratio In the event of suspected hypovolaemia: 3mL/kg/hr **Group 2- Ringer's lactate (Fresenius, Pharma Austria GmbH)** Intraoperatively received: 10mL/kg/hr Compensation for blood loss after tourniquet release: 1:3 blood loss: fluid ratio In the event of suspected hypovolaemia: 7mL/kg/hr **All groups:** Received regional anaesthesia with plain bupivicaine (0.5 an 0.25%) during and 2hr after surgery. Patients actively warmed with fluid warmers and convective warming system. Received 4mg enoxaparin (Lovenox) 12 hr before surgery and cephalosporin during surgery. Before spinal anaesthesia all patients received 500mL RL. All patients received 5mL/kg/hr to	**Volume of study fluid received (mL)** Mean (SD) **Total volume of fluid received*** (mL) Mean (SD)	**Group 1:** 1435 (469)[+] **Group 2:**4801 (1239) **Group 1:** 3405 (532) **Group 2:** 4801 (1239)	**Randomisation:** computer generated randomisation list **Allocation concealment:** Unclear **Blinding:** Unclear **Limitations:** -All patients receiving colloid received Ringer's lactate in addition. -Intraoperative population [+] these groups also had crystalloid administered as follows: Group 1: 1970 (250) Group 2: 1794 (270) **Additional outcomes:** • Haemostasis measurements and coagulation factors. **Notes:** *calculated by NCGC -study also compared a group who received HES (6% Isohas 200/0.5, Fresenius, Pharma Austria GmbH) + lacatated Ringers for resuscitation.

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Austria GmbH) N:20 Age (mean ± SD): 71 (9) Drop outs: NR Tourniquet time (min):83 (29) Duration of surgery (min): 145 (28) Intraoperative blood loss (mL): 336 (168) Total blood loss (mL): 577 (228)	correct IV volume deficit resulting from starving period and basal requirements. After surgery, administered amounts of basis RL reduced to 4mL/kg/hr at observation ward, and blood loss compensated for by group specific fluid administration as during surgery.			

Abbreviations: ASA= American society of anaesthesiologist, CAD=: Coronary artery disease, CVP= central venous pressure, HES= hydroxyethyl starch, HR=hazard ratio, HR= Heart rate, ITT=Intention to treat analysis, ISS=Injury severity score, ITBVI= intrathoracic blood volume index, MAP= Mean arterial pressure, M/F=male/female, mL= millilitres, mEq= millieqivalent, N=total number of patients randomised, NISS=New injury severity score, NS= Not significant, RIFLE= Risk, Injury, Failure, Loss and End-stage serum creatinine criteria, SD= standard deviation, SE=Standard Error, SICU= Surgical ICU, SOFA= Sequential Organ Failure Assessment, $ScvO_2$= Central venous oxygen saturation, UFH= unfractionated heparin

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
GODET 2008[138] **Study design:** RCT **Setting:** Intraoperative and post operative,	**Patient group:** Patients undergoing abdominal aortic surgery. **Inclusion criteria:** Male of female patients aged >18 years scheduled for elective abdominal aortic surgery, with creatinine clearance <80mL/min. **Exclusion criteria:** Endovascular aortic surgery, preoperative serum creatinine >250umol/L, dialysis, anuria, post transplant status, history of or present diagnosis of severe hepatic insufficiency or coagulation disorders. **All patients**	**Group 1- 3% Gelatin (Plasmion, Fresenius Kabi)** **Group 2- 6% HES (130kDa/ 0.4 Voluven, Fresenius Kabi)** -maximum dose 50mL/kg body weight. **Both groups:**	**Mortality**	**Group 1:** 2/33 (6%) **Group 2:** 2/32 (6.3%)	**Randomisation:** randomisation list generated by DATAMAP. Using balanced blocks- 1st block of 8 for each centre, then blocks of 4 for all following blocks. **Allocation concealment:** investigator received set of envelopes identified by the randomisation number with each containing a letter specifying the treatment of the corresponding patient. Envelope opened only when
			Volume of study fluid administered (mL) Mean (SD)	**Group 1:** 2136 (1174) **Group 2:** 2350 (1355)	
			Total volume of fluid	**NR**	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
ICU. **Duration of follow-up:** 6 days post-operatively **Funding:** NR	N: 67 Age (mean): Drop outs: 2 **Group 1- Gelatin** N: 33 Age (mean ± range): 73 (55-86) Drop outs: 1 Serum creatinine on admission (mL/min): 54.3 (30.9-76.8) **Group 2- HES** N: 32 Age (mean ±range): 72.9 (57-89) Drop outs: 1 Serum creatinine on admission(mL/min): 55.1 (22.1-79.7)	Perioperative volume substitution according to anaesthetists judgement, taking into account CVP, arterial pressure, fluid balance and need for catecholamines. - maintenance fluid with crystalloid (>1.5L intraoperatively and >1.5L crystalloids per day postoperatively.	**received** (mL) **LOS (ICU)** (days) Median (range) **ICU (Hospital)** (days) Median (range)	 **Group 1:** 1 (0-7) **Group 2:** 1 (1-33) **Group 1:** 10 (6-24) **Group 2:** 10 (6-48)	patient arrived at pre-anaesthsia room. **Blinding:** unclear **Other limitations:** -patients received crystalloid as maintenance fluid. **Additional outcomes:** **Notes:** -paper states ITT, 2 dropouts-1 did not received study medication and one had surgery delayed.

Abbreviations: ASA= American society of anaesthesiologist, CAD=: Coronary artery disease, CVP= central venous pressure, HES= hydroxyethyl starch, HR=hazard ratio, HR= Heart rate, ITT=Intention to treat analysis, ISS=Injury severity score, ITBVI= intrathoracic blood volume index, MAP= Mean arterial pressure, M/F=male/female, mL= millilitres, mEq= millieqivalent, N=total number of patients randomised, NISS=New injury severity score, NS= Not significant, RIFLE= Risk, Injury, Failure, Loss and End-stage serum creatinine criteria, SD= standard deviation, SE=Standard Error, SICU= Surgical ICU, SOFA= Sequential Organ Failure Assessment, $ScvO_2$= Central venous oxygen saturation, UFH= unfractionated heparin

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
GONDOS 2010[141] **Study design:** RCT **Setting:** 11 ICUs, Hungary.	**Patient group:** Mixed post operative hypovolaemic patients **Inclusion criteria:** Haemodynamically stable patients **Exclusion criteria:** <18 years, active bleeding or shock, severe pulmonary oedema, known uraemia, anaphylactoid reaction to colloid fluid and a life	**Group 1- Gelatin (4% w/v succinylated gelatin)** **Group 2- HES (waxy, maize derived 130/0.4 hydroxyethystarch 6% w/v)** **Group 3- Ringer's lactate**	**Mortality (in ICU)** n (%) **ICU LOS**	**Group 1:** 12/50 (24%) **Group 2:** 14/50 (28%) **Group 3:** 15/50 (30%) **Group 1:** 6 (2-	**Randomisation:** blinded envelope technique **Allocation concealment:** Unclear **Blinding:** Unclear **Limitations:**

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
January 2005-December 2008. **Duration of follow-up:** 1st post operative hour to 10th postoperative day **Funding:** Supported in part by: Fresenius Kabi, Pulsion medical systems AG, MEDIAL, HUMAN BioPlazma LLC. Grants covered PiCCO catheter sets and human albumin infusions)	expectancy of <24 hr. **All patients** **N:** 200 **Age (mean):** NR **Sex (m/f):** NR **Drop outs:** NR **Group 1- Gelatin (4% w/v succinylated gelatin)** **N:** 50 **Age (mean):** 60 (15) **Sex (m/f):**26/24 **Drop outs:** NR **ASA risk category (median, IQR):**3 (2-4) **SAPS II (median, IQR):** 38 (19-50.5) **APACHE II (median, IQR):** 15 (8-22.5) **Creatinine (umol/L):** 93 (78-125) **Number of patients on mechanical ventilation:** 48 **Patients with organ failure at study entry:**37 **Severe sepsis at study entry:**25 **Group 2- HES (waxy, maize derived 130/0.4 hydroxyethylstarch 6% w/v)** N: 50 Age (mean): 59 (13) Sex (m/f): 21/29 Drop outs: NR ASA risk category (median, IQR): 3 (2-3) SAPS II (median, IQR): 37 (22.5- 50)	**Group 4- Albumin (5% w/v)** **All groups:** 10mL/kg of volume loading was given over 30 minutes in each group. Complete haemodynamic profile obtained after 30, 45, 60, 90 and 120 minutes. During this time maintenance infusions of crystalloid limited to maximum of 1mL/kg/hr, and no changes made to any vasoactive agents.	Days (median, IQR)	18) **Group 2:** 7.5 (2-12) **Group 3:** 7 (2-12)	Crystalloid administered as maintenance fluid alongside colloid- not stated what crystalloid was used. **Additional outcomes:** • Outcomes for sepsis and non-sepsis subgroups

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	APACHE II (median, IQR): 15 (8-21.5) Creatinine (umol/L): 102 (75- 135) Number of patients on mechanical ventilation: 48 Patients with organ failure at study entry: 31 Severe sepsis at study entry: 22 **Group 3- Ringer's lactate** N: 50 Age (mean): 58 (16) Sex (m/f): 30/20 Drop outs: NR ASA risk category (median, IQR): 3 (2-3.75) SAPS II (median, IQR): 35 (13.5- 49) APACHE II (median, IQR): 14 (8-21) Creatinine (umol/L): 99 (75-119) Number of patients on mechanical ventilation: 46 Patients with organ failure at study entry: 27 Severe sepsis at study entry: 24 **Group 4- Albumin (5% w/v)** N: 50 NR as not comparator for this review				

Abbreviations: ASA= American society of anaesthesiologist, CAD=: Coronary artery disease, CVP= central venous pressure, HES= hydroxyethyl starch, HR=hazard ratio, HR= Heart rate, ITT=Intention to treat analysis, ISS=Injury severity score, ITBVI= intrathoracic blood volume index, MAP= Mean arterial pressure, M/F=male/female, mL= millilitres, mEq= millieqivalent, N=total number of patients randomised, NISS=New injury severity score, NS= Not significant, RIFLE= Risk, Injury, Failure, Loss and End-stage serum creatinine criteria, SD= standard deviation, SE=Standard Error, SICU= Surgical ICU, SOFA= Sequential Organ Failure Assessment, $ScvO_2$= Central venous oxygen saturation, UFH= unfractionated heparin

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
JIN 2010[198]	**Patient group:**	**Group 1- Gelatin**	**Volume of study**	**Group 1:** 3809 (392)	**Randomisation:** closed envelopes.

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Study design: RCT **Setting:** Intraoperative **Duration of follow-up:** 4 hours after infusion of iv fluid **Funding:** Shanghai Science and technology development fund, China.	Patients undergoing gastrectomy. **Inclusion criteria:** Patients undergoing gastrectomy. **Exclusion criteria:** Cardiac insufficiency, renal insufficiency, altered liver function, preoperative anaemia, preoperative coagulation abnormalities, gelatin or HES allergy, use of anticoagulant or antiplatelet medicine before surgery. **All patients** **N:** 36 **Age (range):** 28-58 **Drop outs:** NR **Group 1- Gelatin** **N:** 12 **Age (mean ± SD):** 55 (10) **m/f:** 6/10 **Drop outs:** NR **Duration of anaesthesia (min):** 213 (40) **Group 2- HES** **N:** 12 **Age (mean ± SD):** 49 (10) **m/f:** 5/11 **Drop outs:** NR **Duration of anaesthesia (min):** 197 (31) **Group 3- RL** **N:** 12 **Age (mean ± SD):** 53 (10)	4% modified fluid gelatin. Gelofusine, Braun company. **Group 2- HES** 6% Hydroxyethylstarch 130/0.4, Voluvenm Fresenius. **Group 3-RL** Lactated ringer's solution. **All groups:** All patients received routine monitoring. Patients were randomised 5 minutes after entering the operating room. All infusions at rate of 30mL/kg/hr from 20 minutes before to 40 minutes after the induction of general anaesthesia.	**fluid received (mL)** Mean (SD)	**Group 2:** 3916 (666) **Group 3**: 4190 (327)	**Allocation concealment:** NR **Blinding:** Patients were managed by anaesthiologists who were not involved in the study and were blinded to the grouping. **Other limitations:** -lack of important baseline demographics -Intraoperative population. **Additional outcomes:** • Haemodynamic data
			Total volume of study fluid administered	As above	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	m/f: 4/6 **Drop outs:** NR **Duration of anaesthesia (min):** 199 (20)				

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Study details	Patients	Interventions	Outcome measures	Effect size	Comments
MAHMOOD 2009[235] **Study design:** RCT **Setting:** Intraoperative **Duration of follow-up:** 24 hours post surgery **Funding:** Fresenius Kabi	**Patient group:** Patients undergoing elective infrarenal abdominal aortic aneurysm surgery. **Inclusion criteria:** Patients undergoing elective infrarenal abdominal aortic aneurysm surgery. **Exclusion criteria:** Patients with renal tansplants, iliac occlusive disease, pre-operative serum creatinine of >177mmol/L, left ventricular ejection fraction of <40% and juxta renal aneurysms. **All patients** **N:** 62 **Age (mean):** NR **Drop outs:** NR **Group 1-Gelatin** **N:** 20 **Age (mean ± SD):** 73 (8)	**Group 1- Gelatin, Gelofusine, Braun** **Group2- HES, 130kDa, 0.4, Voluven, Fresenius Kabi** **All groups:**	**Mortality (at 30 days)**	**Group 1:** 6/20 (30%) **Group 2:**1/21 (5%)	**Randomisation:** blocks of 6 using a random number table. **Allocation concealment:** sealed envelopes **Blinding:** recruitment randomisation and concealment carried out by trial coordinator **Other limitations:** -Results for starches reported separately. -Intraoperative population -lack of useful baseline characteristics - *could not report total fluid administered as crystalloid reported as medican (IQR) and colloid reported as mean
			Volume of study fluid received (mL) mean (SD)	**Group 1:** 4490 (1499) **Group 2:** 3911 (1783)*	
			Volume of crystalloid administered (mL) Median (IQR)	**Group 1:** 4975 (4203- 5565) **Group 2:** 5750 (5110- 6695)	
			Total volume of fluid	**NR***	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	m/f: 15/5 **Drop outs:** 0 **Intraoperative inotropes:**3 **Postoperative inotropes:** 5 **Group 2- HES 130 kDa** **N:** 21 **Age (mean ± SD):** 72 (7) **m/f:** 19/2 **Drop outs:** 0 **Intraoperative inotropes:**6 **Postoperative inotropes:** 9		**administered**		(SD) **Notes:** Study also reported data on use of HES 200 kDa (data not used as pentastarcehs excluded from review protocol)

Abbreviations: ASA= American society of anaesthesiologist, CAD=: Coronary artery disease, CVP= central venous pressure, HES= hydroxyethyl starch, HR=hazard ratio, HR= Heart rate, ITT=Intention to treat analysis, ISS=Injury severity score, ITBVI= intrathoracic blood volume index, MAP= Mean arterial pressure, M/F=male/female, mL= millilitres, mEq= millieqivalent, N=total number of patients randomised, NISS=New injury severity score, NS= Not significant, RIFLE= Risk, Injury, Failure, Loss and End-stage serum creatinine criteria, SD= standard deviation, SE=Standard Error, SICU= Surgical ICU, SOFA= Sequential Organ Failure Assessment, $ScvO_2$= Central venous oxygen saturation, UFH= unfractionated heparin

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
VERHEIJ 2006[376] **Study design:** RCT **Setting:** Postoperative ICU	**Patient group:** Postoperative cardiac and vascular surgery patients **Inclusion criteria:** Presumed hypovolaemia, , systolic bp <110mmHg and reduced filling pressures. At enrolment PWCP had to be <13mmHg and CVP 12mmHg **Exclusion criteria:** Age >79 years, known anaphylactoid reaction to	**Group 1- 4% Gelatin** **Group 2- 6% HES** **Group 3- 0.9% NaCl** **Group 4- 5% Albumin** **Both groups:**	**Mortality**	**Group 1:** 1/16 (6.3%) **Group 2:** 0/17 **Group 3:** 1/16 (6.3%)	**Randomisation:** carried out by hospital pharmacy, sealed envelope technique after stratification. **Allocation concealment:** Unclear **Blinding:** single blind, all perioperative care given by
			Volume of study fluid received (from 0-90	**Group 1:** 1800 (900-1800) **Group 2:** 1400 (750- 1800)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Duration of follow-up: Unclear **Funding:** Unrestricted grant from Braun	colloids. **All patients** **N:** 68 **Age (mean):** NR **Drop outs:** 1 **Group 1- Gelatin (all median. Range unless otherwise stated)** **N:** 16 **Age (median, range):** 63 (41-75) **m/f:** 16/0 **Drop outs:** NR **APACHE II:** 8 (2-18) **Number undergoing CPB:** 7 **Number undergoing aortic clamp:** 14 **Group 2- HES (all median. Range unless otherwise stated)** **N:** 17 **Age:** 66 (38-74) **m/f:** 10/7 **Drop outs:** NR **APACHE II:** 9 (2-14) **Number undergoing CPB:** 11 **Number undergoing aortic clamp:** 13 **Group 3- 0.9% NaCl (all median. Range unless otherwise stated)** **N:** 16 **Age:** 64 (53-75)	At arrival of patient in ICU, study protocol started. Fluids dosed during 90 minutes, on basis of response within predefined pressure limits, as measured by pulmonary artery catheter or central venous catheter according to protocol. Concomitant treatment and ventilator settings remained unchanged during fluid loading.	**minutes)** (mL) Median (range)	**Group 3:** 1800 (1300-1800)	physicians unaware of group assignment. **Other limitations:** - Mixed population of postoperative patients- some received CPB. -reported fluid input in median (range) -No information about manufacturer of fluid, molecular weight, substitution or volume administered. **Additional outcomes:** • Haemodynamic data

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	m/f: 14/2 **Drop outs:** NR **APACHE II:** 8 (3-17) **Number undergoing CPB:** 8 **Number undergoing aortic clamp:** 14 **Group 4- Albumin** **N:** 18 **Other details NR as not comparison of interest.**				

Abbreviations: ASA= American society of anaesthesiologist, CAD=: Coronary artery disease, CVP= central venous pressure, HES= hydroxyethyl starch, HR=hazard ratio, HR= Heart rate, ITT=Intention to treat analysis, ISS=Injury severity score, ITBVI= intrathoracic blood volume index, MAP= Mean arterial pressure, M/F=male/female, mL= millilitres, mEq= millieqivalent, N=total number of patients randomised, NISS=New injury severity score, NS= Not significant, RIFLE= Risk, Injury, Failure, Loss and End-stage serum creatinine criteria, SD= standard deviation, SE=Standard Error, SICU= Surgical ICU, SOFA= Sequential Organ Failure Assessment, $ScvO_2$= Central venous oxygen saturation, UFH= unfractionated heparin

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
WU 2001[408] **Study design:** RCT **Setting:** Emergency room, Taiwan. July 1997 – February 1998 **Duration of follow-up:** Unclear **Funding:** NR	**Patient group:** Adults >16 years admitted to emergency room requiring resuscitation. **Inclusion criteria:** >16 years, MAP <80mmHg or systolic b.p <100mmHg, impression of haemorrhagic or spinal shock. **Exclusion criteria:** Pregnancy, history of congestive heart disease, intubated mechanically ventilated patients; patient's refractory to initial fluid challenge. **All patients** **N**: 41 **Age (mean):** **Drop outs:** 7* **Group 1-** **N:** 18 **Age (mean ± SD):** 41.3 (19.1) **m/f:** 13/5 **Drop outs:** NR **Group 2-** **N:** 16 **Age (mean ± SD):** 47.8 (19.1) **m/f:** 8/8 **Drop outs:** NR	**Group 1- Gelatin + RL** 4% Succinylated gelatin **Group 2- Ringer's lactate** **Both groups:** -Received Ringer's lactate. -1000mL of fluid administered within 10-15 minutes. Measurements taken at 15, 30, 60 minutes. During study period another 1000mL of Ringer's lactate was continually infused in both groups. -No other IV fluids, inotropic drugs or vasopressors agents were administered.	**Mortality**	**Group 1:** 2/18 (11.1%) **Group 2:** 3/16 (18.8%)	**Randomisation:** randomly allocated, method not described. **Allocation concealment:** NR **Blinding:** Unclear **Other limitations:** -Both groups received Ringer's lactate. * does not give detail about which groups those excluded were randomised to. -Lack of relevant patient demographics -demographics include patients in final analysis only **Additional outcomes:** • Haemodynamic variables **Notes:** -Patients who completed the study protocol ere included in the final analysis. -Patients who required surgical intervention, blood transfusion, or intubation with positive pressure ventilation were dropped from the study.

Abbreviations: ASA= American society of anaesthesiologist, CAD=: Coronary artery disease, CVP= central venous pressure, HES= hydroxyethyl starch, HR=hazard ratio, HR= Heart rate, ITT=Intention to treat analysis, ISS=Injury severity score, ITBVI= intrathoracic blood volume index, MAP= Mean arterial pressure, M/F=male/female, mL= millilitres, mEq= millieqivalent, N=total number of patients randomised, NISS=New injury severity score, NS= Not significant, RIFLE= Risk, Injury, Failure, Loss and End-stage serum creatinine criteria, SD= standard deviation, SE=Standard Error, SICU= Surgical ICU, SOFA= Sequential Organ Failure Assessment, $ScvO_2$= Central venous oxygen saturation, UFH= unfractionated heparin

1

2 **E.3.2 Hydroxyethylstarches**

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Dubin et al. 2010 [103] **Study design:** RCT **Randomisation:** Unclear **Comparison**: 6% HES 130/0.4 vs 0.9% sodium chloride solution **Allocation concealment:** Sealed envelopes used; Clinical personnel were not blinded to allocation **Blinding:** No blinding of clinical personnel **Setting:** Hospital setting, Argentina	**Patient group:** Patients with severe sepsis randomized to early goal directed therapy for resuscitation **Inclusion criteria:** 18 years or older; confirmed or suspected infection plus 2 or more signs of of the systemic inflammatory response syndrome (definition of sepsis by the American College of Chest Physicians/ society of Critical Care Medicine criteria); tissue hypoperfusion (MAP <65 mm of Hg despite a crystalloid challenge of 20mL/kg or blood lactate concentration of 4 mmol/L or higher). **Exclusion criteria:** Impossibility to perform sublingual videomicroscopy, age > 18 years, pregnancy, stroke, acute coronary syndrome, hydrostatic pulmonary edema, status asthmaticus, cardiac arrhythmias, contraindication for central venous catheterization, active gastrointestinal haemorrhage, seizures, drug intoxications, burns, trauma, need of immediate surgery, terminal cancer, immunosuppression (organ transplant or systemic illness), no resuscitation order, delayed admission to ICU from emergency department (> 4 hours) or previous resuscitation with more than 1500 mL of fluids. **All patients** **N:** 25 (randomized) **Age (mean):** NR **Drop outs:** 4 (death before 24 hours) **Group 1- 6% HES 130/0.4** **N:** 12 (randomized); 9 (analysed)	**Group 1- 6% HES 130/0.4** Intravenous volume expansion with 6% HES solution 130/0.4 **Group 2- 0.9% sodium chloride solution** Intravenous volume expansion with 0.9% sodium chloride solution Targets to be achieved were: • CVP: 8-12 mm of Hg • MAP: 65 mm of Hg or higher • $ScvO_2$: 70% or greater • If needed, vasopressors, dobutamine, or blood transfusions were administered in	**Morbidity [SOFA score at 24 hours (mean ± SD)]**	**Group 1:** 6.9±2.6 **Group 2:** 8.4±3.7	**Funding:** Agencia Nacional de Promocion Cientifica y Tecnologica, Argentina **Additional limitations:** • Patients receiving saline solution had higher serum creatinine levels at baseline than those receiving 6% HES (p value: 0.0480) • Small sample size **Additional outcomes:** • Improvement in sublingual microcirculation taking into account microvascular flow index (MFI), heterogeneity of perfusion, percent of perfused vessels. • Change in mean arterial pressure, central venous pressure and central venous oxygen

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Duration of follow-up: 24 hours	**Age (mean ± SD):** 62±21 years **Drop outs:** 2 (death before 24 hours); 1 (excluded from analysis as sepsis excluded as diagnosis) **Serum creatinine on admission (mg/dL):** 1.2±0.3 **SOFA score on admission:** 8.1±2.5 **Group 2- 0.9% Sodium chloride solution** **N:** 13 (randomized); 11(analysed) **Age (mean ± SD):** 65±12 years **Drop outs:** 2 (death before 24 hours) **Serum creatinine on admission(mg/dL):** 2.1±1.2 **SOFA score on admission:** 8.9±3.6	addition to above in both groups.			saturation.

Abbreviations: ASA= American society of anaesthesiologist, CAD=: Coronary artery disease, CVP= central venous pressure, HES= hydroxyethyl starch, HR=hazard ratio, HR= Heart rate, ITT=Intention to treat analysis, ISS=Injury severity score, ITBVI= intrathoracic blood volume index, MAP= Mean arterial pressure, M/F=male/female, mL= millilitres, mEq= millieqivalent, N=total number of patients randomised, NISS=New injury severity score, NS= Not significant, RIFLE= Risk, Injury, Failure, Loss and End-stage serum creatinine criteria, SD= standard deviation, SE=Standard Error, SICU= Surgical ICU, SOFA= Sequential Organ Failure Assessment, $ScvO_2$= Central venous oxygen saturation, UFH= unfractionated heparin

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
James 2011[191] **Study design:** RCT **Comparison**: 6% HES vs 0.9% sodium chloride **Randomisation:** By random numbers grouped in blocks of 8 for each category	**Patient group:** Shocked trauma patients requiring greater than 3 litres of fluid resuscitation **Inclusion criteria:** Penetrating or blunt trauma; requiring > 3 litres volume resuscitation; had received a maximum of 2 litres of crystalloids before randomisation; age 18-60 years **Exclusion criteria:** Fluid overload pulmonary edema; known allergy to hydroxyethyl starch; known pre-existing renal failure with oliguria or anuria; patients receiving	**Group 1-** Patients with penetrating trauma and patients with blunt trauma who received HES in saline (Voluven) for resuscitation. **Group 2-** Patients with penetrating trauma and	**All cause mortality [measured at 30 days)** **Morbidity [measured by SOFA scores (median,**	Group 1: 12/56 Group 2: 6/53 P-HES: 2 (0-10) P- saline: 4.5 (0-17) B-HES: 6 (0-19) B-Saline: 4	**Funding:** Fresenius-Kabi provided unrestricted educational grant + fluids **Limitations:** • Injury severity was greater in the B-HES group as compared to

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
of trauma in ratio of 1:1 for the study fluid; pre-packed boxes of fluids placed sequentially **Allocation concealment:** Unclear **Blinding:** Fluids sealed n identical bags in black plastic which concealed label and contents; Blinding of investigators unclear **Setting:** Level 1 trauma unit, South Africa **Duration of follow-up:** 30 days	dialysis treatment before the injury; severe hypernatraemia or hyperchloraemia on admission; severe head injury from which recovery was unlikely; severe intracranial bleeding; severe crush injury; unrecordable arterial pressure unresponsive to 2 litre i.v fluid loading; clinically obvious cardiac tamponade; neurogenic shock (high spinal cord injury); known AIDS or AIDS related complex; patients admitted >6 hours after injury; patients who have already received any colloid before randomization; patients taking part in another clinical trial at the same time; patients refusing consent **All patients** N: 115 (randomised- penetrating and blunt trauma) **<u>Penetrating trauma (P):</u>** N: 70 (randomised) **Group 1: P-HES** N: 36 (randomised), 36(analysed) Age, yrs (mean, range): 27.6 (18-49) Drop outs: 0 ISS (median, range): 18 (9-45) NISS 9median, range): 34(10-57) **Group 2: P-Saline** N: 34 (randomised), 31(analysed) Age, yrs (mean, range):32.6 (21-56) Drop outs: 3 were excluded, all alive -2 (under age), 1(protocol violation) ISS (median, range): 16 (8-34) NISS (median, range): 27(10-66) **<u>Blunt trauma(B):</u>** N: 45 (randomised) **Group 3: B-HES** N: 22(randomised), 20 (analysed)	patients with blunt trauma who received 0.9% sodium chloride for resuscitation. • Fluids were administered using clinical indicators of shock (CVP<12 mm of Hg, HR>100 beats per minute, ScV_{o2}< 70%, lactate>2.5mmol /litre) according to a pre-determined algorithm • Resuscitation was deemed complete when haemodynamic and renal targets were achieved and sustained • Study exit was defined as death or recovery of gastrointestinal function, defined as tolerance of full enteral feeding, from	**range)]** **AKI (n, %)**	(0-11) Group 1: 14/56 Group 2 : 23/53	the B-Saline group (difference in baseline characteristics) **Additional outcomes:** • Recovery of gastrointestinal function Deterioration in coagulation • Measures of resuscitation including heart rate, arterial pressure, central venous pressure and urine output • Skin itching: 7 in HES group and 5 in 0.9% NaCl group **Notes:** AKI includes patients with renal risk, renal injury and dialysis

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Age, yrs (mean, range): 33.0 (18-50) Drop outs: 2 were excluded- 1(received prior colloids, alive), 1(too old, severe head injury, died) ISS (median, range): 29.5 (9-57) NISS (median, range): 36(22-66) **Group 4: B-Saline** N: 23 (randomised), 22(analysed) Age, yrs (mean, range): 35.7 (20-58) Drop outs: 1 was excluded- unresponsive BP, died ISS (median, range): 18 (9-66) NISS (median, range): 27(13-66)	which point, no fluid was administered.			

Abbreviations: ASA= American society of anaesthesiologist, CAD=: Coronary artery disease, CVP= central venous pressure, HES= hydroxyethyl starch, HR=hazard ratio, HR= Heart rate, ITT=Intention to treat analysis, ISS=Injury severity score, ITBVI= intrathoracic blood volume index, MAP= Mean arterial pressure, M/F=male/female, mL= millilitres, mEq= millieqivalent, N=total number of patients randomised, NISS=New injury severity score, NS= Not significant, RIFLE= Risk, Injury, Failure, Loss and End-stage serum creatinine criteria, SD= standard deviation, SE=Standard Error, SICU= Surgical ICU, SOFA= Sequential Organ Failure Assessment, $ScvO_2$= Central venous oxygen saturation, UFH= unfractionated heparin

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Myburgh et al. 2012[270] **Study design:** RCT **Comparison:** 6% HES (130.0.4) in 0.9%	**Patient group:** Adult patients in intensive care unit requiring fluids resuscitation. **Inclusion criteria:** Aged 18 years or older; fluid resuscitation was required to increase or maintain intravascular volume that was in addition to maintenance fluids, enteral and parenteral nutrition, blood products and specific replacement fluids to replace ongoing insensible or fluid losses from other sites; ICU clinician considered that both 6% hydroxyethyl starch (130/0.4) and saline are equally appropriate for the patient and that no specific indication or contraindication for either existed; the requirement for fluid resuscitation was supported by at least one of the following clinical signs: 1.Heart rate > 90 beats per minute	**Group 1- 6% HES (130/0.4) in 0.9% saline (Voluven, Fresenius Kabi)** Fluid administered to a maximum dose of 50 ml per kg of body weight per day, followed by open label 0.9% saline for the remainder of the	**Mortality within 28 days**	Group 1: 458/3313 (13.8%) Group 2: 437/3331 (13.1%) P value: 0.40	**Funding:** National Health and Medical Research Council, New South Wales Department of Health, Fresenius Kabi (unrestricted grant to the University of Sydney through
			Mortality within 90 days	Group 1: 597/3315 (18%) Group 2: 566/3336 (17.0%) P value: 0.26	
			New organ failure*-	Group 1: 540/2062	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
saline solution vs 0.9% saline solution; CHEST study (Crystalloid vs Hydroxyethyl Starch Trial) **Randomisation:** Adequate; encrypted web-based randomisation system with the use of a minimisation algorithm stratified according to institution and admission diagnosis of trauma.	2.Systolic blood pressure (SBP) < 100mmHg or mean arterial pressure (MAP) < 75mmHg or at least 40mmHg decrease in SBP or MAP from the baseline recording 3.Central venous pressure < 10mmHg 4.Pulmonary artery wedge pressure < 12 mmHg 5.Respiratory variation in systolic or mean arterial blood pressure of >5 mmHg 6.Capillary refill time > one second 7.Urine output < 0.5 ml/kg for one hour **Exclusion criteria:** Previous allergic reaction to hydroxyethyl starch solution; primary non-traumatic intracranial haemorrhage or severe traumatic intracranial haemorrhage (mass lesion > 25 ml); Patient was receiving renal replacement therapy or in whom the ICU physician considered renal replacement therapy is imminent (i.e. renal replacement therapy will start in 6 hours); documented serum creatinine value ≥ 350µmol/L and urine output averaging ≤ 10ml / hr over 12 hours; severe hypernatraemia (Serum sodium > 160 mmol/l) or severe hyperchloraemia (Serum chloride > 130 mmol/l); possibility of pregnancy-women of child bearing age (18-49 years old), unless evidence of documented menopause, hysterectomy or surgical sterilisation or negative pregnancy test before randomisation; breastfeeding; patient had received > 1000mL hydroxyethyl starch in the 24 hours before randomization; admitted to the ICU following cardiac surgery, treatment of burns or after liver transplantation surgery; death was deemed imminent and inevitable or the patient has an underlying disease process with a life expectancy of < 90 days; limitation of therapy order was documented restricting implementation of the study protocol or the treating clinician deemed aggressive care unsuitable; patient was previously enrolled in the CHEST study; patient previously received fluid resuscitation that was prescribed within the study ICU during this current ICU admission or patient was transferred to the study ICU from another ICU and received fluid resuscitation for the treatment of volume depletion in that other ICU.	24 hour period Study fluid was stopped in patients who were treated with any mode of renal-replacement therapy. In these patients, treatment with saline was recommended, but any other fluid, apart from HES was permitted. **Group 2- 0.9% saline solution** • Other aspects of patient care including maintenance fluids and nutrition, cardiovascular monitoring, pharmacologic support and respiratory and renal support were	**Respiratory**	(26.2%) Group 2: 524/2094 (25.0%) P value: 0.39	the George institute; no input into design and conduct of trial or into the statistical analysis plan) **Limitations:** Patients recruited after admission to the ICU and administration of resuscitation fluids outside ICU was not controlled. 1863 patients screened were eligible for study but excluded; of these 735 were overlooked for randomisation and 547 were withdrawn by the clinician(reasons not reported) and 235 were excluded for
			New organ failure*-Cardiovascular	Group 1: 663/1815 (36.5%) Group 2: 722/1808 (39.9%) P value:0.03	
			New organ failure*-Coagulation	Group 1: 142/2987 (4.8%) Group 2: 119/3010 (4.0%) P value:0.13	
			New organ failure*-Hepatic	Group 1: 55/2830 (1.9%) Group 2: 36/2887 (1.2%) P value:0.03	
			Renal outcome (RIFLE-R)	Group 1: 1788/3309 (54.0%) Group 2: 1912/3335 (57.3%) P value; 0.007	
			Renal outcome (RIFLE-I)	Group 1: 1130/3265 (34.6%) Group 2: 1253/3300 (38.0%) P value: 0.005	
			Renal outcome (RIFLE-F)	Group 1: 336/3243 (7%) Group 2: 301/3263 (9.2%) P value:0.12	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Allocation concealment: Adequate; Secure password protected file. **Blinding:** Adequate; use of indistinguishable Freeflex 500ml bags **Setting:** Intensive care units. **Duration of follow-up:** 90 days	**All patients** N: 7000(randomised); 6742 (included in the analysis), 6651(included in the 90 day analysis) **Group 1: 6% HES (130/0.4) in 0.9% saline** Age in years (mean±SD): 63.1±17.0 Weight in kg (mean±SD): 79.4±21.0 Surgical diagnosis on admission (n/total no.), %: 1426/3353 (42.5%) Non-surgical diagnosis on admission (n/total no.), %: 1920/3353 (57.3%) APACHE II score (median, IQR): 17.0 (12.0-22.0) Serum creatinine in µmol/liter: 101.5±57.1 **Pre-defined subgroups: n/total no. (%)** Sepsis subgroup: 979/3355 (29.2%) Trauma subgroup: 267/3358(8%) APACHE II score≥25:597/3335(17.9%) Receipt of HES before randomisation: 509/3347 (15.2%) **Group 2: 0.9% saline solution** Age in years (mean±SD): 62.9±16.9 Weight in kg (mean±SD): 78.6±20.8 Surgical diagnosis on admission (n/total no.), %: 1450/3379 (42.9%) Non-surgical diagnosis on admission (n/total no.), %: 1926/3379 (57.0%) APACHE II score (median, IQR): 17.0 (12.0-23.0) Serum creatinine in µmol/liter: 101.5±57.1 **Pre-defined subgroups: n/total no. (%)** Sepsis subgroup: 958/3376(28.4%) Trauma subgroup: 265/3384(7.8%) APACHE II score≥25: 624/3356(18.6%) Receipt of HES before randomisation: 508/3372 (15.1%)	conducted at the discretion of the treating clinicians.	**Length of stay in ICU in days (mean, SD)** **Length of stay in hospital in days (mean,SD)**	Group 1: 7.3±0.2 Group 2: 6.9±0.2 P value: 0.07 Group 1: 19.3±0.3 Group 2: 19.1±0.3 P value: 0.72	other reasons (not reported) Differences in number of patients reported as having sepsis at baseline and at randomisation. **Notes:** Administration of resuscitation fluids outside the ICU was not controlled. *New organ failure was defined as SOFA score of at least 3 for each category in patients who did not have such organ failure at baseline.

Abbreviations: ASA= American society of anaesthesiologist, CAD=: Coronary artery disease, CVP= central venous pressure, HES= hydroxyethyl starch, HR=hazard ratio, HR= Heart rate, ITT=Intention to treat analysis, ISS=Injury severity score, ITBVI= intrathoracic blood volume index, MAP= Mean arterial pressure, M/F=male/female, mL= millilitres, mEq= millieqivalent, N=total

number of patients randomised, NISS=New injury severity score, NS= Not significant, RIFLE= Risk, Injury, Failure, Loss and End-stage serum creatinine criteria, SD= standard deviation, SE=Standard Error, SICU= Surgical ICU, SOFA= Sequential Organ Failure Assessment, $ScvO_2$= Central venous oxygen saturation, UFH= unfractionated heparin

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Perner et al. 2012[300] **Study design:** RCT **Comparison:** 6% HES 130/0.42 in Ringer's acetate vs Ringer's acetate 6S study(Scandinavian Starch for Severe Sepsis/Septic Shock) **Randomisation and allocation concealment:** Adequate; Phone-based randomisation around the clock (CTU) each patient had a unique patient-number and a randomisation number. A computer program (CTU) generated the coding list with the numbers for the bottle. At randomisation, the computer program (CTU) allocated numbered bottles from specific trial site to the patient.	**Patient group:** Patients with severe sepsis in intensive care unit (ICU). **Inclusion criteria:** Aged 18 years or older; needed fluid resuscitation in the ICU, as judged by the ICU clinicians; fulfilled the criteria for severe sepsis* within the previous 24 hours (criteria for severe sepsis: Severe sepsis was defined as sepsis plus at least one organ failure, except when that organ failure was already present 48 hours before the onset of sepsis) **Exclusion criteria:** < 18 years of age; had renal replacement therapy; had kidney or liver transplantation; had burn injury >10% of body surface; had intracranial bleeding; had serum potassium > 6 mmol/liter within 6 hrs before screening; were included in another ICU trial; withdrew from active therapy; received > 1000 ml of synthetic colloid; consent could not be obtained. **All patients** N: 804(randomised); 798 (included in 90 day analysis); 4 excluded after randomisation (2 randomised without consent, 2 violated exclusion criteria and no trial fluid had been given) **Group 1: HES 130/0.42** N: 400(randomised); 398 (included in the 90 day	**Group 1- 6% HES 130/0.42 (Tetraspan 6%, B. Braun)** **Group 2- Ringer's acetate (Sterofundin ISO, B. Braun)** **For both groups:** • Trial fluid used for a maximum of 90 days when ICU clinicians judged that volume expansion was needed. • The maximum daily dose was 33 ml per kilogram of ideal body weight. • The maximum daily dose of trial fluid was based on estimated ideal body weight (men: estimated height in cm – 100; women: estimated height in cm – 105). • The calculated maximum daily dose of trial fluid (ideal body weight in kg x 33 ml/kg) was reduced to the nearest 500 ml. • On the 1st day of the trial, any volume of synthetic	**Mortality at 90 days, n (%)**	Group1: 201/398(51%) Group 2: 172/400 (43%) P value: 0.03	**Funding:** Grants from the Danish Research Council, the Rigshospitalet Research Council, and the Scandinavian Society of Anesthesiology and Intensive Care Medicine (funded by the ACTA Foundation); grant support from Fresenius Kabi. **Limitations:** **Additional outcomes:** **Notes:** *Sepsis was defined as a (1) defined focus of
			Mortality at 28 days	Group1: 154/398(39%) Group 2: 144/400 (36%) P value: 0.43	
			SOFA score at day 5 (median, IQR)	Group1: 6 (2-11) Group 2: 6 (0-10) P value: 0.64	
			Doubling of plasma creatinine level, n(%)	Group1: 148/398(41%) Group 2: 127/400 (35%) P value: 0.43	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Blinding: Adequate; Trial fluid visually identical and delivered in identical 500 ml 'flexibag' plastic bottles, put in black plastic bags and sealed by trial personnel not involved in randomisation or treatment of patients **Setting:** ICU setting. **Duration of follow-up:** 90 days	analysis) Age(Median, IQR): 66 (56-75) Ideal body weight in kg (Median, IQR): 72 (60-80) Admitted to university hospital, n(%): 194 (49%) SOFA score (median, IQR): 7 (5-9) Shock** at randomisation, n (%): 336(84%) AKI, n (%): 142(36%) **Group 2: Ringer's acetate** N: 400(randomised); 400 (included in the 90 day analysis) Age(Median, IQR): 67 (56-76) Ideal body weight in kg (Median, IQR): 72 (60-80) Admitted to university hospital, n(%): 188 (47%) SOFA score (median, IQR): 7 (5-9) Shock** at randomisation, n (%): 337(84%) AKI, n (%): 140(35%)	colloids given in the 24 hours prior to randomization was subtracted from the calculated maximum daily dose of trial fluid allowed. • If doses higher than the maximum daily dose were required, unmasked Ringer's acetate was used, regardless of the treatment assignment. • In the event of severe bleeding, a severe allergic reaction, or the commencement of renal-replacement therapy for acute kidney injury, trial fluid was permanently stopped and 0.9% saline or Ringer's acetatewas given for volume expansion in the ICU until 90 days after randomization. • All other interventions were at the discretion of the ICU clinicians, and crystalloid and albumin solutions were allowed for indications	**Use of mechanical ventilation**	Group1: 325/398(82%) Group 2: 321/400 (80%) P value: 0.61	infection AND (2) at least TWO systemic inflammatory response syndrome (SIRS) criteria. **Shock at randomisation was defined as MAP less than 70 mm of Hg, the need for ongoing treatment with vasopressor or inotropic agents, or a plasma lactate level of more than 4.0 mmol/L in the hour before randomisation.

Abbreviations: ASA= American society of anaesthesiologist, CAD=: Coronary artery disease, CVP= central venous pressure, HES= hydroxyethyl starch, HR=hazard ratio, HR= Heart rate, ITT=Intention to treat analysis, ISS=Injury severity score, ITBVI= intrathoracic blood volume index, MAP= Mean arterial pressure, M/F=male/female, mL= millilitres, mEq= millieqivalent, N=total number of patients randomised, NISS=New injury severity score, NS= Not significant, RIFLE= Risk, Injury, Failure, Loss and End-stage serum creatinine criteria, SD= standard deviation, SE=Standard Error, SICU= Surgical ICU, SOFA= Sequential Organ Failure Assessment, $ScvO_2$= Central venous oxygen saturation, UFH= unfractionated heparin

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Guidet et al. 2012[155] **Study design:** RCT **Comparison:** 6% HES 130/0.4 vs 0.9% saline. **Randomisation and allocation concelament:** Details of randomisation procedure and allocation concealment not reported **Blinding:** investigational and control drugs were identical in appearance and packaging, and were labelled with randomization numbers; No additional details provided. **Setting:** ICU setting, Hospitals in	**Patient group:** Patients suffering from severe sepsis. **Inclusion criteria:** Patients aged ≥18 years, who required fluid resuscitation, and who had clinically defined severe sepsis, were included in the study **Exclusion criteria:** Pre-existing renal impairment (known serum creatinine >3.39 mg/dla, anuria lasting more than 8 hours despite fluid resuscitation, requirement for renal support - either continuous or discontinuous techniques, including intermittent hemodialysis, hemofiltration, and hemodiafiltration); Potential effect on the primary endpoint (volume expansion with >3 L of fluid (crystalloid and/or colloid) since diagnosis of severe sepsis or refractory septic shock, patients receiving norepinephrine or epinephrine at a dose >0.5 µg/kg/min or dopamine at a dose >15 µg/kg/min at the time of screening) **All patients** N: 196 (randomised); **Group 1:** 6% HES 130/0.4 N: 100(randomised), 88 (included in efficacy analysis), 81(completed the treatment period of 4 days) Age in years, mean ± SD: 65.8 ± 15.4 Type of admission; Medical, n(%):73 (73%) Surgical, n(%): 27 (27%) Renal impairment prior to screening*, n (%):62 (63.9%) SOFA at screening, mean: 7.9 Fluid input prior to randomization, ml/kg body weight, mean ± SD: 35.5 ± 25.3	**Group 1- 6% HES 130/0.4 (Voluven)** **Group 2- 0.9% sodium chloride solution** • Patients received either 6% HES 130/0.4 (colloid treatment group) or sodium chloride (NaCl 0.9%) (crystalloid control group), • The maximum allowed dose for both treatment groups was 50 ml/kg/day (≤8 × 500 ml bags/day for patients weighing ≥80 kg) on the first day and 25 ml/kg/day (≤4 × 500 ml bags/day for patients weighing ≥80 kg) from the second to the fourth day. If extra fluid was required beyond this daily volume	**Mortality rate until day 28**	Group 1: 31/100 (31%) Group 2:24/95 (25.3%)	**Funding:** Fresenius Kabi Deutschland GmbH **Limitations:** • Discrepancy in reported numbers of persons randomised (180 in text and 196 in table) • Study not designed or powered to assess effects on mortality **Additional outcomes:** • Number of patients not reaching HDS • Time to reach hemodynamic stabilisation **Notes:** Study designed to determine whether lower volume of resuscitation fluid and a shorter time to hemodynamic stabilisation could be achieved in patients with severe sepsis treated with 6% HES 130/0.4 vs.
			Mortality rate until day 90	Group 1: 40/99 (40%) Group 2:32/95 (34%)	
			Mean total SOFA score	Group 1: 5.8 Group 2: 6.0	
			Length of stay in ICU	Group 1: 15.4±11.1 Group 2: 20.2±22.2	
			Length of stay in hospital	Group 1: 37.7±26.5 Group 2: 42.7±31.6	
			Volume required to reach hemodynamic stabilisation in ml, mean ± SD	Group 1: 1379±886 Group 2: 1709±1164 P value: 0.0185	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Germany and France. **Duration of follow-up:** 90 days; Treatment for 4 days in ICU	**Group 2:** N: 96(randomised), 86(included in efficacy analysis), 83 (completed the treatment period of four days) Age in years, mean ± SD: 65.9 ± 14.7 Type of admission; Medical, n (%):70 (73%) Surgical, n (%):26 (27%) Renal impairment prior to screening*, n (%):65 (68.4%) SOFA at screening, mean: 9.1 Fluid input prior to randomization, ml/kg body weight, mean ± SD: 39.9 ± 28.6	and four day time period, fluid resuscitation was to be carried out using intravenously administered crystalloids (with no volume limitation).			a control group treated with crystalloid (NaCl 0.9%). All randomised patients treated with the study drug who reached hemodynamic stabilisation were called the Full Analysis Set (FAS) and this set was the primary population for statistical analysis of efficacy.

Abbreviations: ASA= American society of anaesthesiologist, CAD=: Coronary artery disease, CVP= central venous pressure, HES= hydroxyethyl starch, HR=hazard ratio, HR= Heart rate, ITT=Intention to treat analysis, ISS=Injury severity score, ITBVI= intrathoracic blood volume index, MAP= Mean arterial pressure, M/F=male/female, mL= millilitres, mEq= millieqivalent, N=total number of patients randomised, NISS=New injury severity score, NS= Not significant, RIFLE= Risk, Injury, Failure, Loss and End-stage serum creatinine criteria, SD= standard deviation, SE=Standard Error, SICU= Surgical ICU, SOFA= Sequential Organ Failure Assessment, $ScvO_2$= Central venous oxygen saturation, UFH= unfractionated heparin

E.3.3 Albumin

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
SAFE2004[2] **Study design:** RCT, double blinded **Funding:** Various health boards, hospitals and	**Patient group:** ICU patients **Inclusion criteria:** 18 years or older Judged by treated clinicians as requiring fluid administration to maintain or increase intravascular volume, supported by at least one objective criterion	**Group 1: 4% albumin (Albumex, CSL)** **Group 2: 0.9% NaCl** Amount and rate of fluid administrations determined by treating clinicians according to patient status and	**All cause mortality** (29 days)	**All patients** **Grp 1:** 726/3473(20.9%) **Grp2:**729/3460 (21.1%) **Trauma** **Grp 1:** 81/596(13.6%) **Grp2**: 59/590 (10.0%) **Severe sepsis** **Grp 1:** 185/603(30.7%)	**Randomisation:** Adequate: Stratified according to centre and whether there was trauma on administration using minimisation algorithm accessed through a secure website **Allocation**

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
research councils in NZ and Australia (not commercially funded by manufacturer of products) **Setting:** 16 multi-disciplinary ICUs in Australia and NZ, between Nov 2001 to June2003 **Duration of follow-up:** 28 days	**Exclusion criteria:** Admitted after cardiac surgery, liver transplantation, or the treatment of burns **All patients** **N:** 6997 **Age (mean):** **Drop outs:** **Group 1- 4% albumin** **N:** 3497 **Age (mean):** 58.6±19.1 **F:** 1424 **Drop outs:** vital status data missing at 28 days -26/3497(0.74%) 3 patients had been randomised twice – analysed according to the first group randomised (NaCl group) 90 patients did not receive assigned study fluid; **Reason of admission:** **Surgical:** 1473 (43%)/ **Medical:** 1955 (57%) **Predefined subgroups:** **Trauma:** 597 (17.4%) **Severe Sepsis:** 603(18.1%) **Acute respiratory distress syndrome:** 61 (1.8%) **APACHE II score:** 18.7±7.9 **No Organ failure (SOFA score):** 1962 (57.2%)	response to treatment **Additional treatment:** All obtained maintenance fluids, replacement fluids, enteral or parenteral nutrition and blood products at discretion of treating clinicians Resuscitation fluids in addition to study fluids received by 309 (8.8%)[189 due to error, 68 due to clinician preference] in albumin group and 375 [190 due to error, 103 due to clinician preference] (10.7%) in saline group		**Grp2:** 217/615 (35.3%) **ARDS** **Grp 1:** 24/61(39.3%) **Grp2:** 28/66 (42.4%)	**concealment:** Adequate: randomisation code accessed through secure website **Blinding:** Adequate: identical 500ml bottles, specially manufactured identical cartons and administration sets designed to maintain masking **Limitations:** **Additional outcomes:** The number of patients with 1, 2, 3, 4 and 5 new organ failures according to SOFA score Additional physiological variables reported at baseline, only central venous pressure – mmHg statistically significant different (p=0.03) (9.0±4.7 vs 8.6±4.6)
			Length of stay (days)[(a)]	**Hospitalisation** **Grp1:** 15.3±9.6 **Grp2:** 15.6±9.6 **Absolute difference:-** 0.24 (95% CI -0.70 to 0.21) **P=**0.30 **ICU** **Grp1:** 6.5±6.6 **Grp2:** 6.2±6.2 **Absolute difference:** 0.24 (95% CI -0.06 to 0.54) **P=**0.44	
			Respiratory failure – number of days with mechanical ventilation[(a)]	**Grp1:** 4.5±6.1 **Grp2:** 4.3±5.7 **Absolute difference:** 0.19 (95% CI -0.08 to 0.47) **P=**0.74	
			AKI – duration of renal replacement therapy[(a)]	**Grp1:** 0.48±2.28 **Grp2:** 0.39±2.0 **Absolute difference:** 0.09 (95% CI -0.0 to 0.19) **P=**0.41	
			New organ failure	**Grp1:** 1252/2649 (47.3%) **Grp2:** 1249/2673 (46.7%)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Mechanical ventilation: 2186 (63.8%) **Renal replacement therapy:** 45 (1.3%) **Albumin in previous 72 hours:** 127 (3.7%) **Group 2- 0.9% NaCl** **N:** 3501 **Age (mean):** 58.5±18.7 **F:** 1376 **Dropouts:** vital status data missing in 41/3501(1.2%) 107 did not receive study fluid **Source of admission:** **Surgical:** 1465 (42.8%) **Medical:** 1958(57.2%) **Predefined subgroups:** **Trauma:** 590 (17.2%) **Severe Sepsis:** 615(18.4%) **Acute respiratory distress syndrome:** 66 (1.9%) **APACHE II score:** 19.0±8.0 **No Organ failure (SOFA score):** 1885 (64.8%) **Mechanical ventilation:** 2217 (63.8%) **Renal replacement therapy:** 41 (1.2%) **Albumin in previous 72 hours:** 135(3.9%)		**Volume of fluids**	**Study fluids:** (Day 1) **Grp 1:** 1183.9±973.6, n=3410 **Grp 2:** 1565.3±1536.1, n=3418 **Non study fluid:** (Day 1) **Grp 1:** 1459.4±1183.2 (n=3392) **Grp 3:** 1505.6±1254.3 (n=3405)	**NOTES:** APACHE II (Acute physiology and Chronic Health Evaluation II) – higher scores indicate more severe illness Organ failure defined as SOFA (Sequential Organ Failure Assessment Score) score of 3 or 4 of any individual organ system
			Quality of life	Not reported	

Abbreviations: ASA= American society of anaesthesiologist, CAD=: Coronary artery disease, CVP= central venous pressure, HES= hydroxyethyl starch, HR=hazard ratio, HR= Heart rate, ITT=Intention to treat analysis, ISS=Injury severity score, ITBVI= intrathoracic blood volume index, MAP= Mean arterial pressure, M/F=male/female, mL= millilitres, mEq= millieqivalent, N=total number of patients randomised, NISS=New injury severity score, NS= Not significant, RIFLE= Risk, Injury, Failure, Loss and End-stage serum creatinine criteria, SD= standard deviation, SE=Standard Error, SICU= Surgical ICU, SOFA= Sequential Organ Failure Assessment, $ScvO_2$= Central venous oxygen saturation, UFH= unfractionated heparin
(a) Number of patients providing the data not reported.

E.3.4 Volume and timing of resuscitation

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Bickell1994[26] **Study design:** Quasi randomised trial **Funding:** None stated **Setting:** US, Houston Emergency Medical Services 1989 November to Dec 1992 to Ben Taub General Hospital **Duration of follow-up** Unclear – till discharge?	**Patient group:** Hypotensive patients with penetrating trauma injuries **Inclusion criteria:** - Adults or adolescents aged≥16 years with a gun shot or stab wound who have had a systolic blood pressure of ≤90mHg at the time of on scene assessments by paramedics **Exclusion criteria:** - Pregnancy - Revised Trauma Score = 0 at the scene - minor injuries not requiring surgery - fatal gunshot wound to the head **All patients** **N:** 598, out of a total of 1069 consecutive patients with hypotension and penetrating injuries to the torso transported. **Age (mean):** **Drop outs;** none. However, 70 patients died before operative intervention. **Group 1- immediate resuscitation group** **N:** 309, 268 survived until the operative intervention **Age (mean):** 31±11 **Male (%):** 88 **Drop outs:** **Systolic blood pressure (mmHg):** 58±35 **Gun wound:** 65%	**Group 1: immediate resuscitation group** - IV fluid resuscitation was given before surgical intervention in both the pre hospital and trauma centre setting. Pre hospital: - Ringer's acetate: 870±667ml Trauma centre: - Ringer's acetate: 1608±1201ml - Packed red cells: 133±393 **Group 2: delayed resuscitation group** - IV fluid resuscitation delayed until operative intervention Pre hospital: - Ringer's acetate: 92±309ml Trauma centre:	**All cause mortality** (up to discharge) **Length of stay (days)*** **Respiratory failure** **AKI** **Quality of life** **Morbidity (SOFA score etc)**	**Grp 1:** 116/309(39.3%) **Grp 2:** 86/289 (42.4%) **Hospitalisation** **Grp1:** 14±24, n=227 **Grp2:** 11±19, n=238 **P=**0.006 **ICU** **Grp1:** 8±16, n=227 **Grp2:** 7±11, n=238 **P=**0.30 Not reported Not reported Not reported Not reported	**Randomisation:** - Quasi-randomised controlled trial. (Allocation by alternation - odd and even numbered days of the month.) Because 3 rotating paramedics and surgical house staff, assignments to the groups were alternated automatically **Allocation concealment:** - Inadequate **Blinding:** - Inadequate **Limitations:** This is a quasi-randomised study; allocation concealment and blinding was not possible. However, the post-operative protocol were the for both groups. **Additional outcomes:**

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Response interval: 8±5 **Scene interval:** 9±8 **Group 2- delayed resuscitation group** **N:** 289, 260 survived until the operative intervention **Age (mean):** 31±10 **Male (%):** 91 **Dropouts:** **Systolic blood pressure (mmHg):** 59±34 **Gun wound: 67%** **Response interval:** 8±5 **Scene interval:** 7±6	- Ringer's acetate: 283±722ml - Packed red cells: 11±88 Similar volumes of fluids given in operating from for each type of fluid, but rate of administration was slower for delayed resuscitation (91±88ml/min vs 117±126/min)			Estimated intraoperative blood loss. Biochemical parameters

Abbreviations: ASA= American society of anaesthesiologist, CAD=: Coronary artery disease, CVP= central venous pressure, HES= hydroxyethyl starch, HR=hazard ratio, HR= Heart rate, ITT=Intention to treat analysis, ISS=Injury severity score, ITBVI= intrathoracic blood volume index, MAP= Mean arterial pressure, M/F=male/female, mL= millilitres, mEq= millieqivalent, N=total number of patients randomised, NISS=New injury severity score, NS= Not significant, RIFLE= Risk, Injury, Failure, Loss and End-stage serum creatinine criteria, SD= standard deviation, SE=Standard Error, SICU= Surgical ICU, SOFA= Sequential Organ Failure Assessment, $ScvO_2$= Central venous oxygen saturation, UFH= unfractionated heparin

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Mao2009B[242] **Study design:** randomised trial **Funding:** Shanghai Leading Academic Project	**Patient group:** Severe acute pancreatitis **Inclusion criteria:** - Atlanta criteria of diagnosis for SAP enrolled within 72 hours after onset of disease from March 2001 through December 2007 **Exclusion criteria:**	**Group 1: rapid fluid expansion group (10-15ml/kg/hour)** Time interval to meet criteria for fluid expansion: 13.5±6.6 hours **Group 2: controlled fluid expansion group (5-**	**All-cause mortality** (up to discharge)	**Grp 1:** 11/36 **Grp 2:** 4/40	**Randomisation:** - Inadequate, no description **Allocation concealment:** - Inadequate, no description **Blinding:** - Inadequate, no description
			Length of stay (days)*	Not reported	
			Respiratory failure(mechanical ventilation)	**Grp 1:**34/36 **Grp 2:**26/40	
			AKI	Not reported	
			Quality of life	Not reported	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Setting: China, Shanghai March2001 to March 2007 **Duration of follow-up** Unclear – till discharge?	- Less than 18m more than 70 years, - Pregnancy - Chronic heart disease, pacemaker installation, chronic renal failure and SAP of uncertain aetiology **All patients** **N:** 67. **Age (mean):** **Drop outs;** none. However, 70 patients died before operative intervention. **Group 1-Rapid fluid expansion** **N:** 36 **Age (mean):** 51.3±14.3 **Male (%):** not reported **Drop outs:** **APACHE II score**: 13.6±5.3 **Heart rate (beats/min):** 140±17 **Mean arterial pressure (mmHg):** 85±18 **Urine output(ml/kg/hr**): 0.7±0.4 **Group 2- controlled fluid expansion** **N:** 40 **Age (mean):** 50.2±12.0 **Male (%):** not reported **Dropouts:** **APACHE score II**: 14.8±5.6 **Heart rate (beats/min):** 140±17 **Mean arterial pressure (mmHg):** 87±19 **Urine output(ml/kg/hr):** 0.6±0.5	**10ml/kg/hour)** Time interval to meet criteria for fluid expansion: 24.0±5.4 hours Both groups received normal saline and/or Ringer's lactate and or HES 6% (200/0.5)	**Morbidity (APACHE II score)**	**At day 3:** **Grp1:** 13.9±6.6 **Grp2:** 10.6±4.9	**Limitations:** Not descriptions provided for randomisation, allocation concealment and blinding **Additional outcomes:** Incidence of sepsis within 2 weeks of disease onset, acs

Abbreviations: ASA= American society of anaesthesiologist, CAD=: Coronary artery disease, CVP= central venous pressure, HES= hydroxyethyl starch, HR=hazard ratio, HR= Heart rate, ITT=Intention to treat analysis, ISS=Injury severity score, ITBVI= intrathoracic blood volume index, MAP= Mean arterial pressure, M/F=male/female, mL= millilitres, mEq= millieqivalent, N=total number of patients randomised, NISS=New injury severity score, NS= Not significant, RIFLE= Risk, Injury, Failure, Loss and End-stage serum creatinine criteria, SD= standard deviation, SE=Standard Error, SICU= Surgical ICU, SOFA= Sequential Organ Failure Assessment, $ScvO_2$= Central venous oxygen saturation, UFH= unfractionated heparin

Study details	Patients	Interventions	Outcomes	Effect sizes	Comments
Rivers2001 [311] **Comparison:** Country of study: USA **Setting:** Emergency department **Study design:** RCT **List who was masked to interventions:** Critical care clinicians **Duration of follow-up:** Up to death or discharge	**Patient group:** Adult patients presenting to ED with severe sepsis, septic shock or sepsis syndrome. **Inclusion criteria:** Fulfilment of 2 of the 4 criteria for the systemic inflammatory response syndrome and a systolic bp no higher than 90mmHg. (after a crystalloid fluid challenge) or a blood lactate of 4mmol/L or more **Exclusion criteria:** <18 years, Pregnancy, Cardiovascular problems, Active GI haemorrhage, seizure, drug overdose, burn injury, requirement for immediate surgery, trauma, active cancer, immunosuppression, DNR status. **All patients** N: 263 Age (mean): **Group 1- GDT** N: 130 Age (mean): 67.1 ±17.4 m/f: 50.8/49.2 Time from arrival at ED to enrolment(hr): 1.3 ±1.5	**Group 1- Early goal directed therapy** Protocol aimed at critical care clinicians treating the patients (intensivists, fellows, residents). Received a central venous catheter capable of measuring central venous oxygen saturation, connected to a computerised spectrophotometer for continuous monitoring Treated for at least 6 hours according to protocol the transferred to first available inpatient beds. <u>Details of protocol:</u> -500mL bolus crystalloid given every 30 minutes to achieve CVP of 8-12 mmHg -If MAP was <65mmHg, vasopressors given until it was 90mmHg or below. -If central venous oxygen saturation was <70% red cells were transfused to	**All cause mortality (in hospital mortality)**	Group 1: 38/130 Group 2: 59/133) RR (95% CI): 0.58 (0.38- 0.87)	**Funding:** Supported by the Henry Ford Health Systems Fund for research, Weatherby Healthcare Resuscitation Fellowship, Edwards life sciences (produce oximetry equipment and catheters) Nova biomedical (provided equipment for laboratory assays). **Limitations:** • Control arm do not have a protocol - possible that other factors other than IV fluid timing and volume affected the outcomes • Unclear what
			All cause mortality (28 day mortality)	Group 1: 40/130 Group 2: 61/133 RR (95% CI): 0.58 (0.39- 0.87)	
			All cause mortality (60 day mortality)	Group 1: 50/130 Group 2: 70/133 RR (95% CI): 0.67 (0.46- 0.96)	
			Length of stay (hospitalisation) Note: Sample size for calculation not reported. NCGC calculations with ITT obtained p value ~0.91 See notes	Group 1: 13.2±13.8 Group 2:13.0±13.7 P=0.54(reported in study) NCGC calculations with ITT obtained p value ~0.91	
			Mean duration of mechanical ventilation Note: Sample size for calculation not reported. See noted	Group 1:9 ±11.4 Group 2: 9±13.1 P value: 0.38 NCGC calculations with ITT or number of patients ventilated	

Study details	Patients	Interventions	Outcomes	Effect sizes	Comments
	chronic coexisting conditions: -alcohol use: 38.5% -Cardiorespiratory disorders (mean of 4 domains): 37.4 -diabetes: 30.8 -HIV: 4.3 -Liver disease: 23.1 -history of cancer: 12.8 - neurologic disease: 34.2 -renal insufficiency: 21.4 -smoking: 29.9 **Group 2 –standard care** N: 133 Age (mean): 64.4 ±17.1 m/f: 50.4/49.6 time from arrival at ED to enrolment: 1.5 ±1.7 chronic coexisting conditions: -alcohol use: 38.7% -Cardiorespiratory disorders (mean of 4 domains): 33.4 -diabetes: 31.9 -HIV: 1.7 -Liver disease: 23.5 -history of cancer: 10.1 - neurologic disease: 31.9 -renal insufficiency: 21.9 -smoking: 31.1	achieve a haematocrit of at least 30% -If CVP, MAP and haematocrit were optimised, if central venous oxygen saturation was <70% dobutamine administration was commenced. Until central venous oxygen saturation was 70% or higher until a maximal dose of 20 ug/kg/min was given. To decrease oxygen consumption, patients in whom haemodynamic optimisation could not be achieved received mechanical ventilation and sedatives The protocol covers assessment, treatment and monitoring. **Group 2- standard therapy** no further information given		obtained p value ~1.0	sample sizes or statistical methods were used for calculations healthcare utilisation. P values reported differed from t-tests conducted by NCGC. • Patients in the standard therapy group may have received some sort of GDT, reducing the treatment effect as the study progressed. **Notes:** • Randomisation by computer generated blocks of 2- 8. Assignments placed in sealed opaque, randomly assorted envelopes. • Majority of baseline data given as %, n calculated by NCGC.
			Length of stay of those patients that survived to hospital discharge	Group 1: 14.6 ±14.5 Group 2: 18.4 ±15 P value: 0.04	
			How was this protocol designed? NR **Was the protocol considered helpful (authors conclusions)?** "Significant benefits with respect to outcome when goal directed therapy was applied at an earlier stage of disease" GDT provided at the earliest stages of severe sepsis and septic shock has significant short and long term benefits. Benefits arise from early identification of patients at risk of cardiovascular collapse and from early therapeutic intervention to restore a balance between oxygen delivery and oxygen demand. **What elements have been identified as helpful/contribut e to better outcomes?** Aspects helpful in identifying need for therapy: decreased mixed venous oxygen saturation and increased lactate concentration. Quality and timing of the resuscitation is important and should be studied. **What elements have been identified as not useful/did not contribute to better outcomes?** "no benefit in terms of outcome with respect to normal and supranormal haemodynamic end points, as well as those guided by mixed venous oxygen saturation" **Adherence to protocol (was the protocol followed)?**		

Study details	Patients	Interventions	Outcomes	Effect sizes	Comments
			NR, but stated that patients in the non-protocol group may have inadvertently had some sort of GDT, reducing the treatment effects		• 13 patients died within 6 hours in group 1, 14 in group 2 • For length of stay, sensitivity analysis was conducted for both number of patients randomised and number of patients who survived until hospital discharge. For duration of mechanical ventilation, sensitivity analysis was conducted for both number of patients randomised and number of patients used mechanical ventilation.

Abbreviations: ASA= American society of anaesthesiologist, CAD=: Coronary artery disease, CVP= central venous pressure, HES= hydroxyethyl starch, HR=hazard ratio, HR= Heart rate, ITT=Intention to treat analysis, ISS=Injury severity score, ITBVI= intrathoracic blood volume index, MAP= Mean arterial pressure, M/F=male/female, mL= millilitres, mEq= millieqivalent, N=total number of patients randomised, NISS=New injury severity score, NS= Not significant, RIFLE= Risk, Injury, Failure, Loss and End-stage serum creatinine criteria, SD= standard deviation, SE=Standard Error, SICU= Surgical ICU, SOFA= Sequential Organ Failure Assessment, $ScvO_2$= Central venous oxygen saturation, UFH= unfractionated heparin

Study details	Patients	Interventions	Outcomes	Effect sizes	Comments
Lin2006 [221] **Comparison:** GDT protocol vs non GDT (no protocol **Country of study:** Taiwan **Setting:** ICU (referred from ED and medical wards) **Study design:** RCT	**Patient group:** Adult ICU patients – septic shock **Inclusion criteria:** Patients from emergency and medical wards, transferred to ICU once sepsis with organ failure was found, and when shock developed during their stay in ICU. Patients with septic shock in the ED or medical wards were included if they were transferred to the medical ICU within 4 hours. Fulfil criteria for septic shock: Known origin of infection At least 2 of the criteria for SIRS Bp not >90 mmHg (after fluid challenge) **Exclusion criteria:** <18 year, Pregnancy Cardiovascular problems, Active GI haemorrhage, seizure, drug overdose, burn injury, requirement for immediate surgery, trauma, active cancer, immunosuppression, DNR status. **All patients** N: 224 Age (mean): Drop outs: 17 Transferred from ED: 86/224 **Group 1** N: 108 Age (mean±SD): 67.2 ±15 Drop outs: NR	**Group 1- goal directed therapy (GDT)** - protocol targeted to doctors - 500mL bolus of crystalloid (Ringers lactate or 0.9% saline) given every 30 mins to achieve CVP of 8-12mmHg. If MAP still <65mmHg after reaching right CVP, vasopressors given to maintain MAP of at least 65mmHg. 50mg hydrocortisone administered iv every 6h for 7 days if relative adrenal insufficiency was diagnosed. -urine output should be >0.5mL/kg/hr. If urine output persistently low Swan-Ganz catheter introduced to determine cardiac index- if decreased dobutamine given. **Group 2- non GDT, no protocol** Standard therapy adjusted by a physician without a fixed protocol.	**All-cause mortality (hospitalisation)**	Group 1: 58/108 Group 2: 83/116 P value: 0.006	**Funding:** National Science Council, Taiwan. **Limitations:** • One arm did not have a protocol, possibility that other treatment factors other than volume and timing of fluid affected differences in outcome • Not blinded design • Mortality rate for whole cohort higher than in other EGDT studies • Indirect population • Protocol included invasive monitoring- outside of scope **Notes:** • Randomisation in computer generated blocks of 2- 8. In sealed opaque randomly
			Length of stay(hospitalisation)	Group 1: 36.6 ±22.9, n=108 Group 2: 33.8 ±23.1, n=116 P value: not significant	
			Quality of life	NR	
			Length of ICU stay (days)	Group 1: 14.3±11.7, n=108 Group 2: 20.3± 16.6, n=116 P value: 0.003	
			Duration of mechanical ventilation (days)	Group 1: 12.9±11.5, n=108 Group 2: 18.8 ±17.1, n=116 P value: 0.003	
			Sepsis associated renal failure	Group 1: 42/108 Group 2: 64/116 P value: 0.015	
			How was this protocol designed? NR **Was the protocol considered helpful (authors conclusions)?** "Large fluid deficits exist in patients with septic shock. Volume repletion in these patients produces significant improvement in cardiac function and systemic oxygen delivery, thereby increasing tissue		

Study details	Patients	Interventions	Outcomes	Effect sizes	Comments
	F: 44 (40.7) APACHE III score: 66.35 (16.9) GCS: 9.2 (3.9) CVP (mmHg): 5.6 (4.7) Chronic co-existing conditions: -diabetes: 30 (27.8) -cardiorespiratory: 105 -renal insufficiency: 14 (13) -neurological disease: 13 (12) History of malignancy: 14 (13) Pneumonia as primary origin of sepsis: 65 (60.2) Transferred from ED: 40 (37) **Group 2** N: 116 Age (mean): 68.7±13.9 Drop outs: NR F: 50 (43.1) APACHE III score: 64.9 (14.4) GCS: 8.9 (3.9) CVP: 6.5 (4.5) Chronic co-existing conditions: -diabetes: 38 (32.8) -cardiorespiratory: 140 -renal insufficiency: 18 (15.5) -neurological disease: 17 (14.7) History of malignancy: 12 (10.3) Pneumonia as primary origin of sepsis: 69 (58.5) Transferred from ED: 46 (39.7)		perfusion and decreasing mortality" "Rapid haemodynamic optimisation caused by aggressive fluid resuscitation and less delayed vasopressor administration in GDT group may prevent the development of major organ dysfunction" "the protective effects against organ failure by GDT may contribute to the reduction in mortality rate and in improvement in clinical outcomes amongst patients with septic shock" **What elements have been identified as helpful/contribute to better outcomes?** Targeting CVP, MAP and urine output in GDT **What elements have been identified as not useful/did not contribute to better outcomes?** NR **Adherence to protocol (was the protocol followed)?** NR		assorted envelopes. • Levels of clinicians in both groups similar- senior residents (3rd or 4th year residents) and attending physicians). • States there was higher mortality than in similar studies, which could be due to higher % transferred from medical wards rather than EDs • High percentage of patients with pneumonia in the study

Abbreviations: ASA= American society of anaesthesiologist, CAD=: Coronary artery disease, CVP= central venous pressure, HES= hydroxyethyl starch, HR=hazard ratio, HR= Heart rate, ITT=Intention to treat analysis, ISS=Injury severity score, ITBVI= intrathoracic blood volume index, MAP= Mean arterial pressure, M/F=male/female, mL= millilitres, mEq= millieqivalent, N=total number of patients randomised, NISS=New injury severity score, NS= Not significant, RIFLE= Risk, Injury, Failure, Loss and End-stage serum creatinine criteria, SD= standard deviation, SE=Standard Error, SICU= Surgical ICU, SOFA= Sequential Organ Failure Assessment, $ScvO_2$= Central venous oxygen saturation, UFH= unfractionated heparin

E.3.5 Low vs high volume

Study details	Patients	Interventions	Outcomes	Effect sizes	Comments
Dutton 2002[107] **Comparison:** Protocol(100mmHg) vs protocol (70mmHg) **Country of study:** Baltimore, Maryland , USA **Setting:** Emergency department **Study design:** RCT	**Patient group:** Patients presenting to trauma centre with haemorrhagic shock. **Inclusion criteria:** Presented directly from scene of a trauma, evidence of ongoing haemorrhage, SBP <90mmHg recorded at least once within the first hour of injury **Exclusion criteria:** Pregnant, CNS injury impairing level of consciousness or motor function, older than 55 years, or had a previous history of diabetes or coronary artery disease. **All patients** N: 110 Age (mean): 31 Drop outs: NR M: 79%	**Group 1** resuscitate to SBP >100mmHg **Group 2** resuscitate to SBP 70mmHg **Both groups:** <u>Components of protocol</u> Check BP- if below target pressure then administer 200-500mL fluid, if at target pressure re-check bp, above target pressure then sedation or analgesia if indicated. Bp checked at least every 5 minutes during active haemorrhage. Treated with administration of crystalloid or blood products to elevate SBP to appropriate level whilst maintaining the haematocrit to at least 25%	**Mortality**	Group1: 4/55 Group 2: 4/55 Relative risk: 95% CI: p value: (If no p-value: Sig/Not sig/NR)	**Funding:** Part funded by a Pangborn grant from the university of Maryland School of Medicine **Randomisation:** Not described **Limitations:** • Methods of randomisation and allocation concealment not reported • Blinding not reported **Additional outcomes:** -predicted survival rate -actual survival rate -site of haemorrhage by treatment group -demographics of patients who died
			Quality of life	NR	
			Was the protocol considered helpful (authors conclusions)? Targeting volume resuscitation to a lower than normal blood pressure during active haemorrhage did not improve survival. Outcome of in hospital mortality criticised- too broad an endpoint to discriminate subtle differences between groups **What elements have been identified as helpful/contribute to better outcomes?** Inclusion of other surrogate markers of resuscitation such as lactate or base deficit, length of stay may have been useful? But each of these measures have subjectivity in interpretation or sensitivity to the patients initial injury. **What elements have been identified as not useful/did not contribute to better outcomes?** Blood pressure is known to be poor surrogate marker for oxygen tissue delivery, but is the measure that is most readily available during early resuscitation., and		

Study details	Patients	Interventions	Outcomes	Effect sizes	Comments
	Group 1 N: 55 Age (mean): 29.7 ±12.98 Drop outs: NR Blunt trauma:23 (42%) Penetrating trauma: 32 (58%) m/f: 46 (84%)/ 9 (16%) **Group 2** N: 55 Age (mean): 32.1 ±10.49 Drop outs: NR Blunt trauma: 31 (56%) Penetrating trauma: 24 (44%) M/F: 41 (75%)/ 14 (25%)	SBP above the target level was managed by restriction of fluids and administration of appropriate doses of anaesthetic or analgesic medication.	the most consistent driver of fluid therapy in actual practice. Continuous haemodynamic monitoring is limited to that which can be quickly applied and easily shifted with the patient. **Adherence to protocol (was the protocol followed)?** Failure to achieve the proposed methodology- targeting a lower than normal bp resulted in an active pressure of 100mmHg during active haemorrhage. Targeting 100mmHg resulted in average pressure of 114mmHg during active haemorrhage.		-Failure to achieve the proposed methodology- patients in low bp group had average bp of 100mmHg **Notes:** End of active bleeding determined in each case by the trauma surgeon and anaesthesiologist on the basis of: visible control of haemorrhage in the operating room, stable blood pressure not requiring fluid administration for support, tolerance of a normal level of analgesia and sedation, CT scan or angiography showing no evidence of ongoing haemorrhage.

Abbreviations: ASA= American society of anaesthesiologist, CAD=: Coronary artery disease, CVP= central venous pressure, HES= hydroxyethyl starch, HR=hazard ratio, HR= Heart rate, ITT=Intention to treat analysis, ISS=Injury severity score, ITBVI= intrathoracic blood volume index, MAP= Mean arterial pressure, M/F=male/female, mL= millilitres, mEq= millieqivalent, N=total number of patients randomised, NISS=New injury severity score, NS= Not significant, RIFLE= Risk, Injury, Failure, Loss and End-stage serum creatinine criteria, SD= standard deviation, SE=Standard Error, SICU= Surgical ICU, SOFA= Sequential Organ Failure Assessment, $ScvO_2$= Central venous oxygen saturation, UFH= unfractionated heparin

Study details	Patients	Interventions	Outcomes	Effect sizes	Comments
WIEDEMANN 2006 [397] **Comparison:** Conservative	**Patient group:** Patients with acute lung injury **Inclusion criteria:** Intubated and received positive-pressure ventilation, had a PaO2/FiO2	**Both groups:** Patients in both groups were assigned to protocol cells on the	**Death at 60 days (%)**	Group 1:128/503 Group 2141/497 P value: 0.30	**Funding:** Supported by contracts with the National Heart, Lung and Blood Institutes,
			Respiratory	Group 1:14.6±0.5	

Study details	Patients	Interventions	Outcomes	Effect sizes	Comments
strategy v liberal strategy of fluid management **Country of study:** USA **Setting:** ICU **Study design:** RCT, 2x2 factorial design. Patients were also randomised to PAC (pulmonary artery catheter) or CVC (central venous catheter) **Duration of follow-up/ or period of time when study was conducted:** June 2000-October 2005	ratio of less than 300; had bilateral infiltrates on chest radiography consistent with the presence of pulmonary edema without evidence of left atrial hypertension; If a participant did not have a central venous catheter, the intent of the primary physician to insert one was required. **Exclusion criteria:** Presence of a pulmonary-artery catheter after the onset of acute lung injury; presence of acute lung injury for more than 48 hours; inability to obtain consent; presence of chronic conditions that could independently influence survival, impair weaning, or compromise compliance with the protocol (e.g., severe lung or neuromuscular disease or dependence on dialysis); irreversible conditions for which the estimated six- month mortality rate exceeded 50 percent, such as advanced cancer. **All patients** N: 1001(randomized) **Group 1-Conservative fluid management** N: 503 (randomised), 503 (analysed) Age in years (mean ± SE): 50, S.E 0.7 Drop outs: 0 Baseline characteristics: Primary lung injury (%) Pneumonia: 46 Sepsis: 22	basis of four variables: • central venous pressure (CVP) or pulmonary-artery occlusion pressure (PAOP)[depending on catheter assignment] presence or absence of shock (defined as MAP below 60 mmHg or the need for a vasopressor • presence or absence of oliguria (defined as urinary output<0.5 ml/kg/hr) • presence or absence of ineffective circulation (defined as cardiac index<2.5l/min/m^2) **Group 1-Conservative strategy group** Target ranges: CVP<4mmHg PAOP<8mmHg **Group 2- Liberal strategy group** Target ranges: CVP: 10-14mmHg PAOP: 14-18mmHg	**failure, measured by ventilator free days (from day 1 to day 28)** **ICU- free days (from day 1 to day 28)** **Cardiovascular failure free days (from day 1 to day 28)** **Renal failure (requiring renal replacement therapy)** **Renal failure free days (from day 1 to day 28)** **Hepatic failure free days (from day 1 to day 28)**	Group 2:12.1, S.E.0.5 P value: <0.001 Group 1: 13.4, S.E.0.4 Group 2: 11.2, S.E.0.4 P value: <0.001 Group 1: 19.0, S.E.0.5 Group 2: 19.1, S.E.0.4 P value: <0.85 Group 1: 50/503 Group 2:70/497 Note: values calculated by NCGC from percentages reported Group 1: 21.5, S.E.0.5 Group 2: 21.2, S.E.0.5 P value: <0.59 Group 1: 22.0, S.E.0.4 Group 2: 21.2 S.E0.5 P value: <0.18	National Institutes of Health **Randomisation & allocation concealment:** Adequate Computer generated randomisation accessed using interactive voice response technology after informed consent. **Limitations:** Blinding not described – likely to be open label study. **Notes:** Indirect population and intervention(ICU setting, Invasive monitoring, use of diuretics)

Study details	Patients	Interventions	Outcomes	Effect sizes	Comments
	Aspiration: 16 Trauma: 8 Multiple transfusions: 1 Other: 8 Co-existing conditions (%) Diabetes: 18 HIV/AIDS: 7 Cirrhosis: 3 Solid tumours: 1 Leukaemia: 3 Lymphoma: 2 Immunosuppression: 9 MAP (mm Hg): 77.1, S.E.0.6 CVP (mm Hg): 11.9±0.3 PAOP (mm Hg): 15.6±0.4 **Group 2- Liberal fluid management** N: 498 (randomised), 497 (analysed) Age in years (mean ± SE): 49.5 ± 0.7 Drop outs: 1 withdrew consent before receiving treatment Baseline characteristics: Primary lung injury (%) Pneumonia: 48 Sepsis: 25 Aspiration: 13 Trauma:7 Multiple transfusions: 0 Other: 7	**All patients:** • Received intravenous fluids or furosemide to move their intravascular pressure to the target ranges • For fluid boluses, clinicians were free to select isotonic crystalloid, albumin, or blood products. Volumes administered were dictated by protocol • Treatment of patients with shock was based on judgement of clinician; only after blood pressure stabilised, weaning from vasopressors was done according to protocol			

Study details	Patients	Interventions	Outcomes	Effect sizes	Comments
	Co-existing conditions (%) Diabetes: 18 HIV/AIDS: 8 Cirrhosis: 3 Solid tumours:3 Leukaemia: 1 Lymphoma: 1 Immunosuppression: 7 MAP (mm Hg): 77.2, S.E.0.6 CVP (mm Hg): 12.2, S.E.0.3 PAOP (mm Hg): 15.7, S.E.0.4				

E.4 Routine maintenance

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
GONZALEZFAJARDO2009[143] **Study design:** RCT, observer blinded **Funding:** None **Setting:** Surgical ward. January and December 2007 in	**Patient group:** At least 24 hours post elective open abdominal vascular surgery. (All patients were shifted to ICU for at least 24 hours before returned to the specialist beds in the vascular surgery unit for the rest of the postoperative period). **Inclusion criteria:** Transperitoneal aorto-iliac approach, through a standard midline laparotomy incision, with infrarenal graft repair.	**Group 1: Restricted fluid (1.5 L per day)** • NaCl 0.9% 1.5L • 40 mmol of potassium • Total post operative fluid used (in surgical ward): 5797.5 ml (95% CI 4581.5 to 7013.4); output =(95% CI 4556.0 to 7005.2) . **Group 2: Standard group (2.5L per day)** • Dextrose 5% – 1 L	**All cause mortality (**30 days)	**Group 1:** 0/20 **Group 2:** 1 /20 Patient died on day 18, at home due to cardiac problems.	**Randomisation:** Adequate: Randomised before operation by computer-generated random number pattern, in blocks of four. **Allocation concealment:** Low risk – unclear if blinding was performed and affect the
			Length of stay (days), mean, (95% CI Criteria for discharge: apyrexial, fully mobile, passing flatus or faeces, and using oral analgesics only for pain control. Discharge delayed by social problems was recorded as such).	**Post operative stay, including ICU (fit for discharge)** **Group 1**: 8.40 (95% CI: 7.75 to 9.05) **Group 2:** 12.40 (95% CI: 8.68 to 16.12) **P value**: 0.003 reported See baseline characteristics for length of ICU stay.	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
university teaching hospital, Spain **Duration of follow-up:** 30 days for all adverse events.	**Exclusion criteria:** • pregnancy • mental disorders • severe physical disability • impaired renal function • congestive cardiac failure • hepatic disease • cancer • inflammatory bowel disease or receiving drugs that affect gastrointestinal motility. **All patients** **N:** 40 patients out of 43 identified. Reasons for non randomisation were anaesthetic cancellations (2) and patient refusal (1). **Weight (kg):** not reported **Group 1: Restrictive** **N=**20 **Age (years, 95%CI):** 65.5(62.1 to 68.9) **Sex (M/F):** 20/0 **BMI(kg/m2)*:** not reported **ASA:** I(0), II(9), III(10), IV(1) **Risk factors** • Diabetes: 6/20(30%) • Hypertension: 13/20(65%) • Hypercholesterolaemia: 10/20(50%) • Cardiac disease: 9/20(45%)	• NaCl 0.9% 1.5 L • 40 mmol of potassium • Total post operative fluid used (in surgical ward): 10773.2 ml (95% CI 8780.5 to 12765.9) , output = 8792.5 (95% CI: 6634.7 to 10950.3). **In both arms:** • All received bowel preparation (a phosphate enema) the night before and were allowed free fluids until 12 h before the surgery • Pre load: Ringers lactate 500ml • During operation: NaCl (0.9%) for third-space loss; Blood loss up to 500 ml – NaCl 0.9% 1-1-1.5 L, more than 500ml- HAES 6%, more than 500ml or significant haematocrit drop- Blood component therapy, including blood transfusion to achieve haematocrit of 30% • Nasogastric tubes or intra-abdominal drains were used.	**Respiratory complications** **AKI –** development of renal failure **Quality of life** **Morbidity** (SOFA score, MODS)	**Group 1:** 0/20 **Group 2:** 1/20 (pulmonary oedema) **Group 1:** 0/20 **Group 2:** 0/20 Not reported Not reported	predictability of block randomisation, but investigators were blinded to treatments. **Blinding:** Masking of intervention type not described. Clinical decisions about discontinuation of IV fluids, resumption of diet and discharge were made by the treating surgical team (unclear if they are blinded) and not by the investigators. The investigators were blinded to the treatment of each patient and did not review the patient. **Others:** Clearly defined criteria for discharge **Limitations:** Patients and

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	• COPD: 4/20(20%) • Smoker: 14/20(70%) **Operating time (min):** 196.5 ± 37 **ICU stay (days**): 1.75 ±0.6 days **Blood transfusions (ml**): 336.1 ± 433.3 **Indication/operation type:** (see notes) • Occlusive: 12/20(60%) • Abdominal aortic aneurysm: 8/20(40%) • aortobifemoral bypass graft : 14 • resection and graft interposition 6 **Group 2: Standard** **N:** 20 **Age (years, 95%CI):** 61.95 (56.7 to 67.2) **Sex (M/F):** 20/0 **BMI (kg/m2)*:** not reported **Risk factors:** • Diabetes: 6/20(30%) • Hypertension: 11/20(55%) • Hypercholesterolemia: 8/20(40%) • Cardiac disease: 5/20(25%) • COPD: 7/20(35%) • Smoker: 14/20(70%) **Operating time (min):** 198.2 ± 52 **ICU stay (days):** 1.90 ± 1.7 days **Blood transfusions (ml):** 405.0 ±367.7	• Received antibiotics post operatively, in the ICU: 3L/day (1L of NaCl 0.9% and 2L of dextrose (5%) with potassium supplementation if required). • Oral fluids were encouraged after the 3rd day following the operation • All patients received chest physiotherapy and commenced active mobilisation from the 2nd postoperative day. • Clinical decisions about discontinuation of intravenous fluids, resumption of diet and discharge were made by the treating surgical team.			healthcare professionals (other than investigator) may not be blinded to intervention. **Additional outcomes:** No difference in serum urea, Creatinine osmolality, albumin ad haemoglobin levels in the postoperative period between arms. Other adverse events; 1 reintervention (thromboectomy), 2 would infections in standard group. Post operative fluid balance: 16.8ml (95% CI 931.5 to 965.2) for restrictive group; 1980.7 ml(95% CI 891.4 to 3070.0)for standard group, statistically significant difference (p=0.007).

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Indication/operation type • Occlusive: 15/20(75%) • Abdominal aortic aneurysm: 5/20(25%) • aortobifemoral bypass graft : 12 • resection and graft interposition 8				Notes: inconsistency in type of surgery in text & table 1 of paper.

Abbreviations: ASA= American society of anaesthesiologist, CAD=: Coronary artery disease, CVP= central venous pressure, HES= hydroxyethyl starch, HR=hazard ratio, HR= Heart rate, ITT=Intention to treat analysis, ISS=Injury severity score, ITBVI= intrathoracic blood volume index, MAP= Mean arterial pressure, M/F=male/female, mL= millilitres, mEq= millieqivalent, N=total number of patients randomised, NISS=New injury severity score, NS= Not significant, RIFLE= Risk, Injury, Failure, Loss and End-stage serum creatinine criteria, SD= standard deviation, SE=Standard Error, SICU= Surgical ICU, SOFA= Sequential Organ Failure Assessment, $ScvO_2$= Central venous oxygen saturation, UFH= unfractionated heparin

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
LOBO2002[223] **Study design:** RCT, open label **Funding:** Main investigator recipient of fellowship from ESPEN and Queen's Medical Centre, Nottingham. **Setting:** August 1999	**Patient group:** Elective hemicolonectomis and sigmoidectomies for cancer **Inclusion criteria:** Elective hemicolonectomies and sigmoidectomies for cancer **Exclusion criteria:** • renal impairment • Congestive cardiac failure • Hepatic disease • Ascites • Peritoneal metastases • Impaired mobility • Anaemia (Hb <100g/L) • Diabetes mellitus	**Group 1: Restricted (No more than 2L of water and 77mmol sodium/day)** • Dextrose 4% /NaCl 0.18% 2L, or 0.5L NaCl 0.9% 0.5L and dextrose 5% 1.5L • Fluid prescription by anaesthetic and surgical team responsible. Actual amount of fluids used: See outcomes section for more details. **Group 2: Standard (3L of water, 154 mmol of Na per day)**	**All cause mortality** (30 days)	**Group 1:** 0/10 **Group 2:** 1/10 Cause of death: lymphagitis carcinomatosii	**Randomisation:** Adequate: Randomisation on an individual basis in blocks of 10, with consecutively sealed enveloped that were opened after patient recruitment and 3-7 days before admission for surgery by a person not involved in the study. **Allocation concealment:** Unclear if envelope was opaque.
			Length of stay (days), median, (IQR)	**Total postoperative hospital stay including ICU** **Group 1:** 6.0 (5.0–7·0) **Group 2:** 9.0 (7.8-14.3) **P =** 0.001 for Mann Whitney U test	
			Respiratory complications (respiratory infections)	**Group 1:** 0/10 **Group 2:** 2/10	
			AKI – development of renal failure	Not reported	
			Quality of life	Not reported	
			Morbidity (SOFA	Not reported	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
to Feb 2001, UK **Duration of follow-up:** Up to 30 days for all cause mortality	• Receiving drugs that affect gastrointestinal mobility **All patients** **N:** 20 patients out of 29 assessed for eligibility. Reasons for non randomisation were did not meet inclusion criteria (3) and patient refusal (5). **Surgery type:** All patients had midline laparotomies, and post operative pain was managed by patient controlled analgesia devices delivering morphine. Epidural analgesia not used. **Group 1: Restrictive** **N=**10 **Age (years), median (IQR range):** 62.3 (52.5 – 67.2) **Sex (M/F):** 8/2 **BMI (kg/m2)*:** 23.6(22.2 -27.5) **Weight (kg), IQR:** 73.3 (61.8-80.3) **Serum Creatinine** (mmol/L): 91.0(72.8 - 97.8) **Haemoglobin** (g/L): 134 (123-148) **Operation type:** • Hemicolectomy: 3 right, 1 left • Sigmoid colectomy:6 **Median intra-operative blood loss:** 275ml (169-381)	• Dextrose 5% – 2 L • NaCl 0.9% - 1L • Prescription given by single investigator once patients left operating theatre, staff can increase fluid input if concentrations of urea in blood rose or clinical indications of salt or water depletion become evident. Actual amount of fluids See outcomes section for more details. **In both arms:** • Allowed free fluids and high calories drinks for up to 4 hours before operation. No bowel preparation, except those having left sided surgery (received a 2 sachets of sodium picosulphate (10mg/sachet)) • Intra-operatively, anaesthetists prescribe fluids. • Patients received 40 to 60mmol potassium per day from 2nd post	score, MODS)		**Blinding:** No blinding. Only the statistician doing analysis not aware of status of randomisation. **Limitations:** • Open label study, with variations of treatment according to patient progress. • Discharge criteria not defined. • Patients on restricted group had more fluids intra-operatively and also had more oral intake. **Additional outcomes:** None **The following outcomes occur in the standard group, but not the restricted group:** Peripheral oedema (7), hyponatraemia
			Volume of fluids Total(up to day 4 post op) Total water input (IV fluid and oral), (L): Na^+ (mmol:)	**Restricted | Standard** 11.6(10.4–12.2) |18.0(16.4-19.3) 520(490–590) |1440(1330–1620) Volume of oral fluid intake increase as IV fluid volume decrease The restricted group had more oral fluid intake than the standard group	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 2: Standard **N:** 10 **Age (years), median (IQR range):** 58.9(55.3-66.7) **Sex (M/F):** 6/4 **BMI (kg/m2)*:** 26.4(24·3–29.6) **Weight (kg), IQR:** 69.6 (67.9-74.7) **Serum Creatinine** (mmol/L): 73.0 (65.8 - 83.8) **Haemoglobin** (g/L): 136 (123-153) **Operation type:** • Hemicolectomy: 2 right, 1 left • Sigmoid colectomy:7 **Median intra-operative blood loss:** 238ml (175-325)	operative day in accordance to patients serum concentration of potassium • Clinical decisions about discontinuation of fluids, commencement of diet and discharge made by surgical team and not by investigators. • None of the patients received artificial nutritional support or blood transfusions			(Na≤130mmol/L) (4 patient days), vomiting on day 4 (3), confusion after day 1(3), wound infection (1), readmission within 30 days (1). There was 2 cases of hypokalaemia (K≤3.5mmol/L) in the standard group and 1 in the restricted group.

Abbreviations: ASA= American society of anaesthesiologist, CAD=: Coronary artery disease, CVP= central venous pressure, HES= hydroxyethyl starch, HR=hazard ratio, HR= Heart rate, ITT=Intention to treat analysis, ISS=Injury severity score, ITBVI= intrathoracic blood volume index, MAP= Mean arterial pressure, M/F=male/female, mL= millilitres, mEq= millieqivalent, N=total number of patients randomised, NISS=New injury severity score, NS= Not significant, RIFLE= Risk, Injury, Failure, Loss and End-stage serum creatinine criteria, SD= standard deviation, SE=Standard Error, SICU= Surgical ICU, SOFA= Sequential Organ Failure Assessment, $ScvO_2$= Central venous oxygen saturation, UFH= unfractionated heparin

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
MACKAY2006 [230] **Study design:** RCT, observer blinded **Funding:** Not stated	**Patient group:** Elective colorectal resection **Inclusion criteria:** Elective colorectal resection with primary anastomosis. **Exclusion criteria:**	**Group 1: Sodium and water restricted group** • 4% dextrose/0.18% NaCl 83m/h (total of 2L of water and 77mmol sodium per day). • All IV fluids stopped on day 1 after operation,	**All cause mortality** (30 days) **Length of stay**	**Group 1:** 1/39 **Group 2:** 1/41 Patients died after operation, one from respiratory failure and one from staphylococcal septicaemia secondary to a central line insertion. **Time to medical discharge:**	**Randomisation:** Adequate: Randomised after operation by automated telephone randomisation to either restricted

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Setting: Nov 2003 to March 2005 Scotland **Duration of follow-up:** 30 days for all adverse events. 3 months for QoL (SF-36)	• Significant renal impairment • Severe physical disability and were in long term cares • Insulin dependent diabetes • Scheduled for total colectomy or low anterior resection requiring a defunctioning stoma. **All patients** **N:** 80 patients out of 97 identified. Reasons for non randomisation were renal impairment (8), anaesthetic cancellations (6), diabetes (2) and patient refusal (1). **Weight (kg**): Not reported **Group 1: Restrictive** **N=**39 **Age(years), median (IQR range) :**73·2(65·3–78·0) **Sex (M/F):** 20/19 **BMI(kg/m2)*:** 26·8(22·5–30·7) **ASA:** I(2), II(30), III(7), IV(0) **Operation type:** • Hemicolectomy: 14 right, 3 left • Hartmannclosure: 3 **Operation technique:** • Laparoscopic: 11 • Open: 28 **Indication:** • Benign: 9	unless there is a clinical reason to maintain them. Actual amount of fluids used: • Volume (L): 4·50(4·00 5·62) • Na+ (mmol): 229(131–332) See outcomes section for more details. **Group 2:** • Dextrose 5% – 2 L • NaCl 0.9% 1L • 3 L of water, 154 mmol of Na per day • IV fluid until day 3, unless decided to continue by consultant Actual amount of fluids used: • Volume (L): 8·75 (8·00-9·80) • Na+ (mmol): 560(477–667) See outcomes section for more details **In both arms:** • Allowed free fluids and high calories drinks for	**(days),** mean, IQR range Fitness for discharge criteria: apyrexial, fully mobile, passing flatus or faeces, and using oral analgesics only for pain control. Discharge delayed by social problems was recorded as such.	**Group 1**: 5·8 (4·1–7·3) **Group 2:** 5·9 (4·1–7·9) **Total hospital stay** (including convalescence) **Group1:** 7·2 (6·1–11·0) **Group 2:** 7·2 (6·1–11·2) Hazard ratio: 1.03 (0.66, 1.61)	intravenous fluids or standard care. **Allocation concealment:** Adequate: As above. **Blinding:** Adequate for observer: • The decision to discharge was made by consultant surgeon, who was blinded to the treatment group, and did not review the patient on the ward day 3, by which time IV fluids had generally been discontinued. • The IV solution was covered with an opaque bag during daily monitoring by the consultant anaesthetist and surgical registrar.
			Respiratory complications	1 patient who died from respiratory failure, but unclear from which group.	
			AKI – development of renal failure	**Group 1:** 0/39 **Group 2:** 0/41	
			Quality of life (measured using SF36 at 3 months)	"No difference between groups in any of the components measured."	
			Morbidity (SOFA score, MODS)	Not reported	
			Volume of fluids	**Restricted | Standard**	
			<u>Day 1 of operation</u> IV fluid (L): Na^+ (mmol:)	 2·00(2·00–2·62) | 2·75(2·50–3·00) 122(60–183) | 169(146–266)	
			<u>Day 1 post-op.</u> IV fluid (L): Na^+ (mmol:)	 2·00(2·00–2·00) | 2·60(2·50–3·00) 60(60–80) | 154(154–231)	
			<u>Day 1 post-op.</u>		

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	• Cancer: 30 • Blood transfusion: 3 **Group 2: Standard** **N:** 41 **Age(years), median (IQR range):** 72·6(67·3–82·9) **Sex (M/F):** 17/24 **BMI (kg/m2)*:** 25·8(23·2–28·7) **Operation type:** • Hemicolectomy: 12 right, 4 left • Anterior resection: 23 • Hartmann closure: 2 **Operation technique:** • Laparoscopic: 11, pen: 30 **Indication:** • Benign: 9 • Cancer: 32 • Blood transfusion: 3	up to 4 hours before operation. No bowel preparation, except those having left sided surgery (received a phosphate enema the night before and on the morning of the surgery). • Received restricted intraoperative fluid regimen (4% dextrose and 0.18% NaCl at 10 ml/kg/h plus 3 times the measures blood loss of less than 500ml). No nasogastric tubes or intra-abdominal drains were used. • Oral fluids encouraged immediately after operation in both groups, with protein drinks and normal food introduced on day 1 after surgery. • Received antibiotics, thromboprophylaxis and analgesics.	IV fluid (L): Na^+ (mmol:) <u>Day 1 post-op.</u> IV fluid (L): Na^+ (mmol:) <u>Total(including day 4 post op</u>) IV fluid (L): Na^+ (mmol:)	0·00(0·00–0·50) | 2·50(2·00–3·00) 0(0–15) | 154(77–21) 0·00(0·00–0·00) | 0·50(0·00–1·50) 0(0–0) | 0(0–77) 4·50(4·00–5·62) | 8·75(8·00–9·80) 229(131–332) | 560(477–667)	**Others:** Clearly defined criteria for discharge. **Limitations:** Patients may not be blinded to intervention. **Additional outcomes:** Serum urea higher in restricted group (P = 0·077), rise from day 2 after operation. This was mirrored by increases in serum creatinine levels on days 1 and 2 after surgery (P = 0·065 and P = 0·042 respectively). "These changes were most likely the result of the dilutional effect of excess fluid in the standard group and were within the range of normal."

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
					Compared to baseline, weight loss in restricted group, Weight gain in the standard group.

Abbreviations: ASA= American society of anaesthesiologist, CAD=: Coronary artery disease, CVP= central venous pressure, HES= hydroxyethyl starch, HR=hazard ratio, HR= Heart rate, ITT=Intention to treat analysis, ISS=Injury severity score, ITBVI= intrathoracic blood volume index, MAP= Mean arterial pressure, M/F=male/female, mL= millilitres, mEq= millieqivalent, N=total number of patients randomised, NISS=New injury severity score, NS= Not significant, RIFLE= Risk, Injury, Failure, Loss and End-stage serum creatinine criteria, SD= standard deviation, SE=Standard Error, SICU= Surgical ICU, SOFA= Sequential Organ Failure Assessment, $ScvO_2$= Central venous oxygen saturation, UFH= unfractionated heparin

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
VERMEULEN2009[377] **Study design:** RCT, double blinded **Funding:** Not stated **Setting:** May 2004 and July 2005 Netherlands **Duration of follow-up:** Up to 30 days after discharge for	**Patient group:** Elective general abdominal surgery **Inclusion criteria:** All types of gastric resections, bowel procedures (small bowel, colon and/or rectum), bile duct restoring procedures, pancreatico-duodenectomies, or partial resections of the pancreas. **Exclusion criteria:** • Scheduled for laparoscopic, liver or esophageal surgery and/or anticipated postoperative stay on the Intensive Care Unit, • age <18 years • emergency operation • pregnancy or breastfeeding	**Group 1: restricted group (1.5L)** • 3 packets of 500ml lactated Ringers solution /24 hours for first 24 hours, followed by • 1000 ml 0.9% NaCl and 500 ml 5% glucose IV per day **Group 2: Standard group (2.5L)** • 3 packets of 500ml lactated Ringers solution /24 hours for first 24 hours, followed by; • 1500 ml 0.9% NaCl and 1000 ml 5% glucose per day	**All cause mortality (**30 days) **Length of stay (days),** median (IQR) [mean (SD)] from day of operation. Criteria: resumed Peristalsis (i.e. flatus, or defecation less than 8 times a day), unhampered oral intake of food and drink, and sufficient mobility to wash and dress. If a patient had received a stoma, its output should be less than 1L /day	**Group 1:** 1/30 **Group 2:** 0/32 **Post operative hospital stay (ITT analysis)** **Group 1:** 9.0 (6.8 -11.3) [12.3 (12.7)] **Group 2:** 7.0(6.0-9.8) [8.3 (4.5)] Note: study also reported mean values, but the data is skewed (median more appropriate) **Post operative hospital stay (per protocol analysis)** **Group 1:** 7.0 (6.0-10.0) n=18 **Group 2:** 7.0 (5.5-8.0) n=25	**Randomisation:** Adequate: Used computer randomisation program, with stratification for gender and age. **Allocation concealment:** Adequate: Result randomisation enclosed in a sealed, opaque envelope and only delivered shortly to the nursing ward shortly before the operation.

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
readmissions	• impaired renal function, • significant cardiac disease (NYHA/CCS ≥ III) • diabetes mellitus • pre-operative IV drip-feeding • contraindications for applying epidural analgesia • failed attempt or logistical reasons. **All patients** **N:** 62 patients out of 343 identified. Reasons for the 281 exclusions were detailed in paper. **Group 1: Restrictive** **N=**30 **Age(years), mean ± sd:** 55.5 ±15.4 **Sex (M/F):** 19/11 **BMI(kg/m2)*:** 23.2 ±4.2 **Weight (kg):** 69.9±12.5 **ASA:** I(4), II(21), III(5), IV(0) **Duration of surgical procedure**, hours mean±sd: 4.3±2.1 **Operation type:** - Gastric: 0 (0%) - Pancreas: 14 (47%) - Bile duct: 7 (23%) - Gall bladder: 0 (0%) - Small bowel: 2 (7%) - Colon: 3 (10%) - Rectum: 3 (10%) - Adrenal gland: 0 (0%)	**In both arms:** • All patients were admitted the day before surgery. • Preoperative bowel preparation regime (two enemas), fasting regime, pre-operative medication, and postoperative nasogastric intubation. were according to Holte2007[179]. 400ml of glucose drink given the evening before and 2 hours before surgery • Had standardised intra-operative IV fluid (published in paper). Fluid disconnected and randomised treatment started immediately post surgery (details of protocol provided in the study) • Postoperatively, the nasogastric tube was removed directly after surgery or on the first postoperative day. Subsequently, patients were free in their oral fluid intake and received the allocated IV fluid	**Respiratory complications**	**Group 1:** 1/30 (respiratory disorder or infection) **Group 2:** 0/32	Disclosure of the randomization took place at the end of the operation. **Blinding:** Adequate: Patients and attending clinicians blinded by immediate covering of the infusion bags and pump by means of an opaque clothing bag. An independent nurse who was not assigned to care for the patient was charged to change the infusion bags every 24 hours and/or solve any pump problems. Clear criteria for unblinding was attached. **Others:** Clearly defined criteria for discharge
			AKI – development of renal failure	**Group 1:** 0/30 **Group 2:** 0/32	
			Quality of life	Not reported	
			Morbidity (SOFA score, MODS)	Not reported	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	- Retroperitoneal tumour: 0 (0%) - Explorative laparotomy: 1 (3%) **Group 2: Standard** **N=**32 **Age(years), mean ± sd:** 53.6 ±15.0 **Sex (M/F):** 21/11 **Weight (kg):** 76.5±17.1 **BMI(kg/m2)*:** 24.5 ±4.7 **ASA:** I(5), II(24), III(3) **Duration of surgical procedure**, hours mean ± sd: 4.2± 1.7 **Operation type:** • Gastric: 1 (3%) • Pancreas: 11 (34%) • Bile duct: 9 (28%) • Gall bladder: 1 (3%) • Small bowel: 3 (9%) • Colon: 4 (13%) • Rectum: 1 (3%) • Adrenal gland: 1 (3%) • Retroperitoneal tumour: 1 (3%) • Explorative laparotomy: 0 (0%)	regime until the attending physician judged this fluid administration could be discontinued, based on evaluation of the oral intake and bowel movements of the patient. <u>Intra-operative fluid:</u> Ringer's lactate : -1st hour : 20 ml/kg -2nd hour and further: 6 ml/kg (in protocol), 8.3 & 9.0ml/kg respectively in restricted & standard respectively. Blood loss ; HAES 6% • At the start : 500 ml • ≥ 500 ml, 2nd 500 ml • ≥ 1,000 ml, 3rd 500 ml ≥ 1,500 ml: Packed RBC, 2 units alternated with 1 unit plasma if >2 packs needed. 4th pack of HAES 6% given if Hb trigger not met, but only if the first one was administered ≥ 6 hours ago.			**Limitations:** Treatment for 12/30(40%) patients in the restricted and 7/32(22%) patients in the standard group were unblinded and protocol discontinued **Additional outcomes:** Leaking of anastomosis: 6 in restricted, 1 in standard, readmission: 3 in restricted, 4 in standard, 2 cardiac complications in restricted, 0 in standard.

Abbreviations: ASA= American society of anaesthesiologist, CAD=: Coronary artery disease, CVP= central venous pressure, HES= hydroxyethyl starch, HR=hazard ratio, HR= Heart rate, ITT=Intention to treat analysis, ISS=Injury severity score, ITBVI= intrathoracic blood volume index, MAP= Mean arterial pressure, M/F=male/female, mL= millilitres, mEq= millieqivalent, N=total number of patients randomised, NISS=New injury severity score, NS= Not significant, RIFLE= Risk, Injury, Failure, Loss and End-stage serum creatinine criteria, SD= standard deviation, SE=Standard Error, SICU= Surgical ICU, SOFA= Sequential Organ Failure Assessment, $ScvO_2$= Central venous oxygen saturation, UFH= unfractionated heparin

E.5 Replacement and redistribution

No studies were identified in this topic area.

E.6 Training and education

E.6.1 What are the barriers faced by healthcare professionals in the effective prescription and monitoring of intravenous fluids in hospital settings?

Study	Casserly et al. 2011[64]
Aim	The determine the effect of the implementation for a Sepsis Intervention Program on the standard processes of patient care using a collaborative approach between the emergency department (ED) and medical intensive care unit (ICU).
Population	Any patient who presented to the ED in a large tertiary care hospital with severe sepsis or septic shock (either hypotension after 30cc/kg resuscitation with a crystalloid fluid or a lactate of more than 4 mmol/l) were eligible for the study. 106 patients had sepsis or septic shock, 87 met the inclusion criteria. 82 had the sepsis intervention protocol initiated, however the sepsis intervention was only initiated in 66 patients (according to the a priori exclusion criteria). Only 42 completely complied with the protocol over the 6 month period. The compliance rate increased to 50% in the last 3 months (42% in first 3 months).
Methods	Prospective cohort study. Intervention protocol was introduced as a change in the standard of care offered to all patients admitted to the ED with severe sepsis and/or hypotension. As a quality improvement study, informed consent was not required. A program of training sessions was undertaken over a 3 month period which involved critical care staff teaching ED residents, attendings and nurses how to identify sepsis and the rationale behind the resuscitation protocol. In addition, a collaborative treatment model was established between the critical care staff and the EF including: 1) early consultation of the critical care staff, 2) enhanced communication through a dedicated 'sepsis beeper' carried by a member of the on-call critical care team, and 3) improvement in patient transfer by predetermining that all patients with severe sepsis for whom the early resuscitation protocol is initiated would be automatically admitted to the ICU. Training in the physiologic concepts and practical logistics of the resuscitation protocol was conducted in both groups. In the first 3 months of implementation of the sepsis intervention protocol an ICU research fellow was available to aid with central venous line insertion at the request of the ED. Patients were excluded if they: 1) refused central line insertion or had a documented contraindication to central line insertion, 2) did not survive long enough to undergo 6 hours of EGDT, or 3) were not candidates for aggressive treatment. The protocol was initiated in the ED by the ED team and then continued during and after transfer to the ICU. The patients were subsequently divided into 2 groups: 1) completed protocol: attempts to reach all the goals of the resuscitation protocol MAP, and $ScvO_2$ measurements had to be recorded where appropriate according to the protocol. Patients were included even if all target goals were not achieved within 6 hour window. 2) Failed to complete protocol: failure to either initiate or complete the protocol. Reasons for no enrolment included ED physician preference, catheter insertion but no protocol started, or patient sent to the ICU without the catheter placed despite the

Study	Casserly et al. 2011[64]	
	patient having no contraindication to catheter insertion. This also included no documentation of CVP, MAP or $ScvO_2$ measurement where appropriate according to the protocol. A single violation of protocol was assessed as failure to complete the protocol. This group of patients served as a comparative group. Primary outcomes: time rom admission to the ED to catheter insertion; time to fluid administration, vasopressors, and antibiotics; and time to transfer from the ED to the ICU. Baseline time for all outcomes was time of arrival in the ED. 6 month analysis was performed. A further analysis was performed using only the patients in the final 3 months of the study, comparing protocol group with non-protocol group. As early in the study, many patients were started on the protocol but did not continue to receive care as per protocol. Median regression analysis was carried out.	
Findings	Baseline characteristics	• Statistically significant increase in APACHE II score between protocol and non-protocol groups over 6 months. As a consequence of this confounder, differences in secondary outcomes were not calculated between these groups. • In the 3 month period, there were no significant differences between the 2 groups with respect to the baseline characteristics tested.
	Time-to-therapy variables	• For all variables, median interval was shorter in the protocol group than non-protocol group. • Significant difference for time to fluid administration and time to catheter insertion. • No significant group differences for secondary outcomes. • Sepsis intervention program was effective in reducing therapy intervals. • Coefficients were positive for all but one of the time variable for the non-protocol group, suggesting factors other than the intervention were not at play in explaining the diminished times exhibited for the protocol subjects. • Over the 6 months the introduction of the protocol led to an increase of 32% in rate lactate levels were obtained in patients with sepsis presenting to the ED.
	Summary	• The use of a collaborative protocol for sepsis intervention may decrease the time to initiation of resuscitation for patients admitted to the ED with severe sepsis and decrease the time to transfer to the ICU. • Many institutions have low compliance rates, suggesting making a sepsis intervention protocol operational may present difficulties.
Limitations	• Number of patients reported are unclear and varies between 82 – 87 included. • Sample size small and evaluation period short. • Patient were not randomised.	

1

Study	Chung et al. 2002[72]
Aim	To find ways to rationalise the use of staff resources and information storage/retrieval process (in relation to fluid balance charts). Main objectives:

Study	Chung et al. 2002[72]	
	• To estimate the magnitude of FB charting in the patient population. • To identify the situations in which fluid balance charting is being prescribed. • To identify nursing and medical staff opinion on the appropriateness and accuracy of fluid balance charts. • To make recommendations for improved use of fluid balance charts.	
Population	For the survey/interview stratified random sampling was undertaken at one volunteer hospital. 124 doctors and 326 nurses from 6 departments (medical & geriatric, surgical, obstetrics & gynaecology, paediatric, orthopaedics & traumatology and neurosurgical) were eligible. Stratification ensured that all selected ranks of nurses and doctors had been adequately represented in the sample. 110 nurses and 80 doctors accepted the invitation to participate and made an appointment for an interview. The final sample was 101 nurses and 72 doctors (required sample sizes of 98 and 74 respectively).	
Methods	Secondary sources of data were used in phase 1 of the study: summation and means of length of stay, amount of paper used, proportion of medical records and accuracy of calculation were recorded by a checklist. Frequencies were used to describe the data. The second part of the study was done by survey – using a structured interview (which was recorded). This was intended to maximise the response rate. All interviews were conducted by one of the study authors. The interview consisted of two parts, review of medical records and an opinion survey.	
Themes with findings	Accuracy of fluid balance charts	• 60.8% had fully accurate calculations. • 14 days recordings were missing with no known reason. • Overall summary is that as many as 32% of the 24-hour fluid balance charts were useless.
	Reasons for starting fluid balance charts	• Main reasons were: vomiting/diarrhoea, fluid restriction, maintaining intake and intravenous infusion. • Nurses gave IV infusion more frequently than doctors. • Doctors gave fluid restriction more frequently than nurses.
	Perceptions of the efficiency of FB charting	• Around 46% of doctors and nurses believe that charts are not always terminated when they are not required. • Almost 20% of doctors and nurses agree that charts are often kept as a routine measure. • Most commonly doctors think that only doctors should discontinue the fluid balance chart and nurses were unanimous in believing they should not do this without the agreement of the doctor.
Limitations	• All interviews conducted by a study author – respondents may not have given their true opinions. • Data collected in Hong Kong and therefore most relevant to their public hospital context. • No thematic analysis undertaken.	

1

Study	Cook 2005[83]
Aim	To determine:

Study	Cook 2005[83]	
	• How nurses see their role in fluid management in patients with subarachnoid haemorrhage. • What cues nurses use to guide their practice.	
Population	Neurosurgical unit consisting of two 29-bed wards catering for all acute neurosurgical services in the region. All first-level nurses registered with the Nursing and Midwifery Council working in the unit were open to inclusion. Quota sampling was used and a list of nurses created with strata for each grade of nurse working in the unit, ensuring all grades were represented. 11 nurses participated in the focus group, intended to maximise the presence of all grades, experience and knowledge.	
Methods	Action research. The first stage involved ascertaining nurses' interpretation of their role and the knowledge that they claim facilitates their practice and decision-making through a focus group. Action research involves re-education, problem-focus and improvement and involvement. Participants take part in the process and validate the concepts and themes derived throughout the research proves. Focus groups were chosen as the qualitative approach with the researcher as the group moderator. Two open-ended questions were asked. Narrative analysis was used from verbatim transcripts obtained from tapes of the focus group session which were blind reviewed. Member checking of the transcripts was also carried out to reduce the bias and validate data (including verifying discussion themes). The first question was analysed by extracting common themes. The second question was analysed using a previously described framework (Stevens 1996).Three groups of data were produced creating three sets of themes for the final stage of analysis. This methods of analysis was chosen to provide rigour by evidencing the source of themes and acknowledging the effects of group dynamics on results. The two questions were: 1. What indicators or cues do you use to guide how you manage, alter and review the fluid/hydration management of patients with subarachnoid haemorrhage in your current practice? 2. How do you perceive your role in managing fluid/hydration management in patients with subarachnoid haemorrhage?	
Themes with findings	From data on group dynamics	• Some nurses felt that standards of care, quality of care, safe practice, and continual improvement of practice grounded the need for the current standard for the administration of intravenous therapies in the unit. • Nurses felt that extended roles emerging in the management of hydration and fluid therapies should not come at the expense of patient care. • Some said that those with specialist roles should be able to work supernumerary for their role to be effective and to avoid a negative impact on patient care.
	What indicators or cues do you use to guide how you manage, alter and review the fluid/hydration management of patients with subarachnoid haemorrhage in your current practice?	• Nurses are knowledgeable about fluid assessment, fluid balance and hydrational needs of their patients with subarachnoid haemorrhage. • Nurses rely on physical appearance, a variety of forms of fluid intake and output, biochemical and physiological values to ascertain hydrational status. • Nurses feel that neurological status is important I monitoring the effect of fluid therapies. • Nurses are knowledgeable about the need for a greater intake in patients with subarachnoid haemorrhage and why this intake can prevent secondary brain injury.

Study	Cook 2005[83]	
	How do you perceive your role in managing fluid/hydration management in patients with subarachnoid haemorrhage?	• Role ambiguity exists among the nurses with regards to the exact parameters of their role. • Nurses felt it was not their role to be aware of sodium and potassium values when administrating 'regular' fluids, but would be aware of such values if alternative fluids were prescribed. • Nurses know that no act or omission on their part should be detrimental to their patient. • Nurses believed their role entailed appropriate fluid administration, patient advocacy, accurate and concise documentation, monitoring for effects of fluid therapies in accordance with orders from medical staff, safe and ethical practice, and protection of patients. • Nurses believed their role was difficult to fulfil owing to understanding and lack of interdisciplinary cohesion. • Nurses believed accountability was jointly held between medical and nursing staff.
Limitations	• Researcher is someone internal to the organisation being studied. • Interviewer bias may occur, but checking carried out by an external researcher. • Limited to nurses only.	

1

Study	Coombes et al. 2008[85]	
Aim	To assess medical students' perceptions of their readiness to prescribe, associated risks and outcome if involved in an error, as well as their perceptions of available support.	
Population	101 students at 2 teaching hospitals 6 weeks before the start of the intern year.	
Methods	Survey by means of a structured questionnaire (6 point Likert scale) which was developed following a literature review, focus groups and a pilot study carried out with 15 interns the previous year. An indication of agreement with 21 closed statements in 4 thematic clusters was sought. The pre-determined themes were: 1. perceived ability to prescribe safely; 2. expectation of available support for prescribing; 3. awareness of the types and frequencies of medication errors, and 4. perceived outcomes of prescribing errors. A factor analysis was undertaken to determine if students' responses bore out the themes identified above. Only those themes and findings relevant to the review protocol are extracted below:	
Themes with findings	General prescribing ability	• I will be able to adequately order IV fluids without having to seek help: two thirds (66) agreed (39 slightly agree, 24 agree and 3 strongly agree). • In my surgical term I am confident that I will manage postoperative electrolyte changes safely in most cases: 70 agreed (51slightly agree, 19 agree).

Study	Coombes et al. 2008[85]	
	Communication regarding prescribing and errors	• The blame culture no longer exists if a colleague makes a mistake: 79 disagreed (8 strongly disagree, 28 disagree, 43 slightly disagree).
Limitations	• Methods of factor analysis not clearly stated. • Study reports that six statements did not correlate well with the pre-determined clusters, but were included because they provided insight into error awareness. Not clear which statement these were.	

1

Study	Dauger et al. 2008[95]	
Aim	To improve compliance with international consensus guidelines about emergent fluid resuscitation of children with sepsis and hypovolaemia by means of a teaching programme.	
Population	Before period: n=8496, Mean age (days) 182 (20-1830), Main diagnosis (n) Dehydration (11), Sepsis (3), Respiratory distress (1). 18 Fluid challenges performed. After period: n=8891, Mean age (days) 191 (9-1988), Main diagnosis (n) Dehydration (10), Sepsis (5), Respiratory distress (1). 21 Fluid challenges performed.	
Methods	A before-after study was conducted collecting data on all fluid challenges given during a 6-week period in the winter encompassing the gastroenteritis seasonal peak in incidence to inform the development of the training programme. Patients were identified prospectively. At the end of the period, compliance with guidelines was evaluated and the knowledge of the physician was assessed by asking them how they would manage a patient described in a fictional scenario agreed closely with international consensus guidelines. These data were used to create a 1-hour training program on the emergent management of hypovolaemia in infants in accordance with the international consensus guidelines. This was delivered each day during one week to ensure that all 12 physicians participated, regardless of their schedule. All 12 physicians working in one paediatric emergency department followed the training programme. Data on fluid challenges were collected during the same 6 week winter period of the following year. Study reports changes in main fluid challenge parameters. Not reported here as not relevant to review protocol.	
Themes with findings	Teaching programme reduced duration of fluid challenges and eliminated use of colloids (consistent with guidelines).	Proportion of patients with fluid challenges was not different, and clinical features of patients didn't differ. Volume of fluid used was the same in the two periods, but infusion duration was significantly shorter after training. Colloids were never used after the training programme.
Limitations	• Follow-up data was not recorded therefore cannot determine whether the training programme influences morbidity and motality nor whether effects of the training programme are sustained. • Indirect population (paediatric).	

2

Study	Hobbs & Abbruzzese 2011[177]	
Aim	To identify the competence of new hospital employees and their compliance in charting IV documentation.	
Population	All patients with an active IV order on a specific day.	
Methods	Narrative review of results of a computer skills test and then monthly audits to assess consistency and compliance (computerised documentation and verifying if IVs were charted correctly). Undertaken over 1 year. After initial phase, a skills lab information packet and computer documentation station, with a focus on IV documentation were created to identify and correct any deficits among the nursing staff. All nurses undertake this annually. Survey also distributed to identify barriers in charting IVs.	
Themes with findings	IV documentation	• Although a major component addressed in orientation and skills lab, review of the initial data raised concern that compliance was below acceptable standards. • After introducing the skills lab information training at 3 months, there was on ly 1 74% compliance in charting in the IV therapy form.
	Barriers preventing nurses from charting IVs	From 74 surveys (37% response rate) responses included: • Having a heavy patient workload • Insufficient staffing • Cumbersome charting formats • Lack of time
	Opinions on how to make documentation easier	Study stated that the IV therapy form could be improved – details not given.
Limitations	• Limited detail given in the narrative review. • Unclear how many nurses were included. • No thematic analysis.	

1

Study	Jensen 2009[195]
Aim	To evaluate students' perceptions of knowledge of and comfort with IV therapy skills. Comparisons were made between students who participated in the new elective educational offering on IV therapy and students who received standard IV instruction.
Population	Convenience sample of students in their last nursing course prior to graduation. The students elected whether to take the course, workshop, or no additional IV educational offering. 124 surveys were completed out of a possible 170 distributed (72.9% return rate) 32 of these participated ni the IV course, 49 in the IV workshop and 41 did not complete either.
Methods	A one-credit IV therapy course was developed which included 9 content areas suggested by the Infusion Nurses Society. It included a 2 hour

Study	Jensen 2009[195]	
	laboratory session when the students inserted 2 different IV catheters in an anatomical model, changed a central line dressing and had an opportunity (but were not required) to insert IV catheters in peers. Students also participated in a 4 hour practicum at a local hospital to insert IV catheters under direct supervision of nursing staff. For students who did not want to commit to the course but wanted additional instruction in IV therapy and perform IV insertions during their leadership clinical experience, a 3 hour IV therapy workshop was developed. The workshop consisted of 1 hour of didactic instruction, including information about peripheral and central venous access devices; identification and treatment of complications; and documentation requirements related to IV therapy. Students in both programmes attended the 2 hour lab session. A survey was developed to determine students' self-assessed level of knowledge of IV therapy and level of comfort performing IV interventions. The knowledge and comfort statements were constructed to assess how well students believed they understood various aspects of IV therapy and how comfortable they were with IV skills. Additionally, open-ended response items were included to elicit information about students' experiences with IV therapy in the programme in general. The survey questions related to comfort with IV skills were structured on a 5-point Likert-type scale with anchors of not very comfortable (10 and very comfortable (5). A choice of 'NA' represented sills that students were not able to perform at any time in the clinical practical. The knowledge statements were also on a 5 point Likert scale with do not understand (1) and understand very well (5) as the anchors.	
Themes with findings	Increased level of students' perceived comfort with skills associated with IV education	Significant differences were observed among IV workshop participants, course participants and those who had no elective IV education: • Central line medication administration – workshop participants more comfortable than credit course participants. • Central line dressing changes – workshop participants more comfortable than those with no elective IV education. • Inserting IVs - workshop and course participants were more comfortable than those with no elective IV education. • Knowledge of chemotherapy – workshop participants more confident in their knowledge than those without IV elective education. • Knowledge of IV therapy related to care of patients through lifespan - workshop and course participants were more confident in their knowledge than students without an elective IV educational activity.
	What was working well in the elective IV educational opportunities	• Workshop: small class sizes, one-t-one attention of instructor, and the 'hands-on' practice with anatomical models and peers. • Credit course: detailed information in an abbreviated course.
	Suggestions for improvement	• More opportunities for practice in the laboratory experience and longer practical's inserting IVs in the hospital settings • Workshop could be improved by allowing more IV insertions per person as practice and adding information on IV medication administration. • An opportunity to follow the IV resource team rather than spending 4 hours in the surgical admission unity for the practical portion of the workshop and course might be beneficial.

Study	Jensen 2009[195]
Limitations	• Small sample size. • Limited to one semester in one school. • Students self-selected the courses they participated in which likely contributes to bias affecting their perceptions of comfort and knowledge. • No thematic analysis undertaken.

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Study	Jeon et al. 2012[196]	
Aim	To determine whether an educational program based on the Surviving Sepsis Campaign guidelines could improve compliance with early goal directed therapy (EGDT) and outcomes of patients with severe sepsis or septic shock in a Korean tertiary referral hospital. In additional, the study evaluated which achievement of end points of resuscitation bundles was associated with in-hospital mortality.	
Population	Consecutive patients with a diagnosis of severe sepsis or septic shock prospectively registered. Severe sepsis defined as sepsis associated with acute organ dysfunction. Septic shock defined as sepsis with acute circulatory failure characterized by persistent arterial hypotension despite adequate volume resuscitation. Patients who were younger than 18 years, who were transferred from other hospitals, who had limitation of care decision, or who had poor performance with metastatic cancer unresponsive to chemotherapy or radiation therapy were excluded from this study. Historical controls n=163, treatment patients n=203.	
Methods	Retrospective observational study of patients presenting to the emergency department (ED) meeting criteria for severe sepsis or septic shock and entered in a sepsis registry from August 2008-July 2009 at Samsung Medical Centre (tertiary referral hospital in Seoul, South Korea). An educational program was organised on severe sepsis and septic shock prior to the study period and introduced over 3 months before the sepsis registry began. It consisted of ED fellows, residents, and nurse training on early recognition and management of patients with severe sepsis or septic shock including hemodynamic monitoring using central venous pressure (CVP) and central venous oxygen saturation ($ScvO_2$)and EGDT protocol. Because the management protocol was designed for use by treating clinicians rather than by a study team, conference lectures, bedside teaching and simulation training based on the Surviving Sepsis Campaign guideline were also provided. A specific protocol for early recognition and management of patients with severe sepsis or septic shock was promoted during the educational phase. Once a patient met these criteria, fluid resuscitation and hemodynamic monitoring were initiated with placement of a central venous catheter with the internal jugular or subclavian vein approach for CVP and $ScvO_2$ monitoring. Hemodynamic resuscitation was conducted according to a predetermined treatment plan First, isotonic crystalloid was administered in boluses to target CVP of 8-12mmHg. Second, systolic blood pressure of ≥90mmHg or MAP of ≥65mmHG, if not achieved with fluid administration, was targeted by initiating and titrating vasopressors to achieve this desired blood pressure.	
Themes with findings	Administration of resuscitation bundles and interventions with the 1st 6 hours	• Time to resuscitation and adequate fluid challenges were not different before and after 3 months of educational program on severe sepsis and septic shock. • Compliance with central line insertion and monitoring of CVP and $ScvO_2$ was significantly improved after the educational program.

Study	Jeon et al. 2012[196]	
	after presentation of severe sepsis or septic shock	• The use of vasopressors and inotropics was significantly increased by the program.
	Outcomes	• End points of CVP and MAP within the first 6 hours were not different before and after the 3 month educational programme. • Goal achievement of $ScvO_2$ of 70% or greater within the first 6 hours was significantly higher in the treatment patients. • In-hospital mortality was 11.8 in treatment patients compared with 18.4% in historical controls, absolute risk reduction 6.6% and relative risk reduction of 35.9%. • In-hospital stay was significantly shortened from 14 days in historical controls to 12 days in treatment patients. Also observed in the surviving populations before and after the 3-month educational program.
	Odds ratios	There was a statistically significant decrease OR for in-hospital mortality in patients who received adequate fluid challenge (OR 0.356; 95% CI 0.150-0.847) and achieved the goals of MAP (OR, 0.085; 95% CI 0.018-0.408) and $ScvO_2$ (OR, 0.191; 95% CI 0.063-0.579)
	Multivariate logistic regression	With adjustment for age, sex and SOFA scores and the 5 completions of interventions or goal achievements of resuscitation bundles indicated that adequate fluid challenge (OR 0.161; 95% CI 0.046-0.559) and goal achievements of MAP (OR 0.056; 95% CI 0.008-0.384) and $ScvO_2$ (OR 0.251; 95% CI 0.072-0.875) within the first 6 hours were independently associated with decreased in-hospital mortality.
Limitations	• Structured interview – not clear how many questions were open ended. • Interview by telephone, including confirming diagnosis of migraine according to IHS criteria. May lead to doubt in diagnosis. • Descriptive statistics only used, no formal qualitative analysis.	

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Study	Keijzers et al. 2012[209]
Aim	To assess the workplace practices and knowledge of tertiary hospital doctors regarding paediatric IV fluid prescription
Population	Convenience sample of doctors (n=150) representing all levels of experience and all specialities that regularly prescribe paediatric IV fluids were invited to participate (including emergency medicine, paediatrics, anaesthetics, intensive care and surgery). 106 (71%) returned a completed questionnaire.
Methods	Prospective, questionnaire-based observational study conducted at a teaching hospital over a period of 5 weeks. Confidential, 3 part questionnaire, 1st part focussing on demographical data, workplace behaviours, methods for calculation and whether participants had previously received formal education regarding fluid prescription. The 2nd part consisted of 8 clinical scenarios for which participants had to calculate a fluid bolus, fluid deficit or fluid maintenance rate. A fluid type also had to be chosen. The last part consisted of 10 multiple choice questions. Main outcomes: demographical data and the ability to correctly prescribe paediatric fluids measured as 'fluid calculation', 'fluid choice' and 'total' percentage scores based on a percentage score of correctly answered questions using 8 clinical scenarios.

Study	Keijzers et al. 2012[209]	
Themes with findings	Method of calculations	• 91.4% had a method for calculating fluid bolus, only 60.6% of these were correct. • 97.2% had a method of calculating maintenance fluid rates, 79.6% of these were correct.
	Fluid calculations / multiple choice questions	• Answered correctly by >75% • Exceptions included a scenario in which a fluid deficit and maintenance rate had to be calculated (55% correct calculation, 46% correct fluid choice) and an infant with the potential to develop an increased secretion of ADH (18% correct calculation and 35% correct fluid choice). • The majority of participants scored at least 85% on the knowledge test.
	Analysis by demographics	• Men and women had similar total scores, although men did score significantly higher than women when comparing calculation alone • Senior doctors scored significantly higher on the total score, fluid calculation score, fluid choice score, but not knowledge score, compared with junior counterparts. • Doctors with previous paediatric experience tended to score higher than those with only paediatric experience derived from medical school or from a mixed ED environment, although this was only significant for fluid calculation. • ED and paediatric doctors scored higher than other specialities. Surgical specialities scored lowest. • Doctors who had received some formal education or ongoing tuition in the prescription of paediatric IV fluids felt more equipped to carry out the task, and also scored higher on their fluid knowledge choice scores. • Doctors who prescribe IV fluids on a more frequent basis (at least weekly) and those who had been previously tested, scored significantly higher on all scores except knowledge score.
Limitations	• Single site only, limiting extrapolation to other settings (especially smaller hospitals or rural settings). • A convenience sample was used – possible selection bias. • Uneven spread of subjects' level of training – interns formed the largest group of respondents and half had not had the opportunity to complete a paediatric or emergency term, which might have influenced their scores. • Questionnaire wasn't validated. • Fluid choices were deemed as correct by agreement by a panel of researchers and clinicians, therefore might have a degree of subjectivity. • Multiple choice questions may have allowed for answers to be guessed.	

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Study	Kelly et al. 2011[210]
Aim	To determine the self-rating of preparedness amongst appointed interns at graduation, and what orientation and two rotations of experience added to this, if anything. A second aim was to identify those tasks most commonly expected of interns as well as interns concerns and

Study	Kelly et al. 2011[210]	
	expectations of their intern year.	
Population	All interns starting in 2009 at one hospital. Of the total of 66 interns, 52 (84%) completed the first survey and 37 (56%) completed the second.	
Methods	Two surveys were undertaken to assess the intern cohort's preparedness for the intern year. The first was completed after their appointment, but before commencement, a follow-up survey was completed at the end of their second rotation (each rotation lasted 11 weeks). Responses to questions in both surveys were via either a 4- or 5-point Likert scale with opportunity to add free text for some questions. Survey was anonymous but a unique identifier allowed matching of pre-and post-survey answers for analysis.	
Themes with findings	Relationship between preparedness and confidence	• The interns pre-employment confidence in their ability to complete a task was related to their self-rated feeling of preparedness and the number of times they reported they had undertaken the task during university. • The interns expressed confidence in undertaking some tasks although they had limited exposure to them (certification of death, handover of care, use of an interpreter; and insertion of a nasogastric tube). • There were a range of tasks in which they were experienced, but comparatively less confident about (ECG review, medication management, routine assessment of patients; and completing routine documentation).
	Concerns and expectations	The most consistent concern was that of feeling unsupported or out of their depth or not knowing how to escalate a clinical concern.
	Confidence to complete tasks – pre-employment to end of second rotation	All but 2 demonstrated an increased in confidence at the end of the second rotation. This was significant for all procedures except for: • Completing documentation on ward rounds (most felt reasonably prepared before start) • Insertion of an IV cannula (most felt very well prepared before start, i.e. high baseline) • Preoperative patient review (most reported feeling somewhat prepared before start) • Patient admissions (most felt reasonably prepared before start).
	Task frequency versus confidence	Tasks frequently undertaken and high reported confidence included: • Insertion of an IV cannula • Documentation • Fluid Management
	Self-reported task preparedness	Tasks interns left less prepared for included: • Fluid status management and review • Assessment of unstable patients
Limitations	• No thematic analysis. • Not all raw data provided for survey responses • Not all related to IV fluids.	

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Study	Mousavi et al. 2012[266]	
Aim	To evaluate IV fluid therapy status and related errors in hospitalised patients in the infectious diseases wards of a referral teaching hospital, Tehran, Iran.	
Population	830 patients were hospitalised in the infectious disease wards during the study period. 450 (248 men, 202 women) received IV fluid therapy during their hospitalisation course. Mean age 45 ± 19.7 years.	
Methods	Retrospective cohort study. IV fluid therapy data were collected by 2 clinical pharmacists of infectious diseases from 2008-2010. Collected data included age, sex, weight, haemodynamic parameters, vital signs, blood sugar, renal function tests, serum electrolytes, causes of hospital admission, past medical history, present illnesses and baseline diseases. The patients' IV fluid therapy information including indication, type, volume and rate of fluid administration was evaluated. A protocol for IV fluid therapy was prepared based on a literature review and available recommendations. Data related to patients' fluid therapy were compared with this protocol. Fluid therapy was considered appropriate if it was compatible with the protocol regarding indication, type, electrolyte content and rate of fluid administration. Any mistake in the selection of fluid's type, content, volume and rate of administration was considered as fluid therapy error. Data were analysed by descriptive tests. Qualitative variables are presented by their frequency of distribution. Quantitative variable were mean & SDs.	
Themes with findings	Errors detected	• 596 IV fluid therapy errors were detected during the study period with an average rate of 1.3 errors per patient. • Patients with diagnosis of endocarditis, HIV and its related opportunistic infections, and sepsis experienced more errors than patients with tuberculosis and urinary tract infections. • Errors in the rate of fluid administration (29.8%), incorrect calculation of required volume of fluid (26.5%) and incorrect selection of the fluid type (24.6%) were the most common types of fluid therapy errors respectively. • Based on vital signs, haemodynamic parameters, physical examination and serum biochemical data, appropriate volume status assessment had not been made in 48.7% of the patients
	Correlations	Significant correlations were found between occurrence of fluid therapy errors and: • Male sex (OR 1.4, 95% CI 1.1-1.8) • Age over 50 years (OR 1.1, 95% CI 1-1.4) • Baseline serum creatinine over 1.2mg/dL (OR 11.8, 95% CI 1.4-2.6) • Diabetes mellitus as a co-morbidity (OR 1.5, 95% CI 1.4-2.4) • Diagnosis of endocarditis (OR 2.3, 95% CI 2.1-3.9), HIV (OR 1.9, 95% CI 1.6-2.8) and sepsis (OR 2.1, 95% CI 1.3-2.5).
Limitations	• All information collected retrospectively from medical charts. • There was no follow up on consequences of fluid therapy errors	

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Study	Potts & Messimer 1999[303]	
Aim	To identify and measure differences in knowledge of paediatric fluid management procedures between students taught by computer tutorial and others taught by lecture or seminar. Hypothesis was that a computer based tutorial could allow medical students to master paediatric fluid management skills more effectively.	
Population	89 third year medical students with no prior paediatric fluid management experience. 48 in microcomputer tutorial programme, 41 in seminar/reading/handout programme.	
Methods	Cohort analytic study. Forty eight students at one community campus completed a microcomputer-based tutorial programme that replaced all teaching sessions in paediatric fluid management. Forty one students from a similar community campus were taught identical content by a paediatric critical care specialist using a seminar, reading material and handouts. Carried out during an 8 week paediatric clerkship. The computer instruction group could complete the programme at any stage during the 8 weeks, as long as they completed it n one session. On average it took 4 hours to complete. The seminar group were given a 90 minute seminar. The handout was provided before the session and references were provided. Students were encouraged to practice sills learnt and practice cases were distributed. No evaluation was made to see if students carried this out. To assess students ability to apply their knowledge, 2 free-answer fluid therapy problems were given to all students at the end of 8 weeks. These involved determination of fluid maintenance requirements and plans for rehydration. All responses were graded by a single evaluator using a pre-determined key and grading form. The evaluator was kept blinded as to the community site of the students.	
Themes with findings	Students taught using computer methods had better factual knowledge and actual practical problem solving than similar students taught using traditional methods.	Exam results, computer vs traditional: Multiple choice: 81.1% vs 62.2% P<0.001 Free-answer: 85.4% vs 61.0% P<0.001
Limitations	• Indirect population (paediatric). • Prior knowledge of paediatric fluid management was not determined in participants (although none had previous exposure to paediatric fluid and electrolyte management techniques prior to the start of the programme) • Study authors acknowledge that the increased amount of time the students needed to complete the computer programme may be responsible for the improvement. The amount of time studying in the seminar group was not determined. • Number of people attending the seminar was not assessed. • The computer instruction group completed their multiple choice exam immediately after undertaking their computer based training rather than at the end of the 8 weeks as in the seminar group. However, both groups undertook the free-answer exam at the end of the 8 weeks so the effect is likely to be small. • The computer instructed group also had to complete an essay exam on their knowledge of 6 core topics in general paediatrics which they were told would include a fluid question. Seminar students did not have this test. If they had, this may have had an effect on improving their other test results.	

Study	Potts & Messimer 1999[303]
	• Differences between groups may also be due to a single method of teaching being used rather than mixed methods. This cannot be determined from this study.

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Study	Tang & Lee 2010[347]	
Aim	To review whether surgical trainees are able to interpret and calculate fluid balance charts correctly.	
Population	All (13) fluid balance charts of surgical patients requiring intravenous fluid and catheterised for urine output monitoring from all 5 surgical wards on 1 day. All surgical trainees (12 at specialty training level and 13 foundation year level trainees) were approached to calculate data from charts. 324 results for each of the parameters were collected. No data was missing.	
Methods	Prospective study. Fluid balance charts from one day collected. Trainees calculated, in the presence of the authors to prevent conferring, the 24-hour total input and output of the charts and to give a rating for the difficulty of interpreting each chart on a generic 1-10 scale (1 extremely difficult – 10 extremely easy). Authors were not allowed to give additional explanation of the charts, but calculators were provided to prevent mathematical errors.	
Themes with findings	Differences between trainee levels	• No difference in calculated total input or output values between surgical trainees and foundation level.
	Differences from original documents	• Significant difference in input calculations for 8 out of 13 charts for both trainee levels (and one further chart in foundation year trainees). • Surgical trainees output calculations differed to original documented values in 3 out of 13 charts, and 4 out of 13 in foundation year trainees.
	Difficulty rating	• Wide variations between charts for both surgical and foundation year trainees. • No difference in ratings between trainee groups.
	Overall conclusion	• Clinical experience does not appear to affect interpretation and calculation ability. • Alarming variation in calculated values from original documentation – a potential risk management hazard.
Limitations	Small sample size (25). One site only. Selected surgical patients' fluid balance charts.	

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Study	Weisgerber et al. 2007[392]	
Aim	To evaluate: • The competency of junior medical students in fluid and electrolyte management upon completion of their paediatric clerkship; • The frequency and perceived helpfulness of fluid and electrolyte management-based interactions with the following sources of education: a lecture, first-year residents (PL1s), senior residents (PL3s), and faculty; and • The relationship between points 1 and 2.	
Population	Paediatric junior medical students (M3s) who completed their clerkship at the Medical College of Wisconsin between July 2003-June 2004. All 200 were invited to participate, 13 declined. Of the 187 who enrolled, 187 completed the multiple choice questions, 183 completed the clinical vignette and 180 completed the survey.	
Methods	Cross-sectional study/survey. In the last 2 weeks of clerkship, students asked to complete a web-based quiz and survey. The quiz contained a multiple choice question section and a clinical vignette concerning the fluid and electrolyte management of a dehydrated child. The survey consisted of questions about the various sources of fluid and electrolyte management education. There were 10 open ended questions , 4 with 10 point Likert-scale questions, and 2 final open ended questions for junior students asking the most helpful source of fluid and electrolyte management training and suggestions to improve training.	
Themes with findings	From survey	• The lecture was rated as the most helpful source of education by 41% of students, and received the highest helpfulness rating on the Likert scale. • The second highest perceived helpfulness rating was given to first-year residents (significantly higher than senior residents and faculty).
	From multivariate regression analysis	• The only factor significantly associated with higher clinical vignette scores was the perceived helpfulness of the lecture.
	Factors associated with perceived helpfulness	• There were significant correlations between the frequency of case-based interactions with each source and source-specific perceived helpfulness. • There were significant correlations between the number of hours spent in fluid and electrolyte management discussion and the perceived helpfulness of first-year and senior residents, but not faculty. • The frequency of case-based interaction with each source remained significantly associated with perceived helpfulness in multivariate analyses. • The number of fluid and electrolyte management discussion hours with senior residents remained significantly associated with perceived helpfulness, but not the number of hours with first-year residents and faculty.
	Suggestions for improving fluid and electrolyte management education	• 33% of medical students suggested that providing more practice problems would improve fluid and electrolyte management education. • 14% suggested that providing more practice problems with immediate feedback would improve fluid and electrolyte management education.

Study	Weisgerber et al. 2007[392]	
		• Other suggestions included making no changes (22%) and providing examples with more detailed explanations (10%).
Limitations	Indirect population (paediatric). Assessment of case-based fluid and electrolyte management exposure was subjective. Inaccurate retrospective assessment of the frequency of events may affect accuracy of results. Reliability of the multiple-choice questions was low. Study conducted at one medical school only – findings may not be generalisable.	

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Appendix F: Economic evidence tables

F.1 Principles and protocols for intravenous fluid therapy

Jones AE, Troyer JL, Kline JA. Cost-effectiveness of an emergency department-based early sepsis resuscitation protocol. *Critical Care Medicine.* 2011; 39(6):1306-1312. *(Guideline Ref ID JONES2011A)*

Study details	Population & interventions	Costs	Health outcomes	Cost effectiveness
Economic analysis: CEA **Study design:** prospective before and after study **Perspective:** US hospital perspective **Time horizon:** Lifetime **Study duration:** 2 years **Discounting:** 3%	**Population:** 285 79 patients in before phase Mean age = 58 M = 59% 206 patients in after phase Mean age = 56 M = 49% **Intervention 1:** Before phase No formal resuscitation protocol was used. Non protocolised care **Intervention 2:** After phase EGDT protocol: central venous pressure, mean arterial pressure and central venous oxygen saturation.	**Total costs (mean per patient):** **Intervention 1:** £8,314 **Intervention 2:** £12,721 **Currency & cost year:** 2006 USD (presented here as 2006 UK pounds‡) **Cost components incorporated:** In-hospital treatment, implementation costs of the protocol, physician director (30 hrs), nurse director (30 hrs), staff training.	**Primary outcome measures:** Sepsis- adjusted life expectancy **Intvn 1** = 5.7 **Intvn 2** = 7.2 Incremental Intvn 2-Intvn 1 = 1.5 QALYs **Intvn 1** = 5.1 **Intvn 2** = 6.4 Incremental Intvn 2-Intvn 1 = 1.3	£2,926 per life year gained £3,384 per QALY gained Probability of cost-effectiveness was 97% at a threshold of £13,000 per QALY. **Analysis of uncertainty:** SA on parameters: Sepsis adjusted life expectancy and QALYs. Results not sensitive to the sepsis adjustment of life expectancy. Results were not sensitive to utility of survivors or discount rate. Using a utility weight of 0.69 would decrease the number of QALYs gained in both groups and increases the ICER to £4,111 per QALY gained.

Data sources

Health outcomes: Life expectancy within first year adjusted according to length of hospital stay and midpoint life expectancies between measurement points. Life expectancy beyond one year estimated according to age and gender specific expected life years using 2005 US life tables. Life expectancy beyond one year decreased by multiplication of 0.51 to account for increased relative risk of death among sepsis survivors. QALYs taken from assigning each patient the average utility level of a person in the general population with the same sepsis adjusted life expectancy (rather than the same age, gender, race and ethnicity) using utility estimates derived from a nationally representative sample from the US population 2000-2002.

Cost sources: Hospital costs for each patient from hospital's cost accounting system.

Comments
Source of funding: Dr. Jones received funding from the National Institutes of Health and a grant from Hutchinson Technology. Dr Kline received funding from the National Institutes of Health. **Limitations:** Outcomes did not include all fluid related adverse events; observational study subject to confounding; protocol did not exclusively manage IV fluid therapy; Long term costs not accounted for because patients were not followed beyond hospital discharge; uncertainty in components of non protocolised care which makes interpretation of results difficult.
Overall applicability*: Partially Applicable **Overall quality**:** Potentially Serious Limitations

*Abbreviations: CEA = Cost Effectiveness Analysis; EGDT= Early Goal Directed Therapy targeting three physiological end points of resuscitation: central venous pressure, mean arterial pressure and central venous oxygen saturation; SA = sensitivity analysis; ‡ Converted using 2006 Purchasing Power Parities [Organisation for Economic Co-operation and Development. Purchasing Power Parities for GDP dataset (Aug 2010). Available from: http://stats.oecd.org/I] * directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious Limitations / Very serious limitations*

Shorr AF, Micek ST, Jackson WLJ, Kollef MH. Economic implications of an evidence-based sepsis protocol: can we improve outcomes and lower costs? Critical Care Medicine. 2007; 35(5):1257-1262. (Guideline Ref ID SHORR2007)

Study details	Population & interventions	Costs	Health outcomes	Cost-effectiveness
Economic analysis: CCA Study design: Retrospective analysis of before-after study (b) Perspective: US hospital perspective Time horizon: 28 days Study duration: 1 year	Population: 120 presenting to Emergency Department with septic shock Mean age: 64.7 M = 44.2% Intervention 1: non protocolised care 60 patients Intervention 2: protocolised care (b) 60 patients	Total costs (median per patient): Intervention 1: £13,986 Intervention 2: £10,244 Currency & cost year: 2005 USD (presented here as 2005 UK pounds‡)(a) Cost components incorporated: Hospital costs including 20 hrs of nursing educator time for in-services before implementation, information services support time to set up computer system, protocol development.	Hospital Length of Stay (LOS) >2 wks Intvn 1 =36.7% Intvn 2 = 13.3% Hospital Length of Stay>20 days Intvn 1 =20% Intvn 2 = 8.3% 28 day mortality rate: Intvn 1 = 48% Intvn 2 = 30%	Intvn2 dominates Intvn1. Analysis of UncertaintyResults were robust to sensitivity analysis which restricted comparison of costs to subgroup of patients who survived the hospital admission only.
Data sources				
Health outcomes: As observed in Micek ST, Roubinian N, Heuring T, Bode M, Williams J, Harrison C, Murphy T, Prentice D, Ruoff BE, Kollef MH (2006) Before-after study of a standardized hospital order set for the management of septic shock. Crit Care Med 34:2707–2713. Cost sources: Not stated, assumed to be the hospital charge database				

Shorr AF, Micek ST, Jackson WLJ, Kollef MH. Economic implications of an evidence-based sepsis protocol: can we improve outcomes and lower costs? Critical Care Medicine. 2007; 35(5):1257-1262. (Guideline Ref ID SHORR2007)
Comments
Source of funding: Dr. Kollef received grant/research funds from Pfizer, Merck, Elan and Bard and is on the speaker's bureau of Pfizer, Merck, and Elan. Limitations: observational study subject to confounding; Outcomes did not include all fluid related adverse event; Long term costs not accounted for due to lack of data ; protocol did not exclusively manage IV fluid therapy; uncertainty in components of non protocolised care which makes interpretation of results difficult.
Overall applicability*: Partially Applicable Overall quality**: Potentially Serious Limitations

*Abbreviations: CCA = Cost Consequence Analysis ; Protocol EGDT : appropriateness and timeliness of antibiotic administration, fluid resuscitation amounts and goals, role for vasopressors and inotropic support, indications for packed red blood cell transfusion and use of other adjunctive measures- drotrecogin alfa and corticosteroids from ; SA = sensitivity analysis; ‡ Converted using 2005 Purchasing Power Parities [Organisation for Economic Co-operation and Development. Purchasing Power Parities for GDP dataset (Aug 2010). Available from: http://stats.oecd.org/I] (a) = not stated, assumed as publication date; (b) Micek ST, Roubinian N, Heuring T, Bode M, Williams J, Harrison C, Murphy T, Prentice D, Ruoff BE, Kollef MH (2006) Before-after study of a standardized hospital order set for the management of septic shock. Crit Care Med 34:2707–2713; * Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious Limitations / Very serious limitations*

Talmor D, Greenberg D, Howell MD, Lisbon A, Novack V, Shapiro N. The costs and cost-effectiveness of an integrated sepsis treatment protocol. Critical Care Medicine. 2008; 36:1168-1174:1168-1174. (Guideline Ref ID TALMOR2008)				
Study details	Population & interventions	Costs	Health outcomes	Cost effectiveness
Economic analysis: CEA Study design: Prospective Cohort study Perspective: US 3rd party payer perspective Time horizon: lifetime Study duration: 2 years (historical controls 2000-2001; MUST study 2003-2004)	Population: 130 patients presenting to the emergency department with septic shock. Cohort settings: mean age = 69.5 M = 45% Intervention 1: 51 historical controls from a cohort of prospectively collected patients presenting to ED between 2000-2001 with infection as evidenced by a clinician ordering a blood culture Conventional care - where lactate screening was not routine in the control period.	Total costs (mean per patient): Intervention 1: £18,818 Intervention 2: £24,386 Intvn 2- Intvn 1 £5,569 Currency & cost year: 2004 USD (presented here as 2004 UK pounds‡) Cost components incorporated: All direct, medical and in-hospital treatment costs. Consisting staff training costs, excludes costs incurred after hospital discharge	Primary outcome measures: Life expectancy per patient: Intvn 1: 5.346 Intvn 2: 6.128 Incremental Intvn 2-Intvn 1 = 0.782 QALYs per patient: Intvn 1: 3.689 Intvn 2: 4.228: Incremental Intvn 2-Intvn 1 = 0.540	Primary ICER (Intvn 2 vs Intvn 1): £7,122 per life year gained £10,312 per QALY gained Probability that intvn2 is cost-effective at £20,000 per QALY gained=c60%. Analysis of uncertainty: SA performed for parameters: life expectancy, relative risk of death for sepsis survivors, utility weights and discount rate. If utility of survivors <c0.4then the ICER is >£20,000 and is not cost effective (base case=0.69). Otherwise the results were robust to sensitivity

Talmor D, Greenberg D, Howell MD, Lisbon A, Novack V, Shapiro N. The costs and cost-effectiveness of an integrated sepsis treatment protocol. Critical Care Medicine. 2008; 36:1168-1174:1168-1174. (Guideline Ref ID TALMOR2008)				
Discounting: 3%	Intervention 2: 79 patients Integrated sepsis protocol: the MUST protocol			analysis.
Data sources				
Health outcomes: long term life expectancy from US national life table, life expectancy then adjusted for risk of death for survivors of sepsis according to American cohort study(a). Utility value is the average of utility values presented in three other studies with ICU and severe sepsis patients. Cost sources: All hospital treatment costs from hospital detailed accounting systems, Costs for historical control cohort adjusted for CPI and inflation of physician costs to 2004 figures.				
Comments				
Source of funding: Author Nathan Shapiro received speaking fees from Eli Lilly and Edwards Lifesciences Limitations: protocol did not exclusively manage IV fluid therapy; Outcomes did not include other fluid related adverse events; management protocol not specific to intravenous fluid therapy; Long term costs not accounted for because patients were not followed beyond hospital discharge; observational study subject to confounding; uncertainty in components of non protocolised care which makes interpretation of results difficult.				
Overall applicability*: Partially Applicable Overall quality**: Potentially Serious Limitations				

*Abbreviations: CEA = Cost Effectiveness Analysis; MUST protocol= Multiple Urgent Sepsis Therapies, utilizes the treatment of a) EGDT; b) antibiotics; c) steroids in adrenal suppression; d) assessment for activated protein C therapy; e) tight glycemic control and f) low tidal volume ventilation for patients with acute lung injury; SA = sensitivity analysis; ǂ Converted using 2004 Purchasing Power Parities [Organisation for Economic Co-operation and Development. Purchasing Power Parities for GDP dataset (Aug 2010). Available from: http://stats.oecd.org/l]; (a) Magnitude and duration of the effects of sepsis on survival. Department of Veterans Affairs Systemic Sepsis Cooperative Studies Group. JAMA 1997; 277 1058-1063 * Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious Limitations / Very serious limitations*

F.2 Assessment and monitoring- No studies were identified in this topic area

F.3 Resuscitation

Guidet B, Mosqueda GJ, Priol G, Aegerter P. The COASST study: cost-effectiveness of albumin in severe sepsis and septic shock. Journal of Critical Care. 2007; 22(3):197-203. (Guideline Ref ID GUIDET2007)				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost-effectiveness analysis	**Population:** 11 137 patients from 35 ICUs in	**Total costs (mean per patient):** Incremental Intvn 2- Intvn1 = £191	**Primary outcome measures:** Life expectancy (mean	**Primary ICER (Intvn 2 vs Intvn 1):** Cost per life year gained = £425

Guidet B, Mosqueda GJ, Priol G, Aegerter P. The COASST study: cost-effectiveness of albumin in severe sepsis and septic shock. Journal of Critical Care. 2007; 22(3):197-203. (Guideline Ref ID GUIDET2007)				
Study design: Model (a) **Perspective:** French third-party payer **Time horizon:** Lifetime **Discounting:** None Reported	hospitals located in Paris and suburbs (b) **Cohort settings:** Mean Start Age = 61 M =64.8% Medical Cases : 77.4% Surgical Cases : 22.5% **Intervention 1:** Fluid support with normal saline infusion **Intervention 2:** Fluid support with albumin infusion	**Currency & cost year:** 2005 Euros (presented here as 2005 UK pounds‡) **Cost components incorporated:** Intravenous Fluids (c)	per patient) Intvn 1 = 4.528 Intvn 2 = 4.978 Incremental Intvn 2-Intvn 1 = 0.45	**Analysis of uncertainty:** If the mortality difference is only 1% then the ICER=400% of the base case scenario (4.6%). If there is no mortality difference then saline infusion dominates. If quantity of albumin 4.5L, ICER= 200% base case scenario (2.25L).
Data sources				
Health outcomes: Relative risk of mortality from sepsis subgroup patients in SAFE study [2] ; National French Statistics for baseline life expectancy and mortality rates **Cost sources:** SAFE study for quantity of albumin administered; cost of albumin from Paris area in 2005.				
Comments				
Source of funding: Laboratoire Francais du Fractionnement et des Biotechnologies; Limitations: is based on the French system and therefore may not be directly applicable to the UK NHS case. It was somewhat unclear as to which costs other than albumin, if any, were included. Hospital costs (DRG cost plus ICU cost) were referred to but it is unclear whether or not they were included in the incremental analysis.				
Overall applicability*: *Partially applicable* **Overall quality**:** *Potentially serious limitations*				

(a). Baseline mortality rates from Prospective Cohort study; Relative risk of mortality from SAFE study (see Abbreviations for reference of study).
(b) 11, 137 patients were included with severe sepsis, a hospital stay of longer than one day and with a minimum of circulatory, renal, or respiratory failure were included. Exclusion criteria: Patients with burns, mediastinitis, grafts, and cardiac surgery
(c) Non-fluid hospital costs were believed to be largely similar because there was no evidence of differential length of stay.
*Abbreviations: SAFE Study = Saline versus Albumin Fluid Evaluation; ICU= Intensive Care Unit; ‡ Converted using 2005 Purchasing Power Parities [Organisation for Economic Co-operation and Development. Purchasing Power Parities for GDP dataset (Aug 2010). Available from: http://stats.oecd.org/I] * Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious Limitations / Very serious limitations*

F.4 Routine maintenance

No studies were identified in this topic area

F.5 Replacement and redistribution

No economic analysis was undertaken for this topic area.

F.6 Training and education

No economic analysis was undertaken in this topic area.

Appendix G: Forest plots

G.1 Principles and protocols for intravenous fluid therapy

G.1.1 Protocol vs. no protocol

Figure 1: All cause mortality

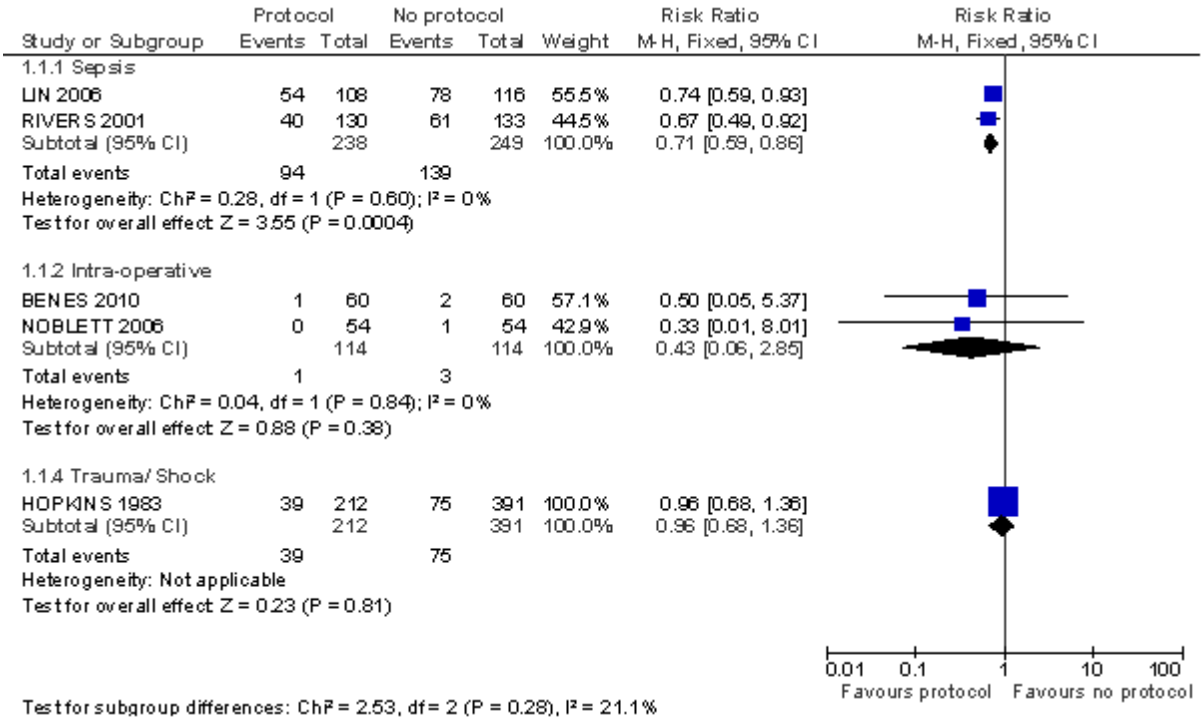


Figure 2: Length of hospital stay

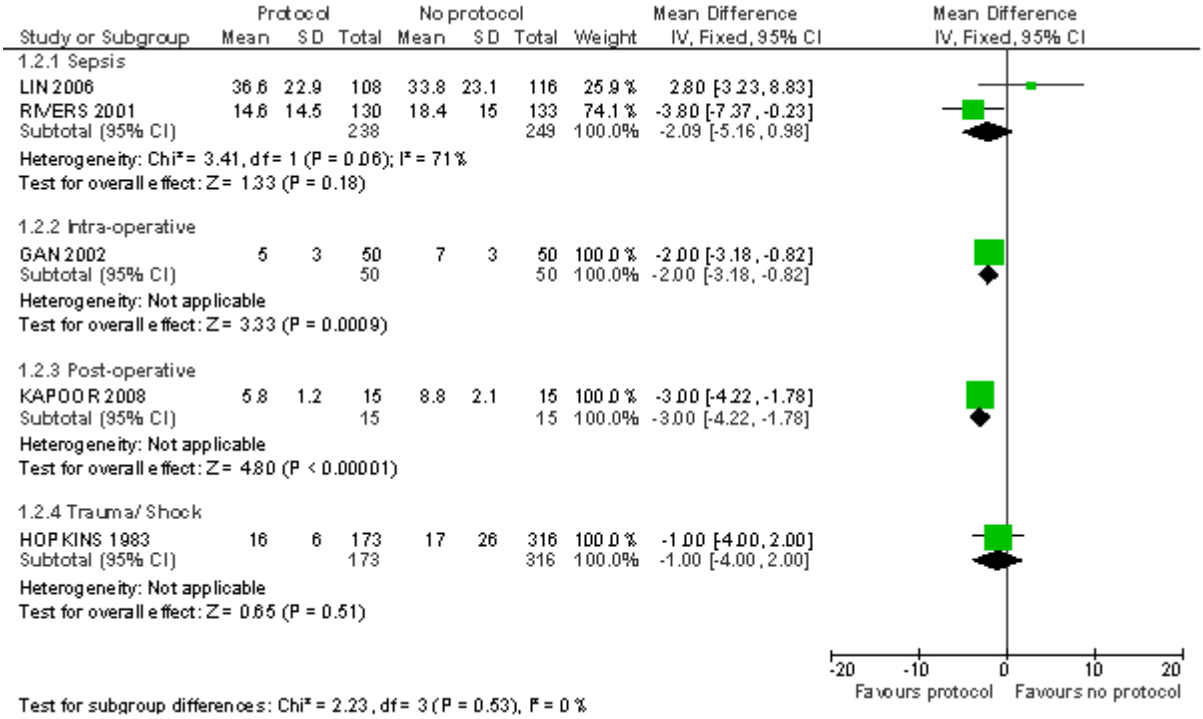


Figure 3: Length of ICU stay

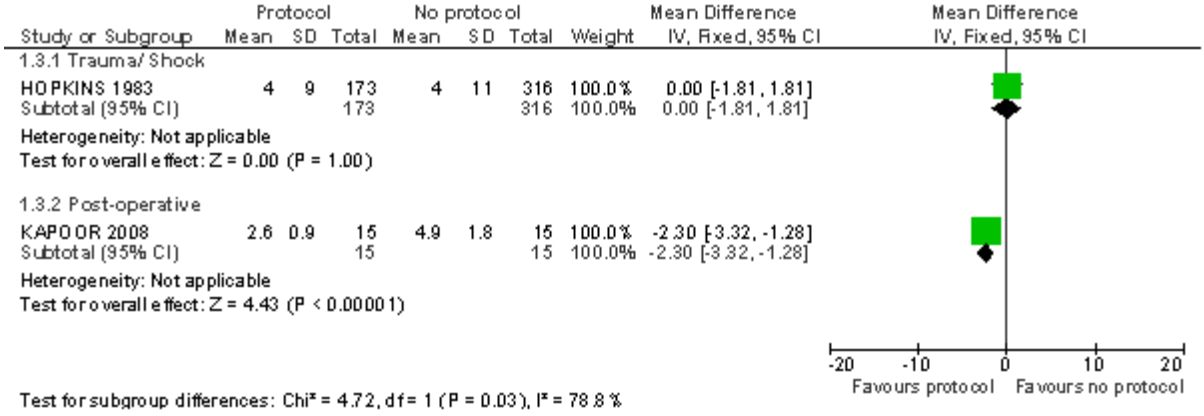
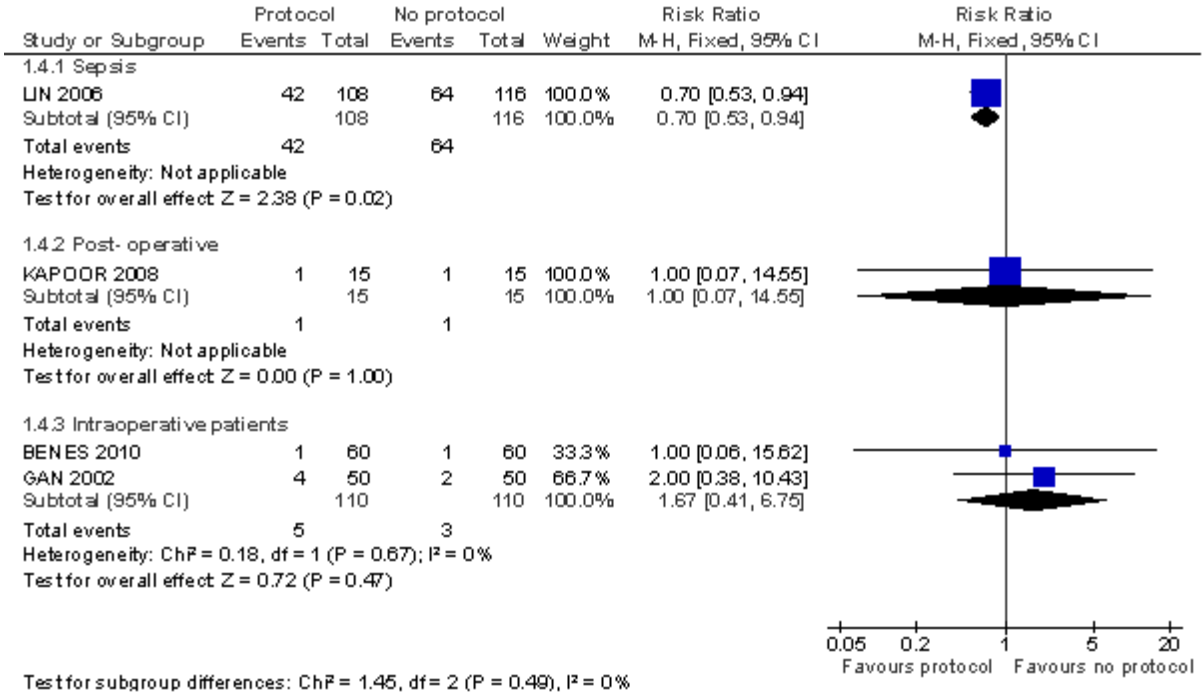


Figure 4: Renal complications



G.2 Assessment and monitoring

G.2.1 Measurement of serum chloride

G.2.1.1 Fluids with chloride concentration less than 120mmol/l vs Fluids with chloride concentration greater than 120mmol/l

Figure 5: Mortality- Waters et al. 2001

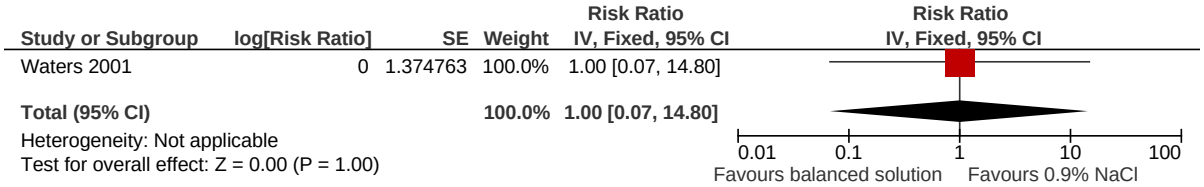
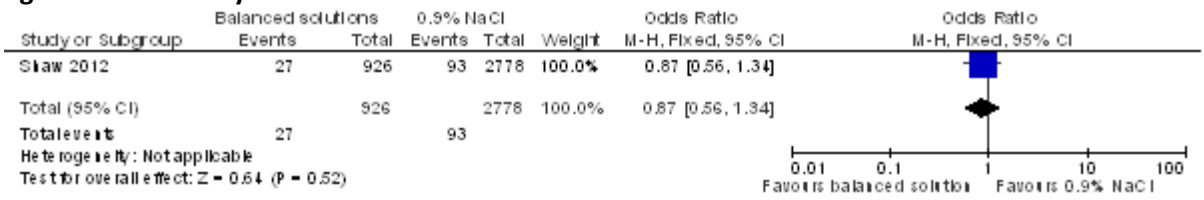
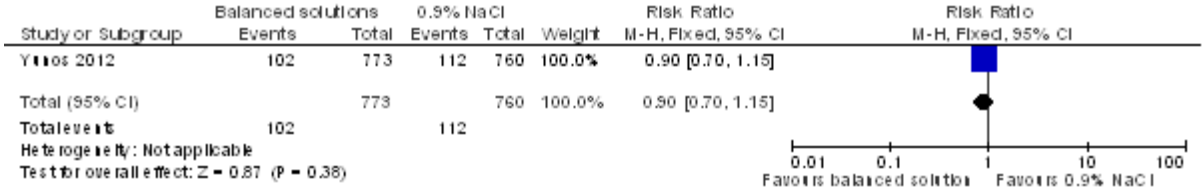


Figure 6: Mortality- Shaw et al. 2012



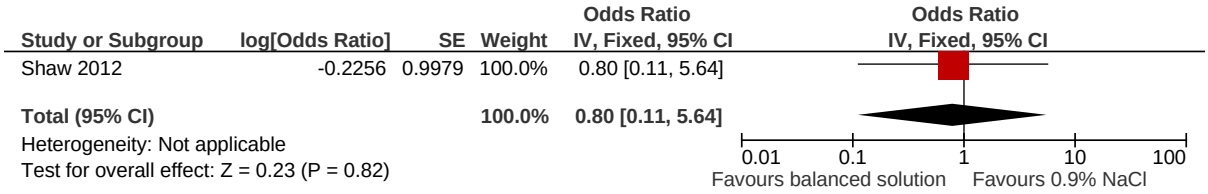
1

Figure 7: Mortality- Yunos et al. 2012



2

Figure 8: Morbidity (Major complication index)



3

Figure 9: Electrolyte disturbances

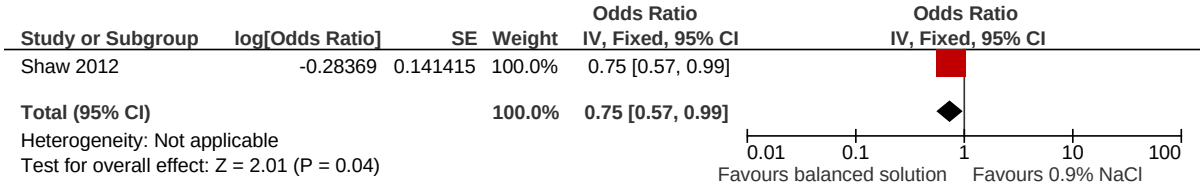
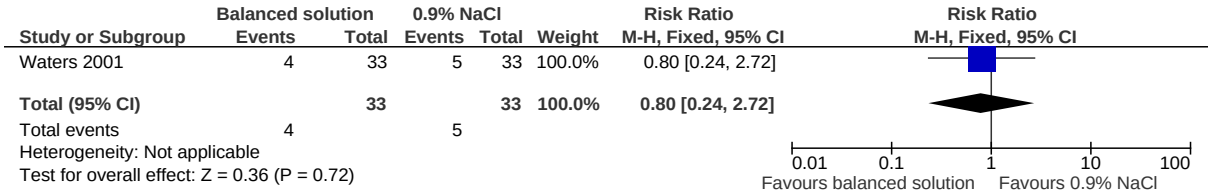


Figure 10: Renal insufficiency (Waters et al. 2001)



4

Figure 11: Renal insufficiency (Shaw eta l. 2012)

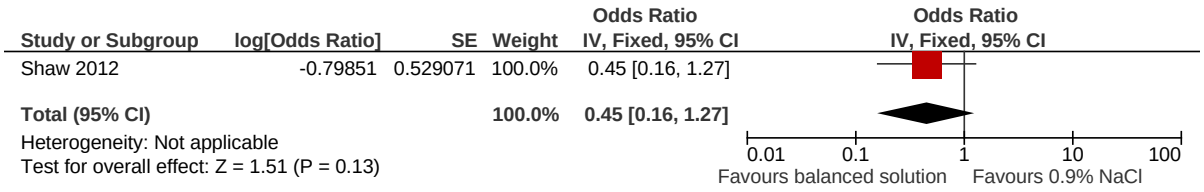
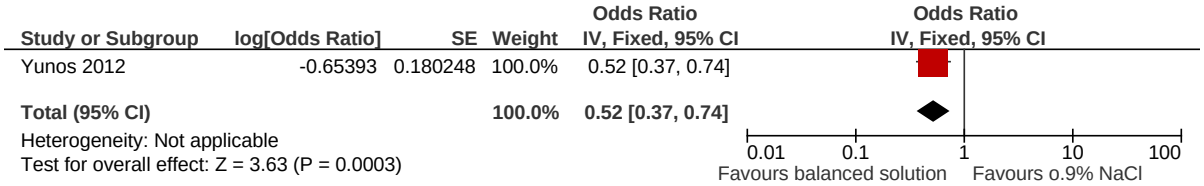
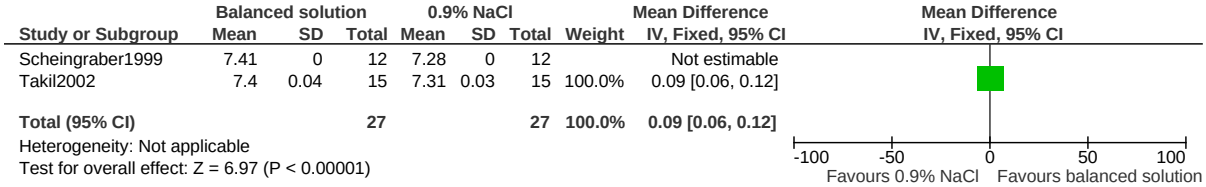


Figure 12: Renal insufficiency (Yunos et al. 2012)



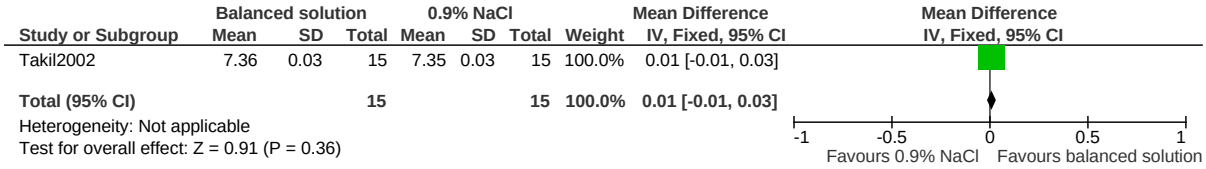
1

Figure 13: Acidosis at 2 hours post infusion



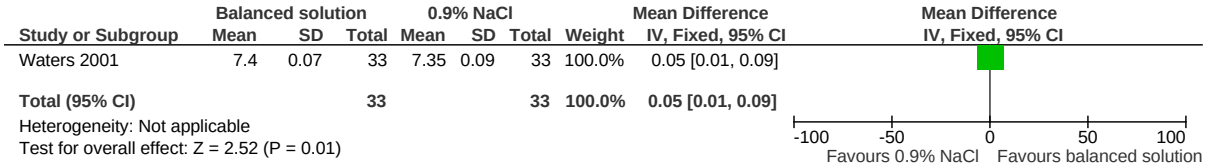
2

Figure 14: Acidosis at 12 hours post infusion



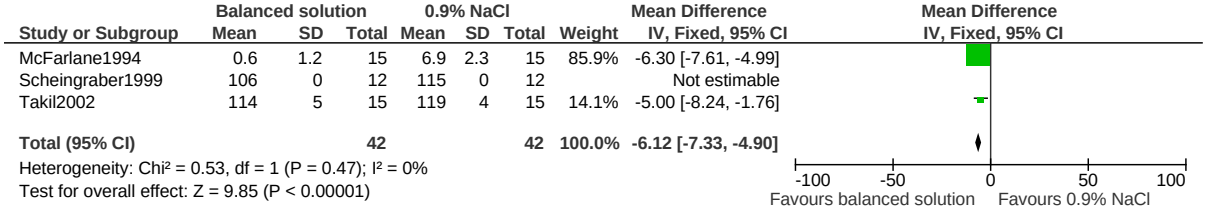
3

Figure 15: Acidosis on admission to ICU



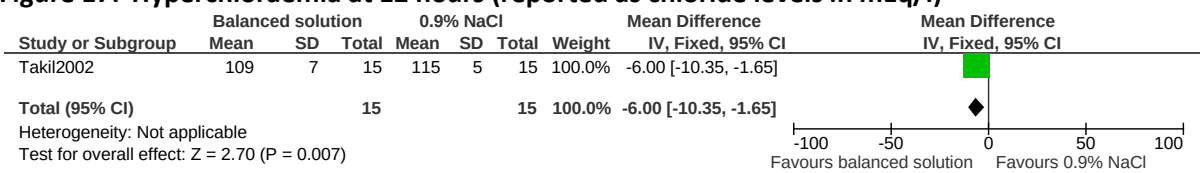
4

Figure 16: Hyperchloraemia at 2 hours (reported as chloride levels in mEq/l)



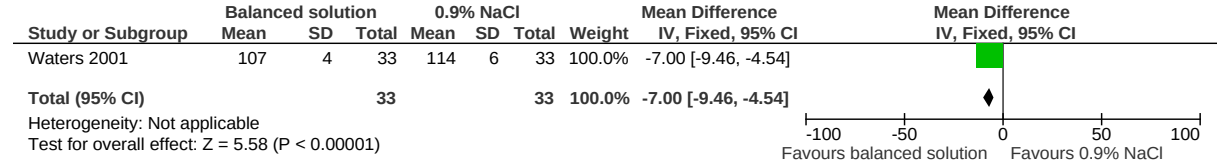
5

Figure 17: Hyperchloraemia at 12 hours (reported as chloride levels in mEq/l)



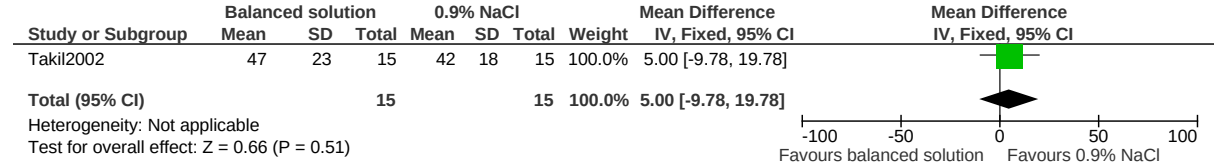
6

Figure 18: Hyperchloraemia at ICU admission (reported as chloride levels in mEq/l



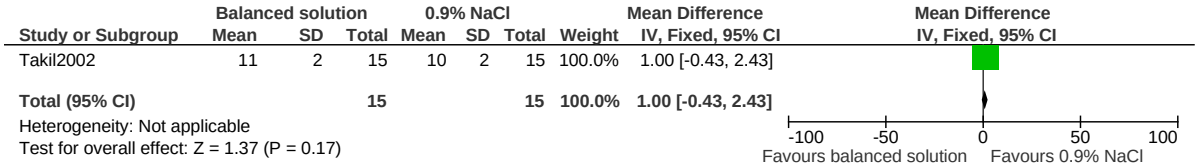
1

Figure 19: Length of stay in ICU in hours



2

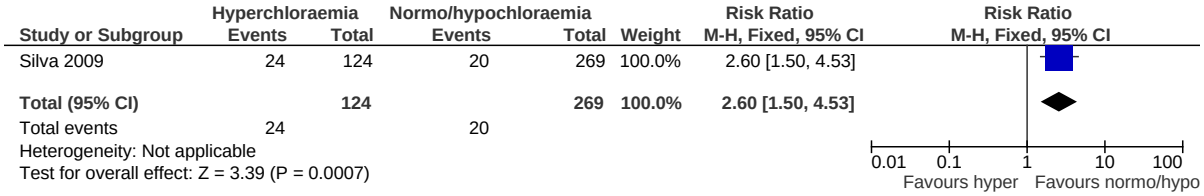
Figure 20: Length of hospital stay in days



3

4 G.2.1.2 Hyperchloraemia vs Normo/Hypochloraemia

Figure 21: Mortality



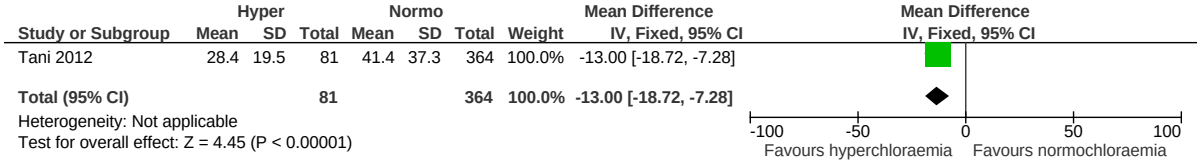
5 G.2.1.3 Hyperchloraemia vs. Normochloraemia

6

Figure 22: Mortality

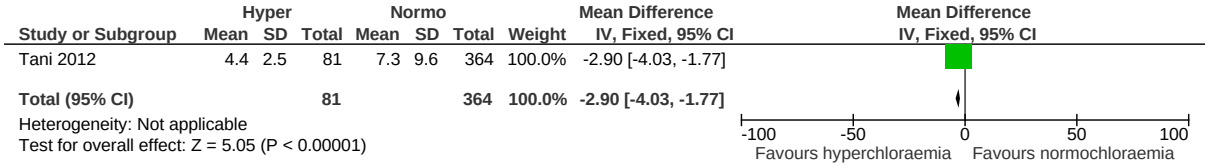
7

Figure 23: Length of stay in hospital in days



1

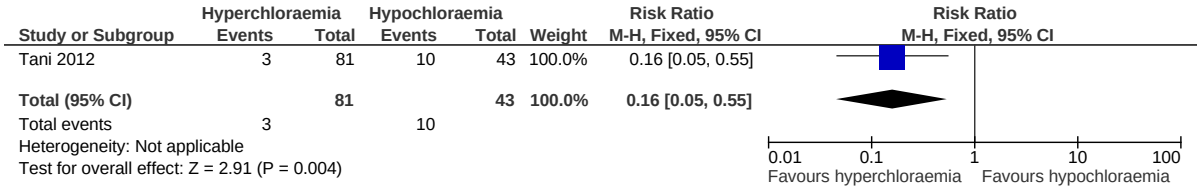
Figure 24: Length of stay in ICU



2

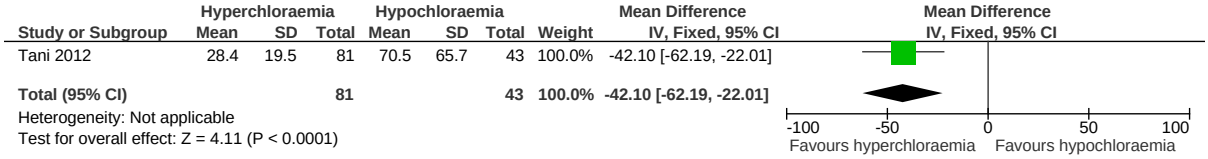
3 **G.2.1.4 Hyper chloraemia vs. Hypochloraemia**

Figure 25: Mortality



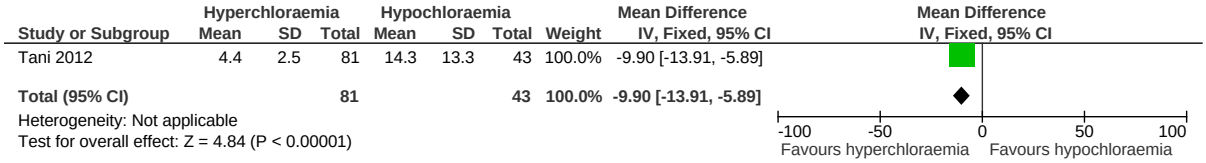
4

Figure 26: Length of stay in hospital



5

Figure 27: Length of stay in ICU



G.3 Resuscitation

G.3.1 Gelatin

Figure 28: Gelatin vs Tetrastarch- Mortality

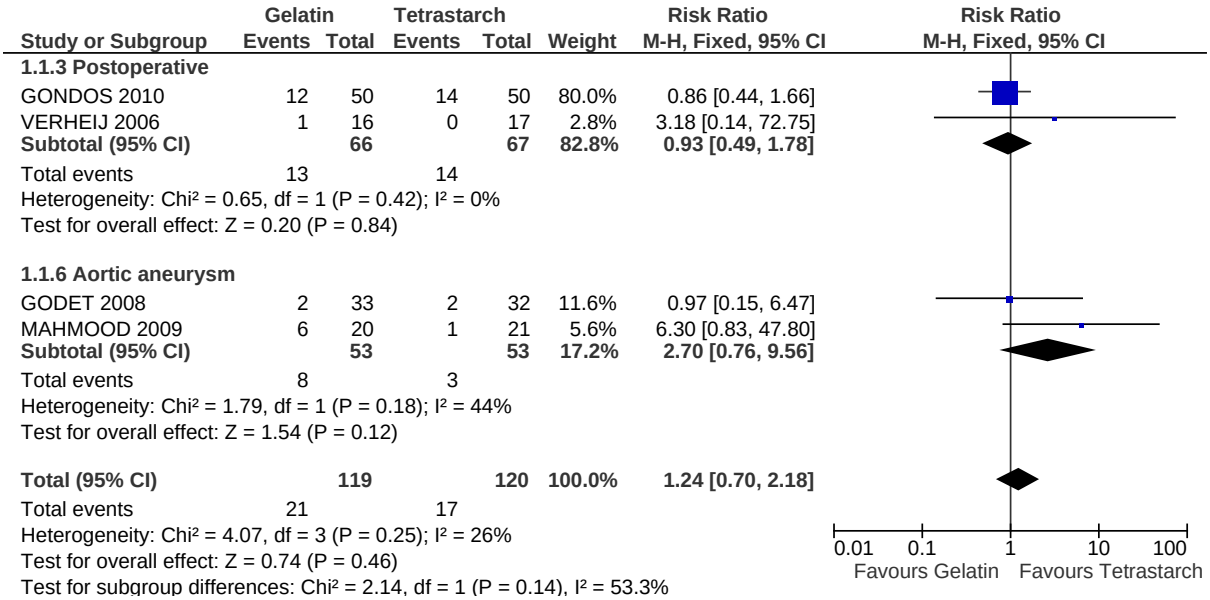


Figure 29: Gelatin vs Tetrastarch- Volume of study fluid received

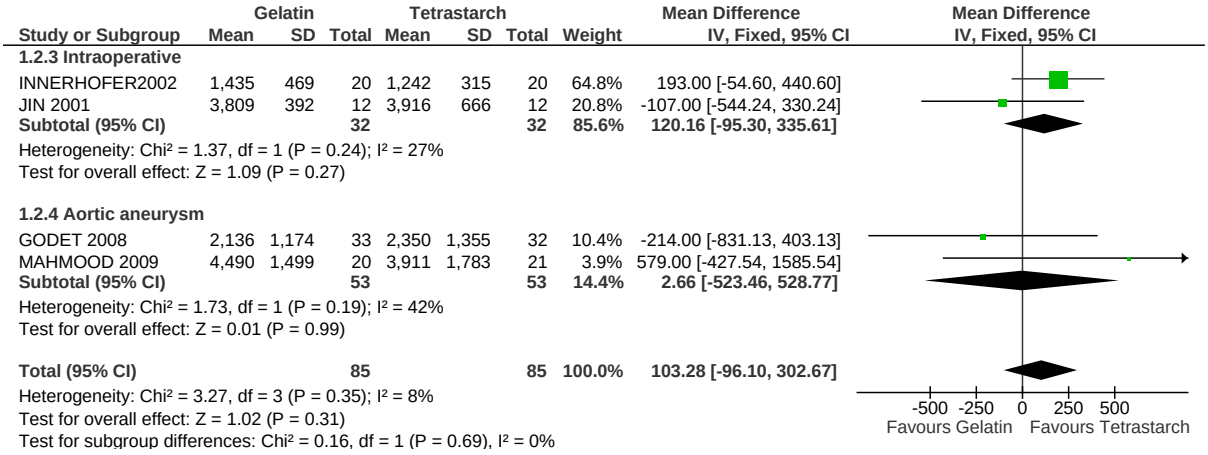


Figure 30: Gelatin vs Tetrastarch- Total volume of fluid received

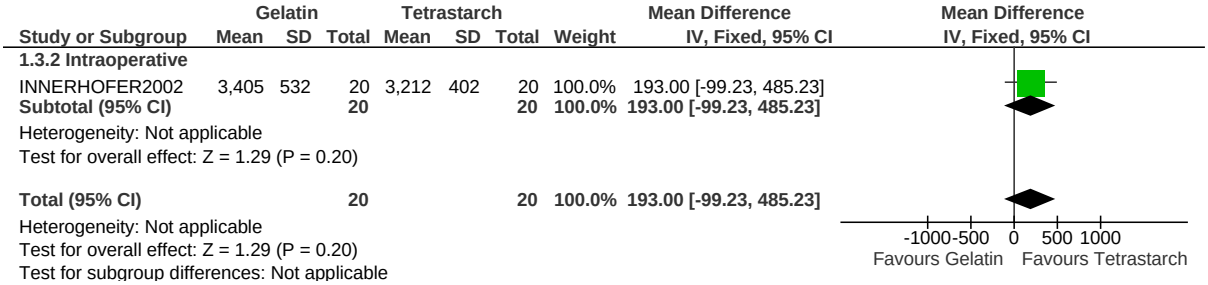
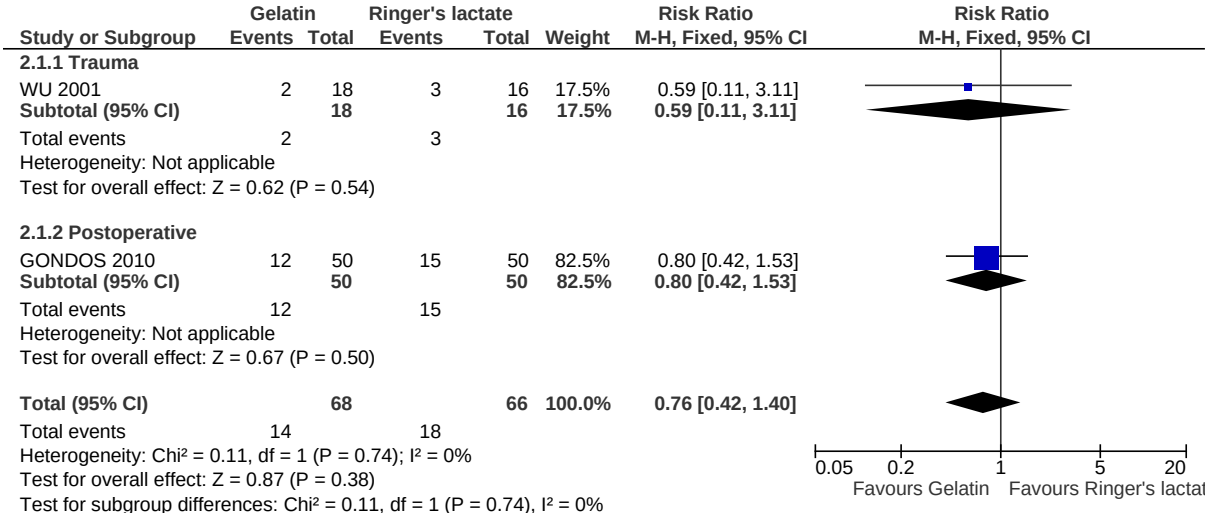
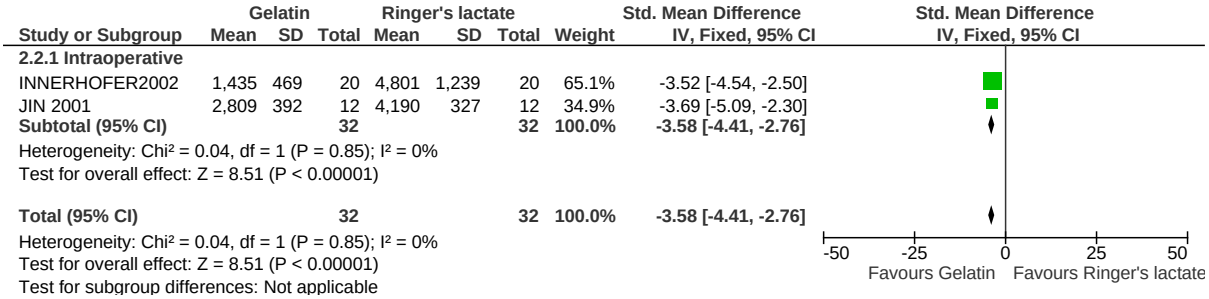


Figure 31: Gelatin vs lactated Ringer's solution- Mortality



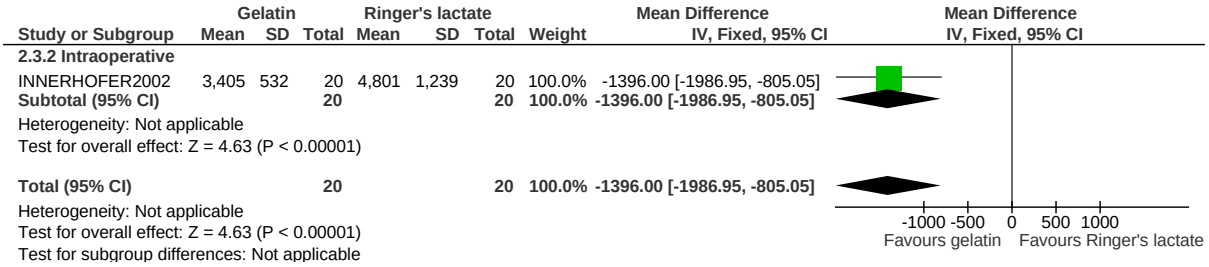
1

Figure 32: Gelatin vs lactated Ringer's solution- Volume of study fluid received



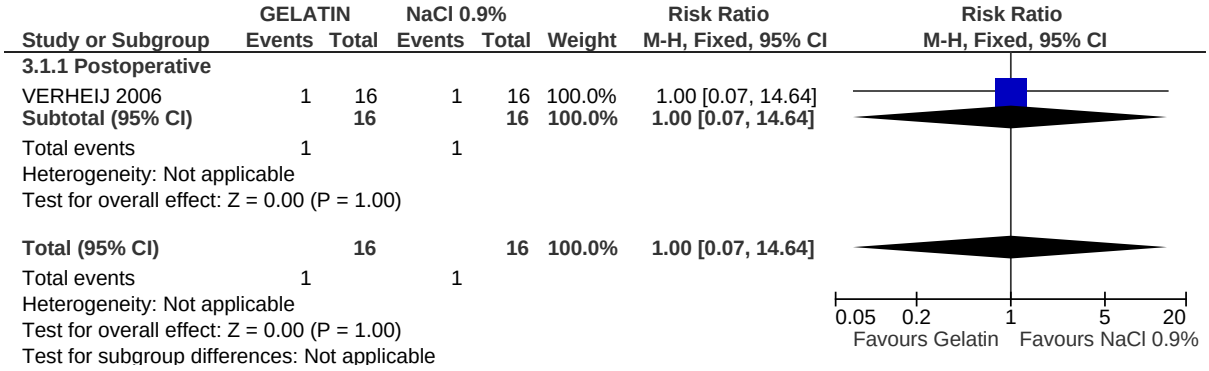
2

Figure 33: Gelatin vs lactated Ringer's solution - Total volume of fluid received



3

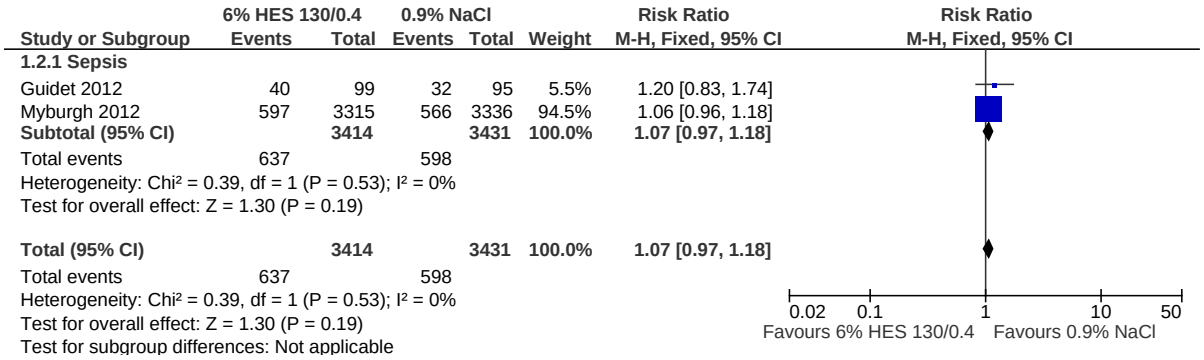
Figure 34: Gelatin vs sodium chloride 0.9%- Mortality



1 G.3.2 Hydroxyethylstarches (Tetrastraches)

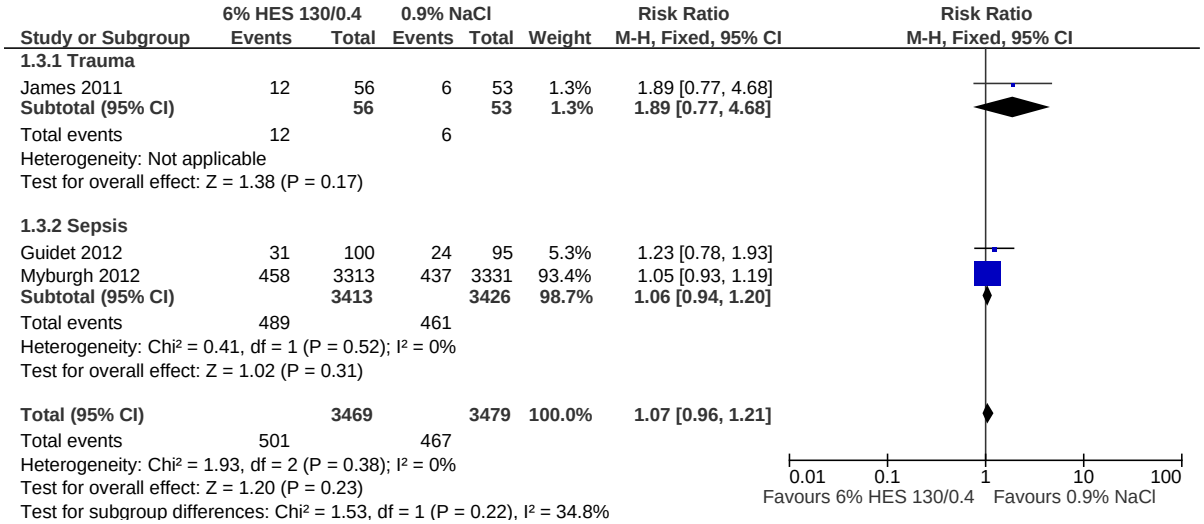
2 G.3.2.1 Comparison: 6% HES 130/0.4 vs 0.9% NaCl

Figure 35: All cause mortality (90 days)



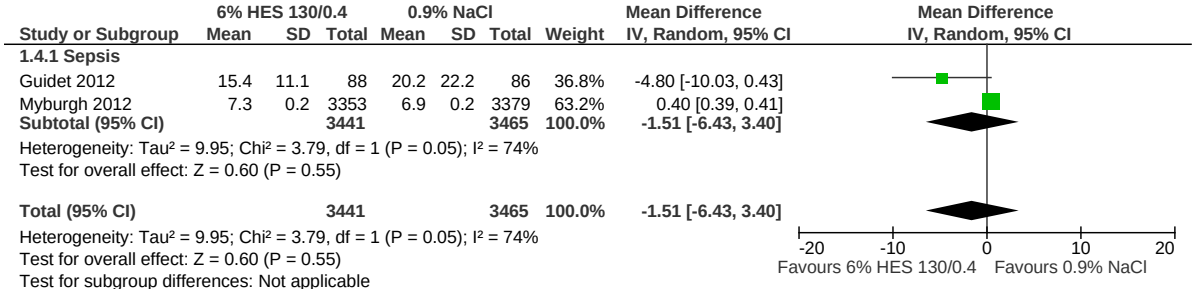
3

Figure 36: All cause mortality (30 days)



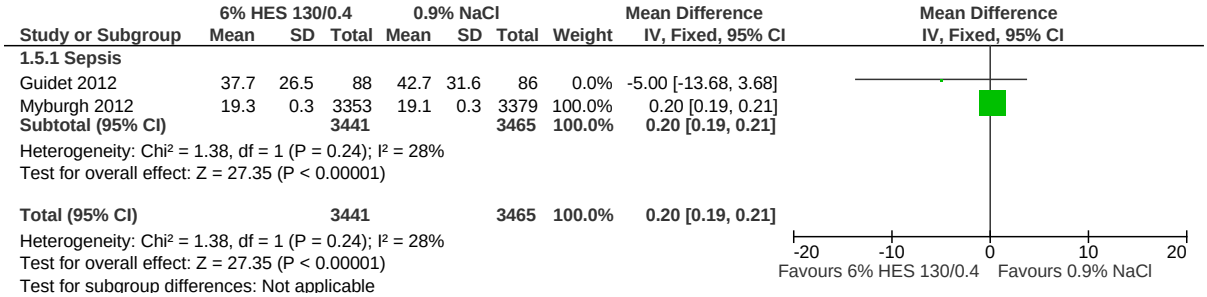
4

Figure 37: Length of stay in ICU



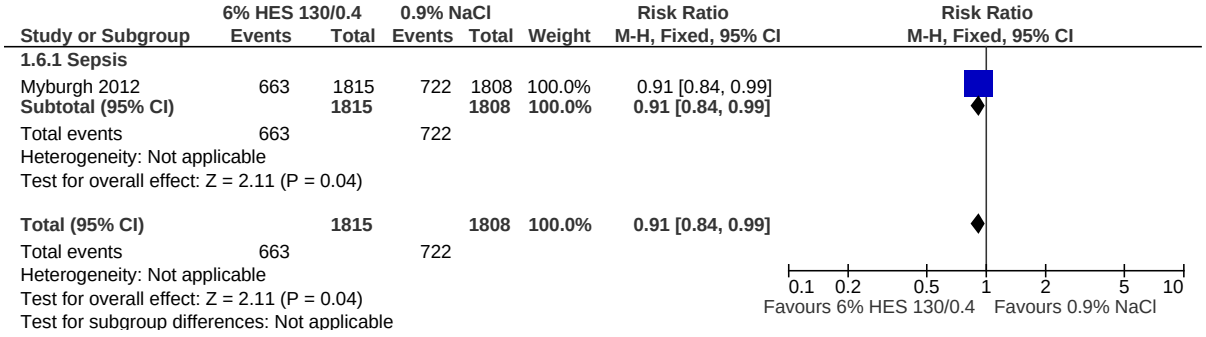
1

Figure 38: Length of stay in hospital



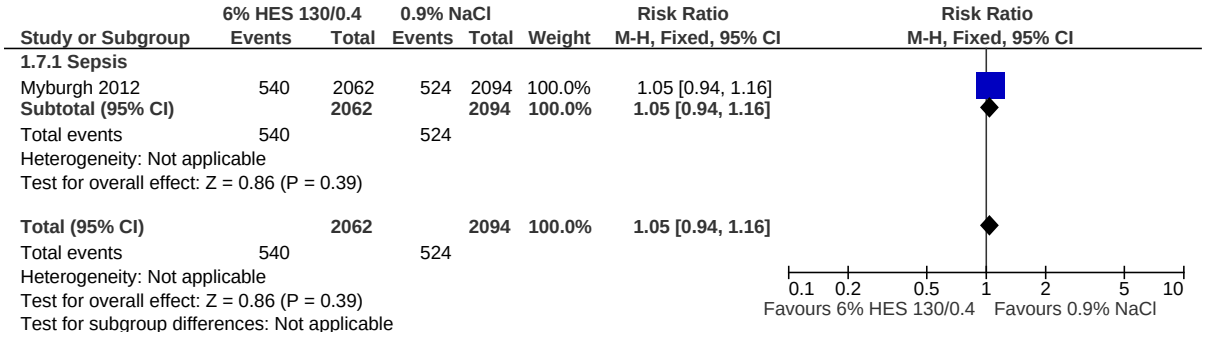
2

Figure 39: New organ failure- Cardiovascular (SOFA score≥3)



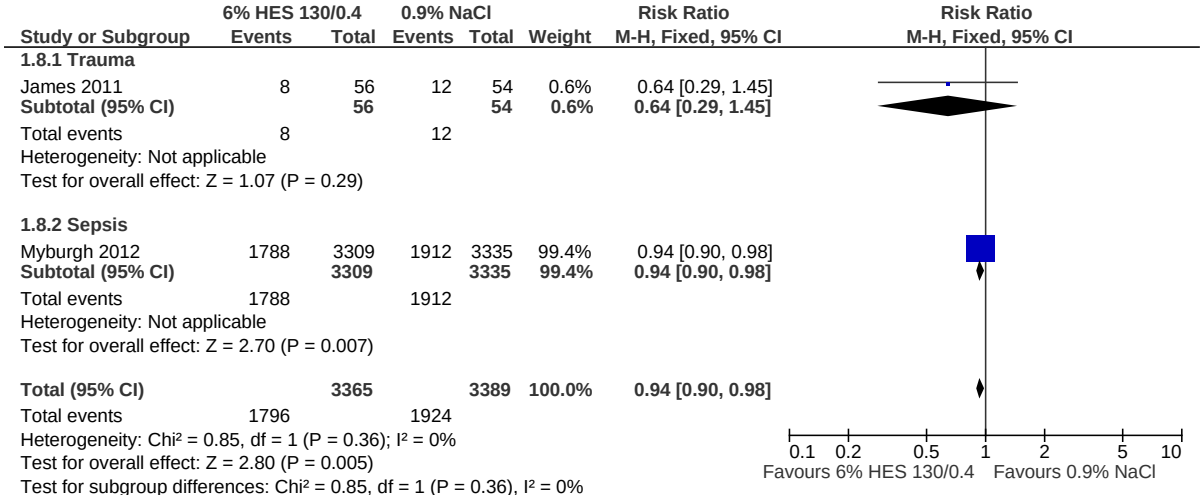
3

Figure 40: New organ failure- Respiratory (SOFA score≥3)



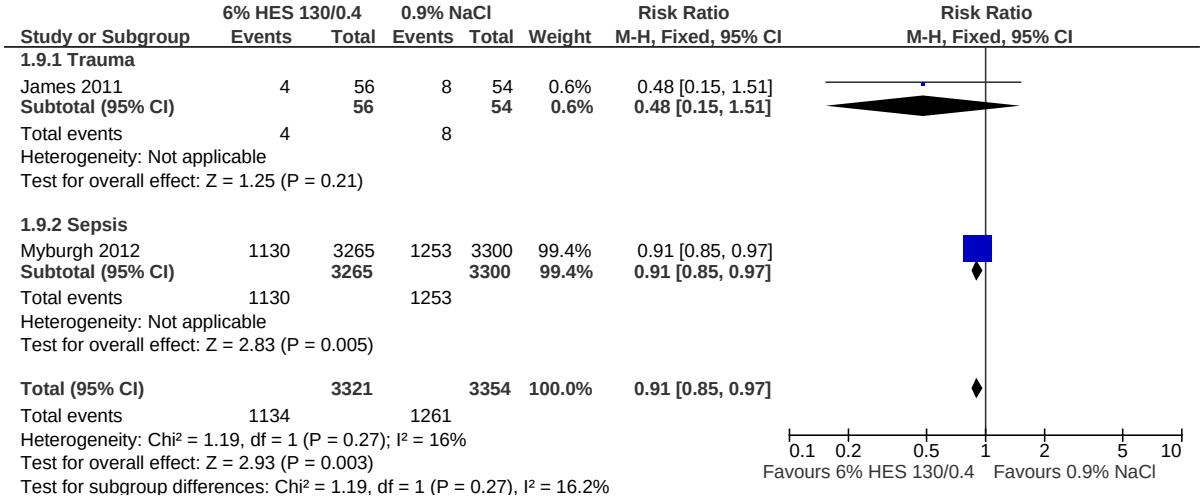
4

Figure 41: AKI- RIFLE- Risk



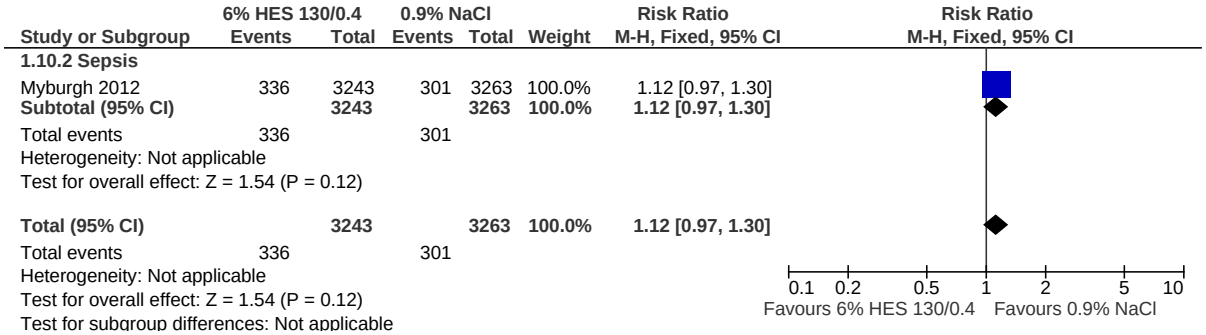
1

Figure 42: AKI- RIFLE- Injury



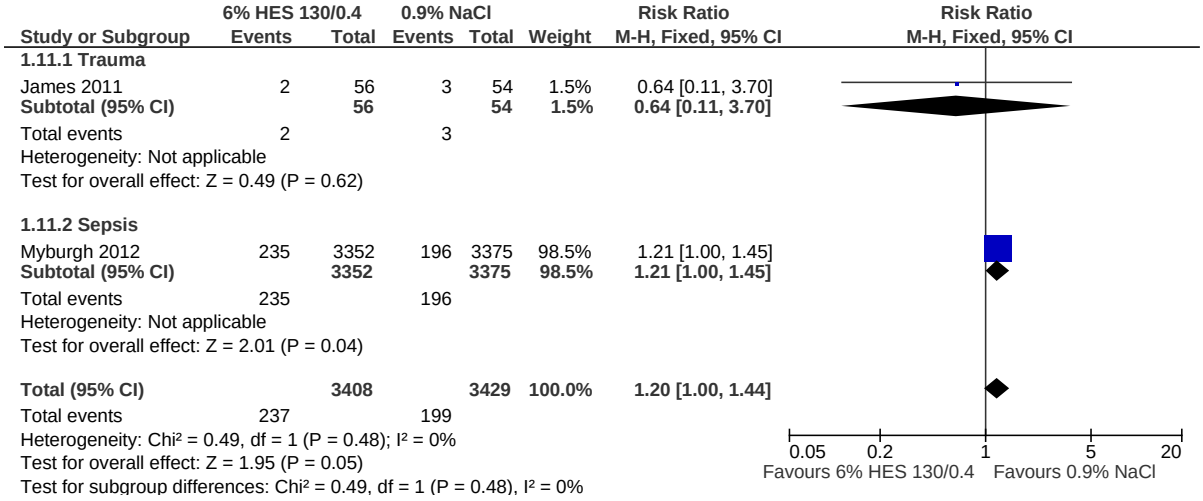
2

Figure 43: AKI- RIFLE- Failure



3

Figure 44: AKI-Use of renal replacement therapy



G.3.2.2 6% HES 130/0.4 vs. Ringer's acetate solution

Figure 45: All cause mortality (30 days)

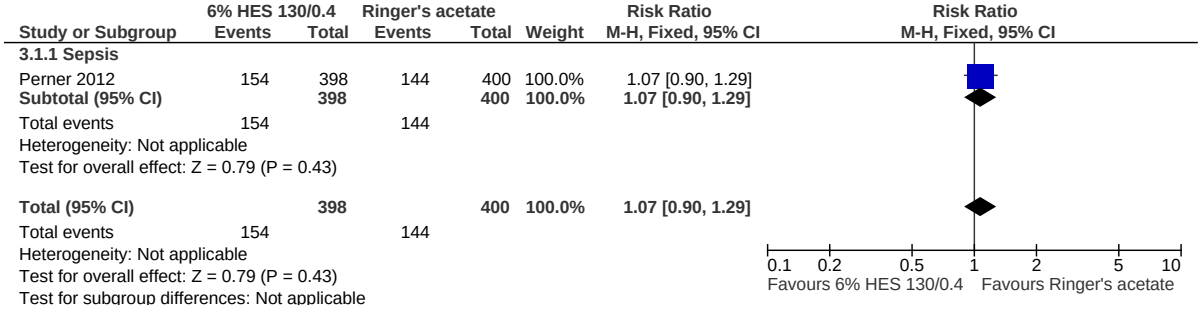


Figure 46: All cause mortality (90 days)

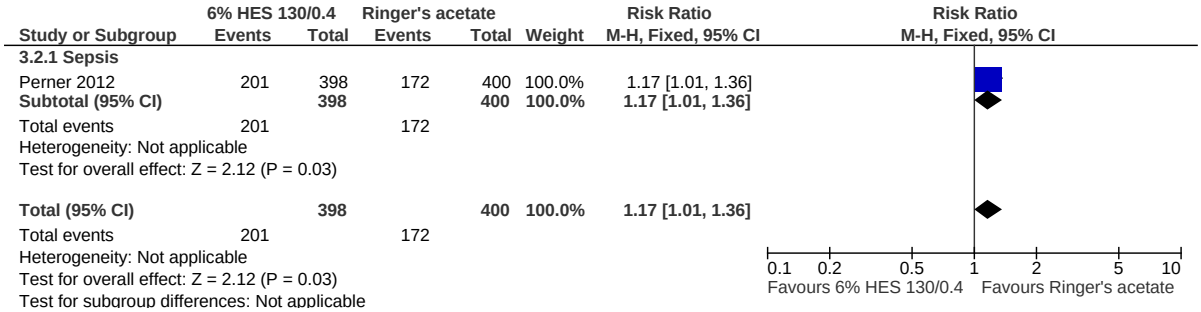
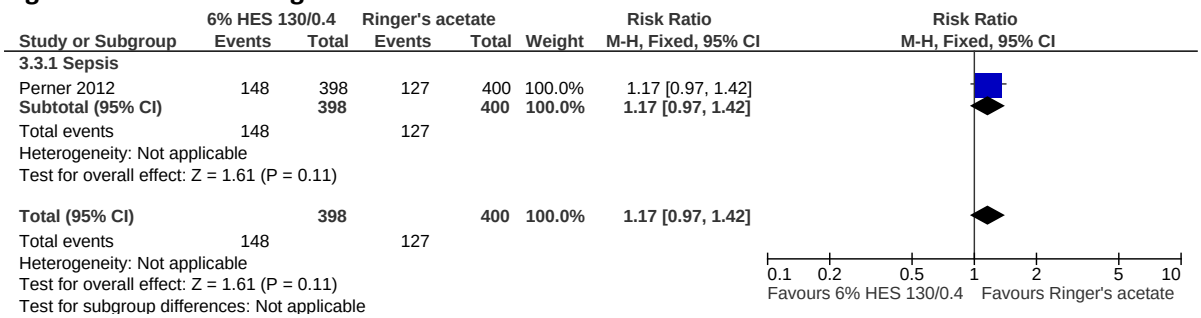
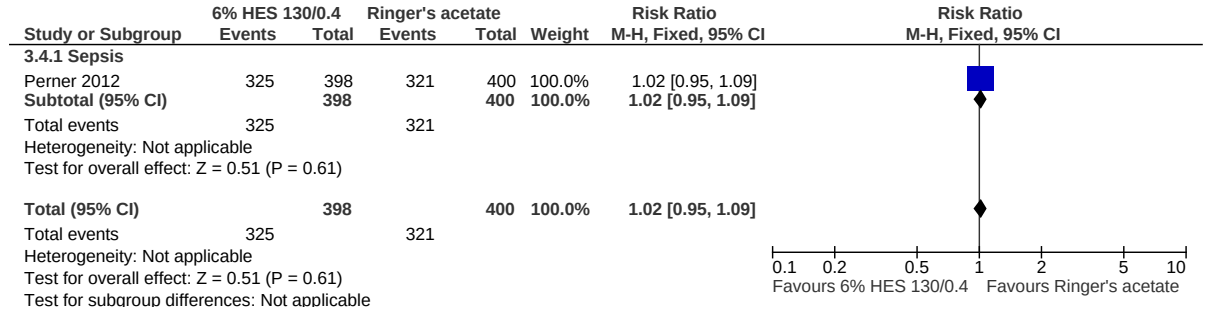


Figure 47: AKI- Doubling of serum creatinine level



1

Figure 48: Use of mechanical ventilation



2 G.3.3 Albumin

3 G.3.3.1 Albumin vs 0.9% sodium chloride (SAFE study)

Figure 49: All cause mortality

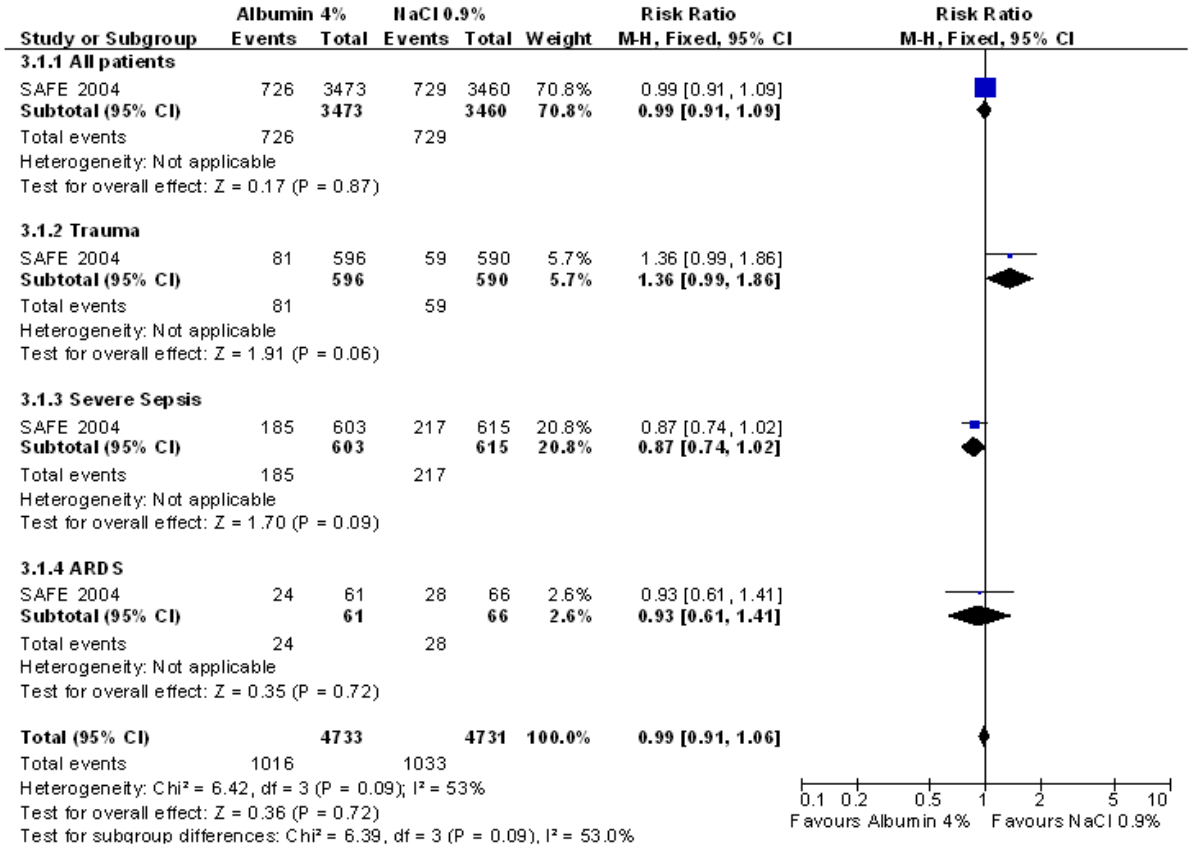
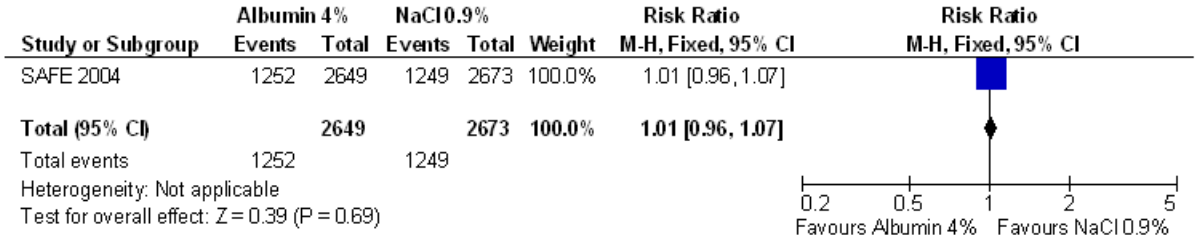
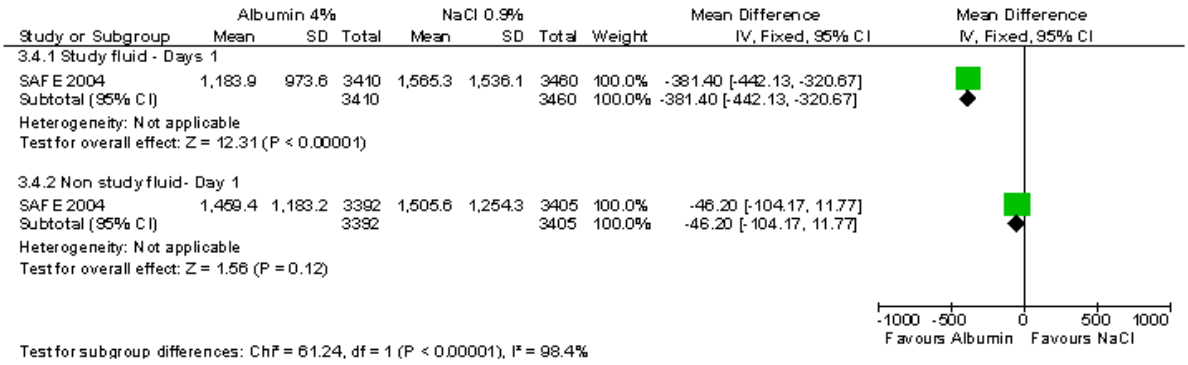


Figure 50: New organ failure



1

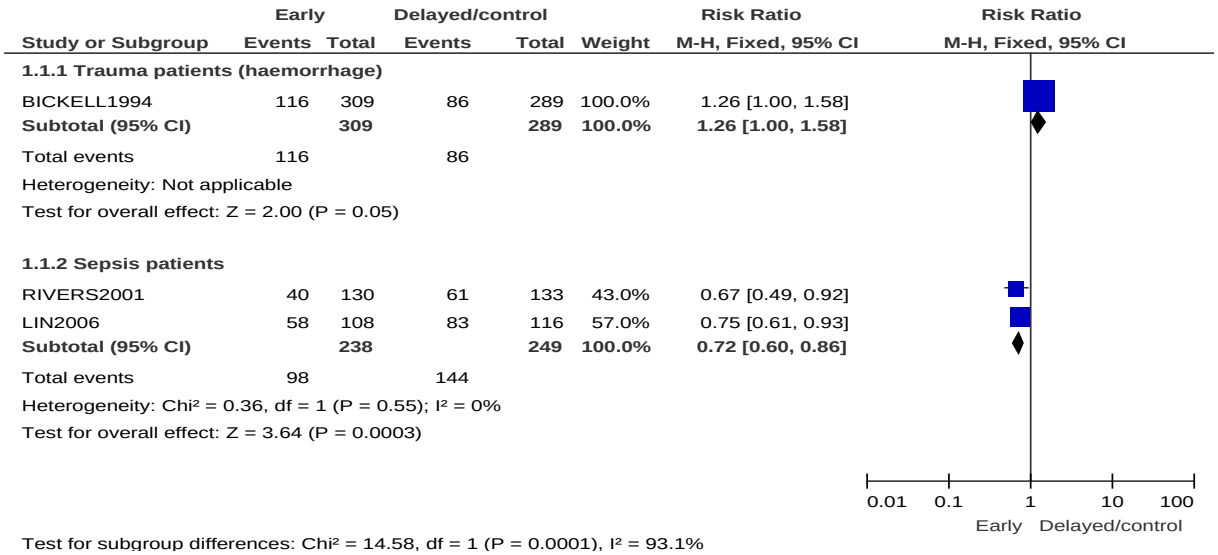
Figure 51: Volume of fluid used



G.3.4 Volume and timing of resuscitation

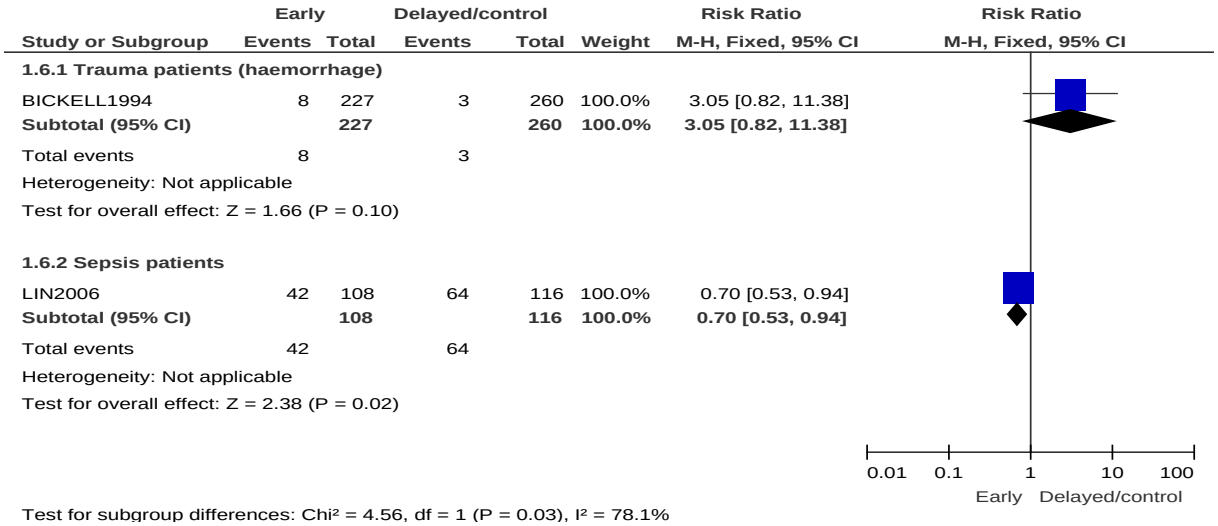
G.3.4.1 Timing of resuscitation : Early vs late/control group resuscitation

Figure 52: All cause mortality



Test for subgroup differences: Chi² = 14.58, df = 1 (P = 0.0001), I² = 93.1%

Figure 53: Renal failure



Test for subgroup differences: Chi² = 4.56, df = 1 (P = 0.03), I² = 78.1%

Figure 54: Respiratory failure: Duration of mechanical ventilation (days)

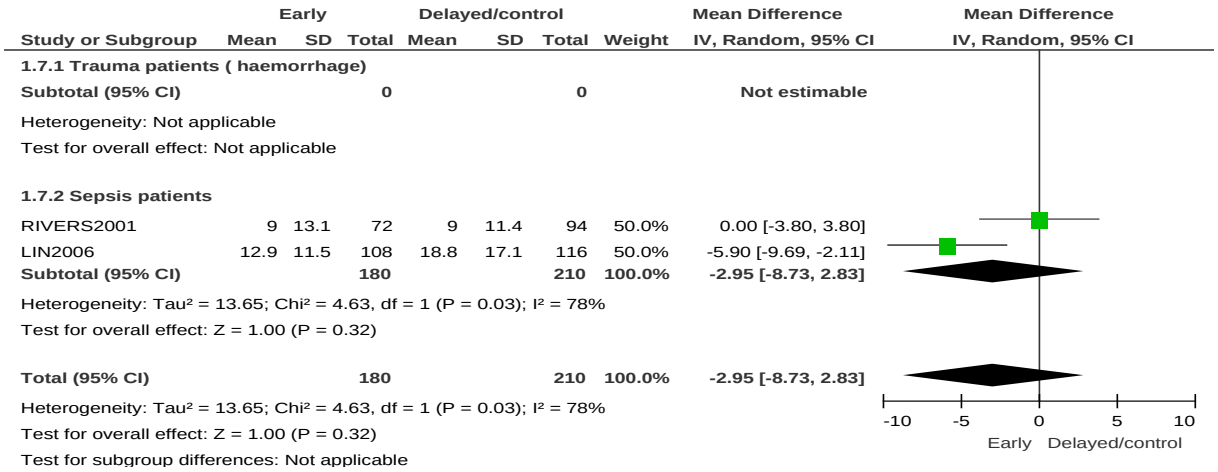


Figure 55: Duration of hospitalisation (days) – all studies

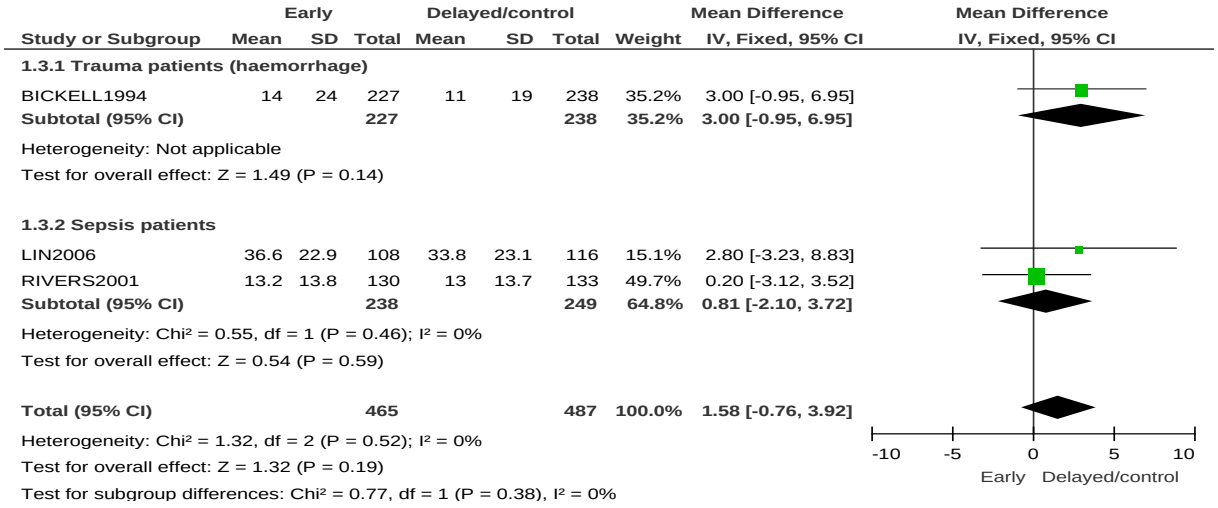


Figure 56: Duration of hospitalisation (days) of patients who survived until discharge (sensitivity analysis)

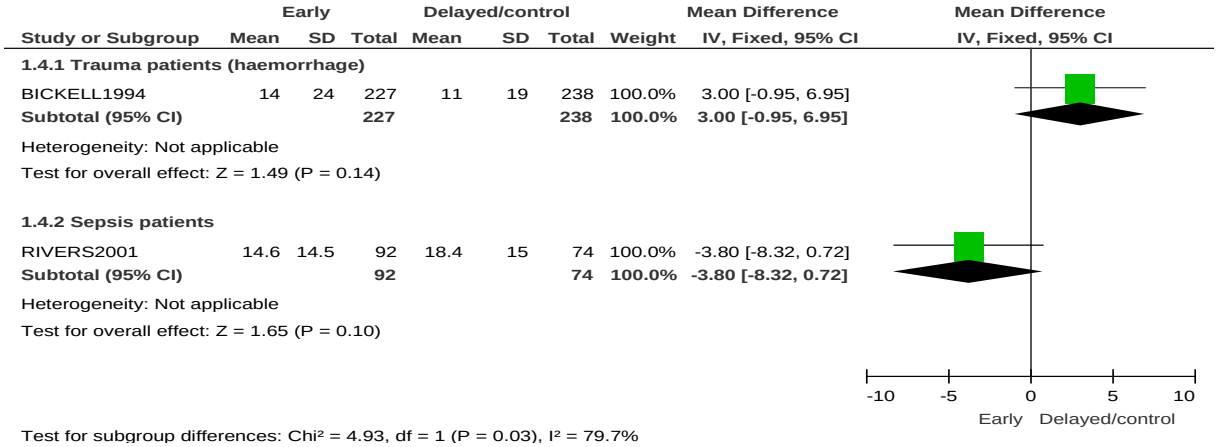
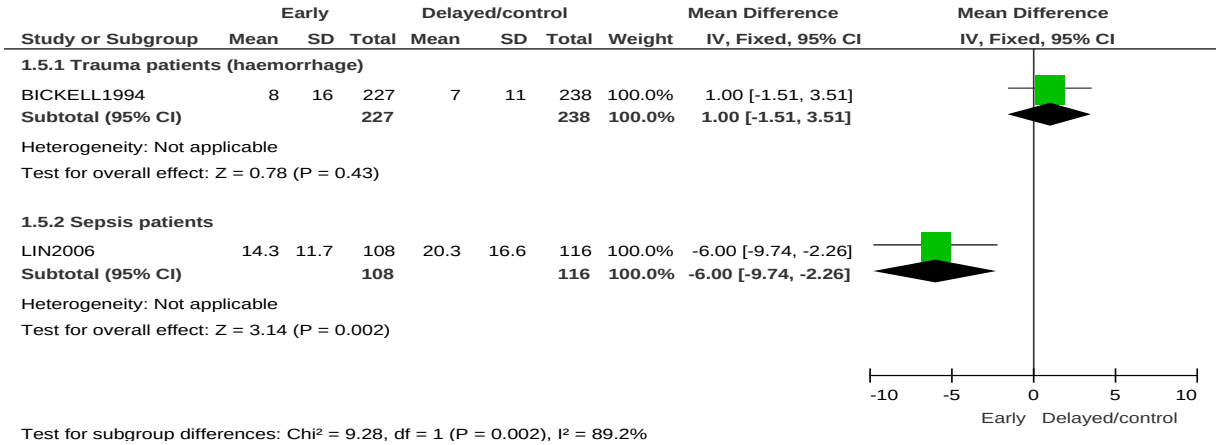


Figure 57: Duration of ICU stay (days) – all studies



Sensitivity analysis of duration for survivors only not shown. Lin 2006 included all patients enrolled in the average, Bickel1994l included all patients who survived.

G.3.5 Rate of fluid administration : Fast vs controlled

Figure 58: All cause mortality

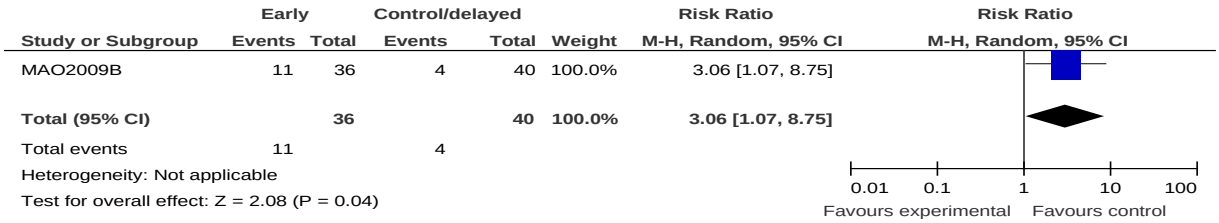
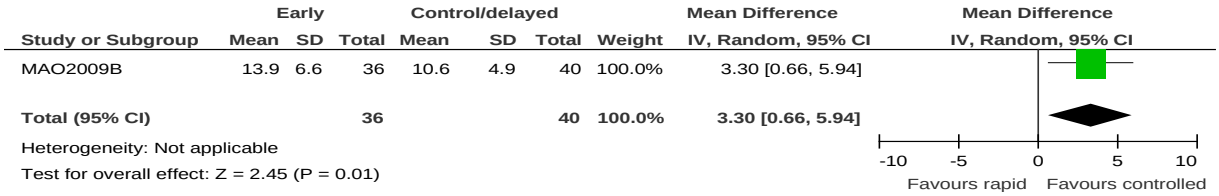


Figure 59: Morbidity (APACHE score)



G.3.6 Volume of fluid: High vs low volume for resuscitation

Figure 60: All cause mortality

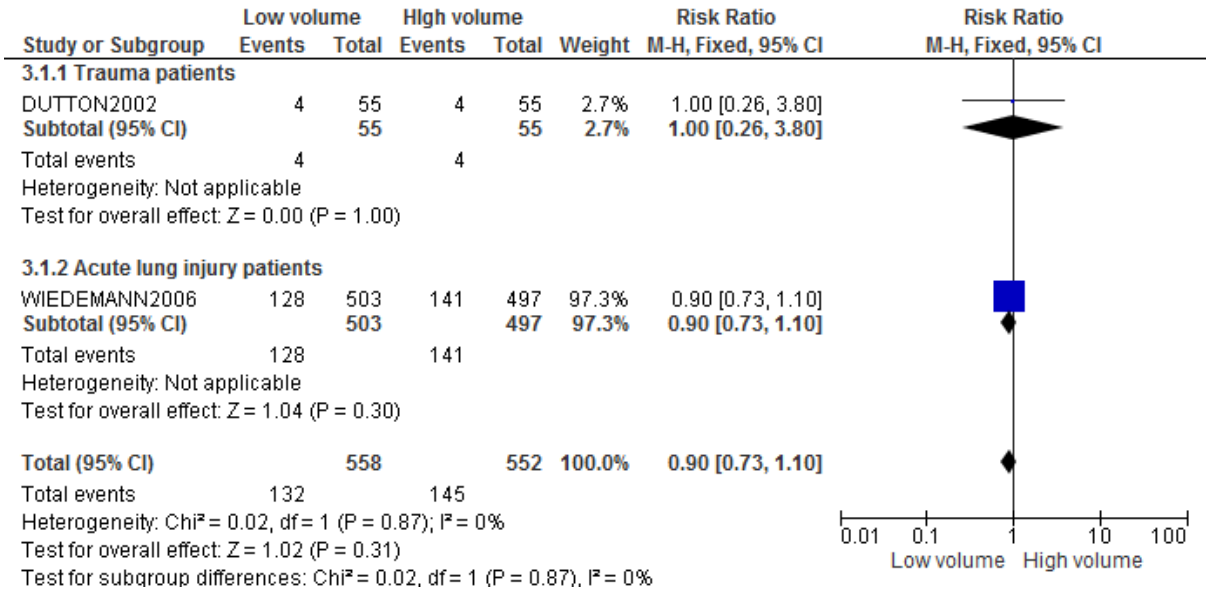


Figure 61: Renal failure

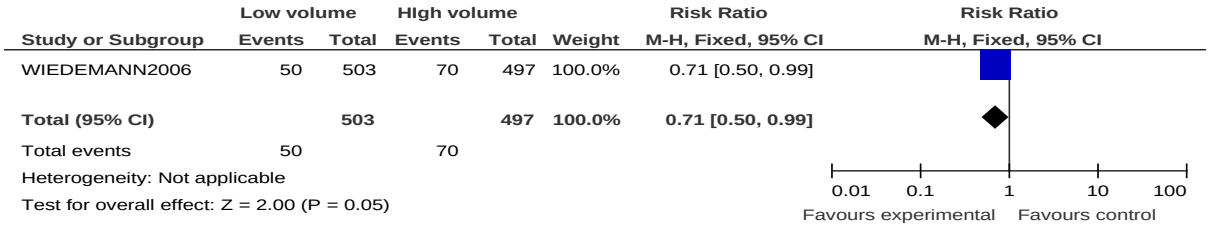
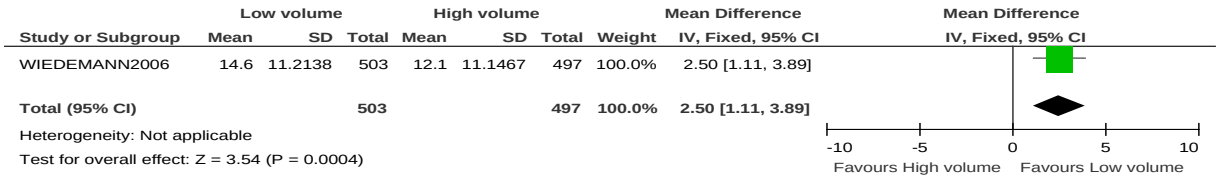
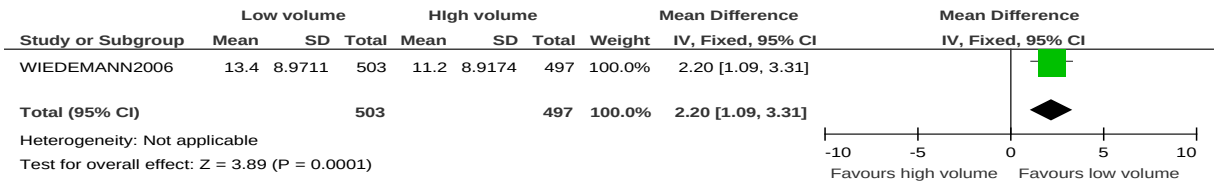


Figure 62: Respiratory failure, measured by ventilator free days (within first 28 days) (Better indicated by higher values)





G.4 Routine maintenance

Figure 63: All cause mortality (up to 30 days)

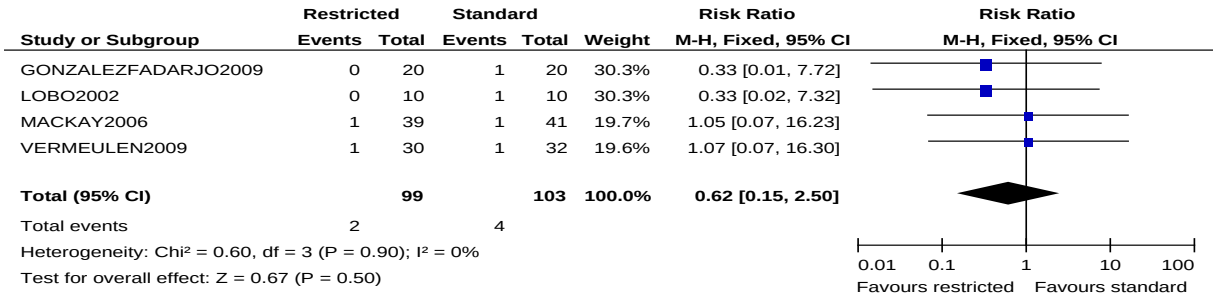


Figure 64: Respiratory complications

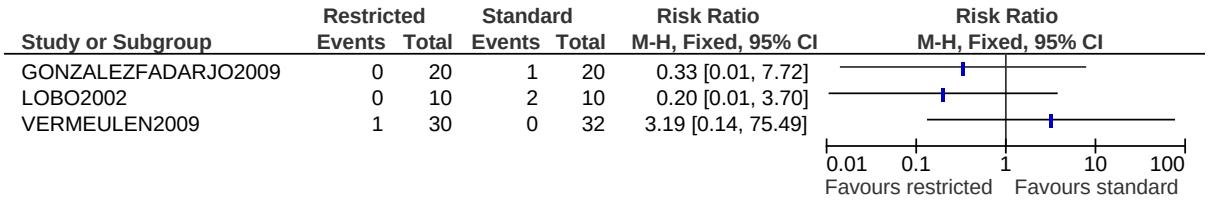
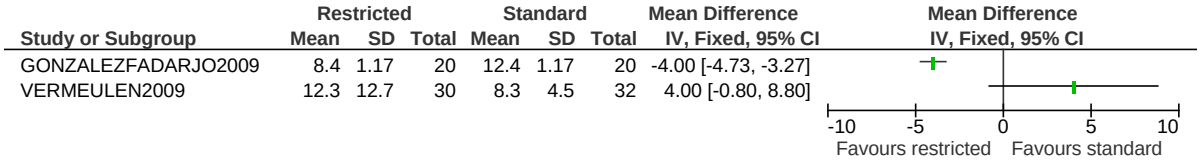


Figure 65: Length of stay (days)



G.5 Replacement and redistribution

No evidence was identified in this topic area.

G.6 Training and education

Evidence presented in narrative format (qualitative review)

Appendix H: Excluded studies

H.1 Standard principles

Table 13: Studies excluded from clinical review on use of algorithms

Excluded studies	Reasons for exclusion
Abraham et al. 2012 [5]	Compared two different types of protocols
Akers et al. 1991[11]	Does not compare algorithms to standard care, not relevant to protocol
Argalious et al. 2012[14]	Review
Balk et al. 2004[16]	Review (narrative)
Barochia et al. 2010[19]	Review
Barton et al. 1998[20]	Algorithms for improving and maintaining vascular access, not relevant to protocol
Bisgaard et al. 2013[28]	Gdt, less focus on ~IVF mgmt., use of inotropes
Bisgaard et al. 2013A[29]	GDG with use of inotropes
Bozza et al. 2010[48]	Review
Bundgaard-Nielsen et al. 2007[54]	Review
Burney et al. 2012	Survey
Challand et al. 2012[65]	GDT algorithm valuated in patients undergoing surgery
Chestovich et al. 2013[68]	Narrative paper
Cohn et al. 2010[78]	Compares standard fluid resuscitation to restricted fluid resuscitation(not relevant to review protocol)
Corcoran et al. 2012[87]	Meta-analysis
Csontos et al. 2008 [90]	Compares two different protocols, not relevant to review protocol
Dutton et al. 2002[107]	Compares two types of protocols
Elsolh et al. 2008[110]	Observational study
Fahlstrom et al. 2013[120]	Population not appropriate- Burns
Feeman et al. 1984[122]	Review (narrative)
Gurnani et al. 2010[158]	Before and after study
Hartin et al. 2003[166]	Narrative outline of a protocol
Haydock et al. 2013[170]	Review
Hijazi et al. 2005[175]	Compares protocols for specific electrolyte replacement
Kapoor et al. 2008[203]	Compares one protocol to another
Karadag et al. 2000[204]	Compliance study
Lobo et al. 2011[224]	Use of inotropes in management
Matot et al. 2012[247]	Does not evaluate protocolised care
McCaul et al. 2011[251]	Compares two different protocols, not relevant to review protocol
Pasqualetto et al. 2009[295]	Compares two different protocols, not relevant to review protocol
Prowle et al. 2012[306]	Review
Russell et al. 2012[316]	Study not on utility of protocolised care, not relevant to review protocol
Sebat et al. 2005[323]	Narrative paper
Srinivasa et al. 2013[340]	Evaluated GDT within an enhanced recovery protocol
Wiedemann et al. 2006[397]	Compares two different protocols, not relevant to review protocol

Excluded studies	Reasons for exclusion
Zhang et al. 2012[418]	Compares two different protocols, not relevant to review protocol

H.2 Assessment and monitoring

Table 14: Studies excluded from clinical review on serial measurement of body weight

Study Title [Study ID]	Reasons for exclusion
Abraham et al. 2011[4]	Compared body weight with impedance
Agarwal et al. 2009[7]	Incorrect population, dialysis patients
Boren et al. 2009[42]	Review about educational content for self management of CHF
Boyd et al. 1992[47]	Narrative review
Choong et al. 2007[71]	Incorrect population- paediatrics, literature review
Eastwood et al. 2006[109]	Not an RCT or prospective cohort study (body weight and fluid balance chart measured within same patients who underwent cardiac surgery)
Gonzalez et al. 1995[142]	Compared weight with bio-impedance within same patients.
Herrod et al. 2010[174]	Audit
Ind et al. 2006[186]	Discursive review article
Inrig et al. 2007[188]	Secondary analysis of a retrospective study looking at relationship between dialysis weight gain and blood pressure
Kataoka et al. 2010[206]	Retrospective study
Kataoka et al. 2009[207]	Not RCT or prospective cohort (compared body weight and bioelectrical impedance within same patients)
Kinton et al. 2005[212]	Semi-structured interviews
Leypoldt et al. 2002[220]	Incorrect population; dialysis, not receiving IV fluids
Lobo et al. 1999[222]	Retrospective study
Madias et al. 2007[232]	Incorrect intervention; ultra filtration
Mank et al. 2003[241]	Not an RCT or prospective cohort (compared body weight with fluid input/output measurement within same patients)
Martin et al. 2002[244]	Incorrect intervention- use of furosemide vs placebo in acute lung injury; change of weight was an outcome
Meiner et al. 2002[257]	Case report of one patient
Oh et al. 2007[289]	Retrospective review
Perren et al. 2011[301]	Observational study
Roos et al. 1993[312]	Not a comparative study – body eight, fluid balances and impedance measured within same patients.
Schneider et al. 2012[322]	Not relelvant to review protocol
Snaith et al. 2008[336]	Retrospective review
Varol et al. 2002 [367]	Retrospective review
Walshet al. 2005[387]	Audit
Welch et al. 1996[393]	Incorrect population or intervention of interest; evaluated risk of of dehydration for four days after adding oral hydration solution to daily intake- not in patients receiving IV fluids
Wise et al. 2000[402]	Does not directly compare body weight to fluid balance, provides correlation only

Table 15: Studies excluded from clinical review on measurement of urinary output

Study Title [Study ID]	Reasons for exclusion
Jonsson et al. 2011[200]	Not intervention of interest
Malisova et al. 2011[239]	Not intervention of interest
Porter et al. 2003[302]	Not intervention of interest
Rowat et al. 2011[314]	Not intervention of interest
Shamir et al. 2011[327]	Not intervention of interest
Shashaty et al. 2010[329]	Not intervention of interest
Solares et al. 2009[339]	Not intervention of interest
Steiner et al. 2007[342]	not population of interest
Thompson et al. 2009[353]	Not study design of interest
Wise et al. 2000[402]	Not study design of interest
Yeh et al. 2010[412]	Not intervention of interest

Table 16: Studies excluded from clinical review on measurement of serum chloride

Reference	Reason for exclusion
Agarwal et al. 2011[8]	Abstract
Base et al. 2006[21]	Abstract
Base et al. 2011[22]	Excluded population
Boaz et al. 2011[31]	No comparison group
Boniatti et al. 2009[40]	Abstract
Brill et al. 2002[52]	Wrong comparison
Brown et al. 2010[53]	No comparison group
Clark et al. 2012[74]	No comparison group
Constable et al. 2005[81]	Narrative opinion
Ellachtar et al. 2009[112]	Abstract
Eti et al. 2004[118]	No comparison group
Funk et al. 2004[130]	No comparison group
Gillespie et al. 1952[137]	Case report
Gonzalez- Suarez et al. 2011[144]	Abstract
Grobler et al. 2009[149]	Abstract
Gross et al. 2011[150]	Abstract
Gunnerson et al. 2006[156]	Data not relevant
Handy et al. 2008[165]	Narrative
Jacques et al. 2010[190]	Abstract
Katyal et al. 2012[208]	Abstract
Levit et al. 2011[218]	Abstract
Mallat et al. 2012[240]	Data not relevant
Masevicius et al. 2010[246]	Abstract
McCluskey et al. 2010[252]	Abstract
Noritromi et al. 2009[285]	Descriptive study of composition of metabolic acidosis on admission and 5 days of ICU stay
Vassar et al. 1990[373]	Wrong intervention/exposure: Hypertonic saline used

H.3 Resuscitation

Table 17: Studies excluded from the clinical review on gelatin

Author/title REF ID	Reason for exclusion
Awad2012[15]	Population - laparoscopic cholesectomy and non- resuscitation patients. Fluid administered during induction of anaesthesis (1 L per arm), any patients requiring more fluid would be excluded
Beards1994[23]	Wrong comparison (Hetastarch)
Boldt et al. 1993A[35]	Boldt first author
Gondos et al. 2009[139]	Abstract only
Gondos et al. 2009A[140]	Abstract only
Gunusen et al. 2010[157]	Spinal anaesthesia, C-section (wrong population)
Haas et al. 2007[159]	Children
Haisch et al. 2001[163]	Retracted
Haisch et al. 2001A[162]	Retracted
Himpe et al. 1991[176]	CPB priming fluid
Huebner et al. 1999[183]	Abstract only
Huttner et al. 2000[185]	Retracted
Karanko et al. 1987B[205]	Wrong comparison- dextran
Kuitunen et al. 2007[213]	Post operative cardiac surgery
Kumar et al. 2008[214]	Fluid pre- load
Kumle et al. 1999[215]	Boldt co-author
Mazhar et al. 1998[248]	Wrong comparison- 7.2% saline
Mittermayr et al. 2007[261]	Maintenance fluid
Mittermayr et al. 2008[260]	Maintenance fluid
Mortelmans et al. 1995A[264]	Normovolaemic haemodilution
Muralidhar et al. 2010[267]	Intraoperative cardiac surgery
Niemi et al. 2006[281]	Post operative CPB
Osthaus et al. 2009[292]	Children
Parker et al. 2004[294]	Pre operative fluid loading
Soares et al. 2009[338]	Intraoperative cardiac surgery
Upadhyay et al. 2005[361]	Children
Vanderlinden et al. 2004[363]	Intraoperative cardiac surgery
Vanderlinden et al. 2005	Intraoperative cardiac surgery
Vercauteren et al. 1996[375]	Spinal anaesthesia, C-section (wrong population)
Watkins et al. 1990[391]	Letter/ abstract
Witt et al. 2008[403]	children

Table 18: Studies excluded from the clinical review on tetrastarches

Author/title REF ID	Reason for exclusion
Anon et al. 2009[3]	Ongoing trial, no results published
Argalious et al. 2012[14]	Review
Bisgaard et al. 2013[28]	Not relevant to this review protocol(ordered for review on use of algorithms)
Bisgaard et al. 2013[29]	Not relevant to this review protocol(ordered for review on use of algorithms)
Boldt et al. 2004A[33]	Retracted article (Boldt first author)

Author/title REF ID	Reason for exclusion
Boldt et al. 2010D[36]	Retracted article (Boldt first author)
Bothner et al. 1998[45]	Not in resuscitation patients (minor elective surgery)
Bunn et al. 2011[56]	Review
Burdett 2012[57]	Review
Choi et al. 1999[70]	Review
Cifra et al. 2003[73]	Study conducted in children
Cook et al. 2001[82]	Commentary
Chest et al. 2011[352]	Protocol for trial
Davidson et al. 2006[96]	Review
Desaint et al. 2007[99]	Commentary
Feldheiser 2013[123]	Use of GDT in resuscitation
Fernandez et al 2005[124]	Does not report relevant comparisons
French et al. 1999[126]	Pre- loading before spinal anaesthesia, not resuscitation
Friedman et al. 2008[127]	Does not report relevant comparisons
Gallagher et al. 1985[132]	Post cardio-pulmonary bypass
Green et al. 2010[146]	Discussion paper on Brunkhorst 2008
Guidet et al. 2010[154]	Review
Haase et al. 2013[160]	Review
Hamaji et al. 2013[164]	Fluid given fro pre-load
Hartog et al. 2011[167]	Review
Haupt et al. 1982[169]	Does not report relevant comparisons
Haydock et al. 2013[170]	Not relevant to this review protocol(ordered fro review on use of algorithms)
Haynes et al. 2011[172]	Letter to editor
Kang et al. 2012[202]	Evaluated compliance with a resuscitation bundle, not relevant to review protocol
Lang et al. 2001[216]	Retracted article (Boldt co-author)
Lang et al. 2003[217]	Retracted article (Boldt co-author)
London et al. 1989[225]	Does not report relevant comparisons
Ley et al. 1990 [219]	Does not report relevant comparisons
Magder et al. 2010B[233]	Abstract
Moretti et al. 2003[263]	Does not report relevant comparisons
Myburgh et al. 2012[270]	Already included
Nadeua et al. 2013[271]	Review
Perel et al. 2013[298]	Review
Perner et al. 2011[299]	Protocol for trial- trial results to be available in March 2012
Perner et al. 2012[300]	Commentary
Puskarich et al. 2012[307]	Review
Rackow et al. 1983[309]	Does not report relevant comparisons
Saxena et al. 1997[320]	Does not report relevant comparisons
Senagore et al. 2009[324]	Does not report relevant comparisons
Sharma et al. 1997[328]	Does not report relevant comparisons
Srinivasa et al. 2013[340]	Not relevant to this review protocol(ordered fro review on use of algorithms)
Trof et al. 2010[358]	Results reported for Colloid v saline, but not separately for 6% HES; also no outcomes reported

Author/title REF ID	Reason for exclusion
Vanderheijden et al. 2009[362]	Results reported for Crystalloid v colloid although include 0.9% NaCl and Pentastarch in addition to gelatin and albumin in respective groups.
Van der Lindon 2013[364]	Review
Vercauteren et al. 1996[380]	Pre- loading before spinal anaesthesia, not resuscitation
Vlachou et al. 2010[380]	Burn patients
Wu et al. 2010 [399]	Letter to editor
Woessner et al. 2003[404]	Compares 6%HES 130/0.4 to unnamed electrolyte solution, outcomes not reported.
Xue et al. 2001[409]	Foreign language paper
Yang et al. 2011[411]	Patients with severe liver insufficiency included, out of scope
Zhang et al. 2012[418]	Not relevant to this review protocol(ordered fro review on use of algorithms)
Zhao et al. 2011[419]	Abstract

Table 19: Studies excluded from the clinical review on albumin

Study	Reason for exclusion
Binkley et al. 1993[27]	Population - hypoalbuminaemia
Boldt et al. 1993[35]	Incorrect population - CABG
Boutros et al. 1979[46]	Publication date - Pre 1990
Clift et al. 1982[75]	Publication date - pre 1990
Cooper et al. 2006[86]	Incorrect population - burns
Dubois et al. 2006[104].	Incorrect population - hypoalbuminaemia
Ernest et al. 1999[114]	Follow up only for only 1 hour infusion and in sepsis patients
Ernest et al. 2001 [115]	Follow up only for 40 minutes after infusion and post cardiac surgical patients
Gallagher et al. 1985[132]	Publication date - Pre 1990
Goodwin et al. 1983[145]	Incorrect population – burns and pre-1990
Greenhalgh et al. 1995[147]	Incorrect population – paediatric burns
Greenough et al. 1993[148]	Incorrect population – hypoalbuminaemia and paediatrics
Grundmann et al. 1982[152]	Publication date - pre 1990
Jelenko et al. 1978[193]	Population – burns and pre-1990
Jelenko et al. 1979[192]	Population – burns and pre-1990
Jelenko et al. 1979[194]	Population –burns and pre 1990
Lowe et al. 1979 [226]	Publication date - pre 1990
Lucas et al. 1980[227]	Publication date - pre 1990
Lucas et al. 1978[228]	Publication date - pre 1990
Maitland et al. 2005[237]	Population - paediatric
Maitland et al. 2005[238]	Population - paediatric
Maitland et al. 2011 [236]	Population - paediatric
McIntyre et al. 2012[254]	Design - this is a report of the pilot study, emphasising on feasibility of study, no relevant outcomes data reported.
McNulty et al. 1993[256]	Population - CABG patients
Metildi et al. 1984[258]	Publication date - pre 1990
Moss et al. 1981 [265]	Publication date - pre 1990
Myburgh et al. 2007[269]	Population - Traumatic brain injury

Study	Reason for exclusion
Nielsen et al. 1985[278]	Publication date - pre 1990
Nielsen et al. 1985[279]	Publication date - pre 1990
Nielsen et al. 1989[280]	Publication date - pre 1990
Oca et al. 1999[288]	Population - paediatric
Oca et al. 2003[287]	Population - paediatric
Prien T, et al. 1990[304]	Intervention - 20% alg albumin Whipple's operation, concentration of albumin
Quinlan et al. 2004[308]	Population - hypoalbuminaemia
Rackow et al. 1983 [309]	Publication date - pre 1990
Rubin H et al. 1997 [315]	Population - hypoalbuminaemia
Shah et al. 1977[326]	Publication date - pre 1990
Skillman et al. 1975[335]	Publication date - pre 1990
So et al. 1997[337]	Population - paediatrics
Svennevig et al. 1996 [344]	Population - open heart surgery
Tollofsrud et al. 1995 [356]	Population - CABG
Virgilio et al. 1979[379]	Publication date - pre 1990
Timmer et al. 1998[354]	Population - hypoalbuminaemia
Wojtysiak et al. 1992[405]	Population - hypoalbuminaemia
Zetterstrom et al. 1981[417]	Publication date - pre 1990
Zetterstrom et al. 1981[416]	Publication date - pre 1990

Table 20: Studies excluded from crystalloids in balanced vs. unbalanced solutions review

Study	Reason for exclusion
Boldt et al. 2002C[34]	The main author implicated scientific fraud investigation
Bomberger et al. 1986[39]	Published before 1990, non RCT?
Dung et al. 1999[105]	Not population of interest - children
Ghafari et al. 2008[136]	Not intervention of interest - hypertonic 5% saline
Hadimiloglu et al. 2008[161]	Not population of interest - transplant patients
Hasman et al. 2010[168]	abstract
Heidari et al. 2011[173]	Not fluid resuscitation cases?
McKnight et al. 1985[255]	Not intervention of interest - crystalloid bypass pump priming fluids
Moss et al. 1981[265]	Not intervention of interest - albumin
Ngo et al. 2001[277]	Not population of interest - children
Shackford et al. 1983[325]	Not intervention of interest - hypertonic lactated solution vs ringer's lactatd, published before 1990
Wilkes et al. 2001[400]	Not intervention of interest - this study look at Hespan vs Hextend, is comparing colloid in balanced vs unbalanced solution

Table 21: Studies excluded from colloids in balanced vs. unbalanced solutions review

Study	Reason for exclusion
Ahn et al. 2008[9]	Liver transplantation
Base et al. 2006[21]	Abstract only
Base et al. 2011[22]	Intra-operative cardiac surgery patients
Gan et al. 1999[133]	Use of hetastarches in both arms (excluded from interventions list)

Study	Reason for exclusion
Wilkes et al. 2001[400]	Use of hetastarches in both arms (excluded from interventions list)

Table 22: Studies excluded from volume and timing review

Study	Exclusion reason
Grundmann et al. 1985[151]	Published before 1990. Used different target COP (24 vs 29) for starting albumin in post-operative ICU patients.
Brandstrup et al. 2003[49]	Exclude - Perioperative regimen covering pre-operative to post-operative, using different solutions & between arms
Chin et al. 2006[69]	Exclude - Not resuscitation. The study used dextrose saline vs RL vs saline in the 1st two hours of surgery elective surgery patients not expected to have more than 500 ml loss in that period. Same volumes.
Dunham et al 1991[106]	Exclude – no relevant information. Used rapid vs usual system. No target rate, but rapid system patient received more fluid in the first hour (presumably enabled by the system).
Martin et al. 1992 [245]	SAME study as BICKELL1994 - preliminary report
Ellger et al. 2006[113]	Intervention This compared dual vs single agent (HES200/0.5 + gelatin vs HES130/0.4). Both used a total of 50ml/kg.
Gondos et al. 2010[141]	Interventions compared fluid types rather than volume /rate or timing (already included in fluid type)
Hutchin et al 1969[184]	Published before 1990, no relevant outcome and there was only a total of 12 patients in 3 arms.
Kern et al. 2002[211]	Meta-analysis of early vs late hemodynamic optimisation (interventions not just limited to IV fluids)
Vasheghani-Farahani et al. 2009 [369]	Not population of interest (contrast induced nephropathy prevention)
Vasheghani-Farahani et al. 2010 [370]	Not population of interest (contrast induced nephropathy prevention)
Vassar et al. 1988[371]	Study design - Retrospective chart review of 180 trauma patients in ICU
Vassar et al. 1991[372]	Interventions are hypertonic, severe head injury patients (excluded group)
Vassar et al. 1993[374]	Interventions are hypertonic, severe head injury (excluded group)
Vretzakis et al.2009[382]	Population - cardiac surgery group
Benes et al.2010[24]	Intervention - Not a comparison of volume or timing of IVF resuscitation
Gan et al.2002[134]	Intervention - Not a comparison of volume or timing of IVF resuscitation
Hopkins et al. 1983[182]	Publication date – before 1990. Intervention - Not a comparison of volume or timing of IVF resuscitation
Noblett et al. 2006[284]	Intervention - Not a comparison of volume or timing of IVF resuscitation
Kapoor et al. 2008[203]	Population - Coronary artery bypass surgery patients excluded from resuscitation review
Csontos et al. 2008[90]	Intervention - Not a comparison of volume or timing of IVF resuscitation This is a comparison of different ways of monitoring
Hayes et al. 1994 [171]	Intervention - Not a comparison of volume or timing of IVF resuscitation

Table 23: Studies excluded from the economic review for resuscitation

Reference	Reason for exclusion
Bisonni et al. 1991 [30]	Interventions compared were not applicable – crystalloids vs colloids; Colloids included hetastarch
Boldt et al. 2001 [37]	Author discredited - Boldt

Reference	Reason for exclusion
Boldt et al. 2000[38]	Author discredited – Boldt
NICE 2004 [274]	Pre- hospital setting not applicable.
Vogt et al. 1999 [381]	Interventions compared not applicable – blood replacement strategies.

H.4 Routine maintenance

Table 24: Studies excluded from fluid types review

Reference	Reasons for exclusion
Ali et al. 2003[13]	Incorrect intervention (not maintenance regimen)
Baraka et al. 1994[18]	Incorrect intervention (hypertonic saline)
Bennett et al. 1999[25]	Incorrect intervention
Bohm et al. 1994[32]	Incorrect intervention
Bomberger et al. 1986[39]	Incorrect population (Post operative management after aortic surgery; more of resuscitation population)
Brazel et al. 1996[50]	Incorrect intervention (hypertonic saline)
Butscher et al. 1996[58]	Not in English language
Coe et al. 1990[77]	Incorrect intervention
Colilles et al. 1992[79].	Abstract (not in English language)
Croft et al. 1992[88]	Incorrect intervention (hypertonic saline)
Cross et al. 1989[89]	Incorrect intervention (hypertonic saline)
Heidari et al. 2011[173]	Incorrect intervention (Pre-loading solution given to decrease PONV)
Jackson et al. 1995[189]	Incorrect intervention (Pre-loading before spinal anaesthesia)
Mackenzie 1969[231]	Incorrect intervention (Intra-operative management)
McCaul et al. 2003[250]	Incorrect intervention
McFarlane 1994[253]	Incorrect intervention (Intra-operative management)
Nuutinen 1973[286]	Incorrect intervention (hypertonic glucose solution)
Omigbodun 1989[290]	Incorrect population (women in labour)
Park et al. 1996[293]	Incorrect intervention (Pre-loading before spinal anaesthesia)
Rout et al. 1992[313]	Incorrect intervention (Preload before spinal anaesthesia)
Saringcarinkul et al. 2009[319]	Incorrect intervention (Intra-operative management)
Shires et al. 1983[331]	Incorrect intervention
Sirvinskas et al. 2007[334]	Incorrect intervention (colloids)
Stratton et al. 1995[343]	Incorrect population (women in labour)
Takil et al. 2002[345]	Incorrect intervention (Intra-operative management and post operative management within 12 hours of major surgery)
Terajima 2000[350]	Incorrect intervention (Intra-operative management)
Tollofsrud et al. 1995[356]	Incorrect intervention
Tollofsrud 1998[355]	Incorrect intervention (hypertonic saline)
Turner et al. 1998[360]	Incorrect intervention
Vasavada et al. 2009[368]	Incorrect intervention (Irrigating fluid for eye during surgery, not for iv use)
Vassar et al. 1991[372]	Incorrect intervention (hypertonic saline)
Vassar et al. 1993[374]	Incorrect intervention (hypertonic saline)
Veroli 1992[378]	Incorrect intervention (hypertonic saline)
Wade et al. 1997[384]	Incorrect intervention (hypertonic saline)

Reference	Reasons for exclusion
Wade et al. 1997[383]	Incorrect intervention (hypertonic saline)
Walsh et al. 1983[385]	Incorrect intervention (Intra-operative management)
Wang et al. 1997[388]	Incorrect intervention (hypertonic saline)
Waters et al. 2001[390]	Incorrect intervention (Intra-operative management)
Wennberg et al. 1992[395]	Incorrect intervention
Wennberg et al. 1990[396]	Incorrect intervention
Wilkes et al. 2001[400]	Incorrect intervention (Intra-operative management)
Wu et al. 2011[407]	2x2 factorial design
Yorozu et al. 2002[413]	Incorrect intervention (colloids)
Yung et al. 2009[414]	Incorrect population (paediatric)

Table 25: Studies excluded from the volume and timing review

Excluded studies	
Abraham Nordling et al. 2012 [5]	Incorrect intervention (intraoperative, Restrictive vs standard fluid regimen, the only difference in regimen is during the (colorectal) surgery)
Adupa et al. 2003[6]	Late vs early post surgery feeding; Post C-section. No details of types of IV fluids
Ali et al. 2003[13]	Incorrect intervention (Prespinal anaesthesia loading) Pre-operative loading on Post op PONV, Laparoscopic or gynaecological surgery lasting at least 1 hour
ARDS 2006[273]	Incorrect population (Acute lung injury); ICU patients. Specialised management.
Brandstrup et al. 2003[49]	Incorrect intervention (perioperative)
Bundgaard-Nielsen et al. 2009 [55]	Review of perioperative regimens
Butwick et al. 2007[59]	Incorrect population and Intervention (Prespinal anaesthesia loading in C-Section)
Camps et al. 2011[61]	Abstract
Canet et al. 2009[62]	Abstract (cohort study)
Capel Cardoso et al. 2004[63]	Incorrect population and Intervention (Prespinal anaesthesia loading in C-Section)
Chantarasorn et al. 2006[66]	Late vs early post surgery feeding; Post C-section. No details of types of IV fluids
Coco et al. 2010[76]	Incorrect population (pregnant women)
Cook et al. 1990[84]	Incorrect intervention (Compared compound sodium lactate vs compound sodium lactate/dextrose)
Corcoran et al. 2012[87]	Review of perioperative regimens
Cucereanu Badica et al. 2010[91]	Abstract; Intervention (Prespinal anaesthesia loading)
Cuthbertson et al. 2010[93]	Protocol only
Dyer et al. 2004[108]	Incorrect population and Intervention (Prespinal anaesthesia loading in C-Section)
Elakabawy et al. 2011[111]	Abstract
Eruyar et al. 2011[116]	Incorrect intervention (Prespinal anaesthesia loading); Elderly patients, cardiovascular outcomes
Eslamian et al. 2006[117]	Incorrect population (pregnant women)

Excluded studies	
Ewaldsson et al. 2005[119]	Incorrect intervention (Prespinal anaesthesia loading)
Freedman et al. 2011[125]	Incorrect population (paediatric, 3 months to 11 years old)
Futier et al. 2010[131]	Incorrect intervention (intra-operative, Fluid replacement (resuscitation), major abdominal surgery; different volumes of crytalloids and colloids)
Gan et al. 2002[134]	Incorrect intervention (Intra-operative difference in fluid)
Gondos et al. 2010[141]	Incorrect intervention (perioperative); Hypovolaemic patients, not maintenance
Holst et al. 2008[178]	Incorrect intervention (oral fluids)
Holte et al. 2004[180]	Incorrect intervention (Intra-operative liberal vs conservative)
Holte et al. 2007[179]	Incorrect intervention (perioperative); Different fluid regimen before, during and after surgery .Post surgery - IV versus no IV
Holte et al. 2007A[181]	Incorrect intervention (perioperative); Different fluid regimen before, during and after surgery
Hutchin et al. 1969[184]	Incorrect intervention (Variation in type and volume of fluids in all arms on day of surgery); Design – uncertain if randomised.
Jones et al. 1986[199]	Incorrect population and Intervention (Prespinal anaesthesia loading in C-Section)
Levit et al. 2011[218]	Abstract
McArdle et al. 2009[249]	Incorrect intervention (perioperative); Different regimens before, during, and after surgery
MacKay et al. 2007[229]	Letter
Maharaj et al. 2005[234]	Incorrect intervention (Prespinal anaesthesia loading)
Marathias et al. 2006[243]	Preoperative fluid (12 hours) before cardiac surgery in CKD patients (eGFR<45ml/min)
Matot et al. 2012[247]	Incorrect intervention (intra-operative)
Mintz et al. 2004[259]	Letter
Mojica et al. 2002[262]	Incorrect intervention (Prespinal anaesthesia loading vs co loading)
Muzlifah et al. 2009[268]	Incorrect population and Intervention (Prespinal anaesthesia loading in C-Section)
Nager et al. 2010[272]	Incorrect population (paediatric, 3-36 month)
Neville et al. 2010[276]	Incorrect population (paediatric)
Nisanevich et al. 2005[282]	Incorrect intervention (intra-operative)
Nishikawa et al. 2007[283]	Incorrect population and Intervention (Prespinal anaesthesia loading in C-Section)
Orji 2009[291]	Late vs early post surgery feeding; Post C-section. No details of types of IV fluids
Patolia et al. 2001[296]	Late vs early post surgery feeding; Post C-section. No details of types of IV fluids
Pearl et al. 1998[297]	Late vs early post surgery feeding; Gynaecologic intraabdominal surgery
Rout et al. 1992[313]	Incorrect population and Intervention (Prespinal anaesthesia loading in C-Section)
Saringcarinkul et al. 2009[319]	Incorrect intervention (Fluid type ; Same rates, volume and timing for protocol, different fluids); Population (pre-operative maintenance)
Siddik-sayyid et al. 2009[332]	Incorrect population and Intervention (Prespinal anaesthesia loading in C-Section)
Tamilselvan et al. 2009[346]	Incorrect population and Intervention (Prespinal anaesthesia loading in C-Section)

Excluded studies	
Teoh et al. 2009[349]	Incorrect population and Intervention (Prespinal anaesthesia loading in C-Section)
Tercanli et al. 2002[351]	Incorrect population and Intervention (Prespinal anaesthesia loading in C-Section)
Travers et al. 2007[357]	Incorrect intervention (oral fluids)
Van Samker 2011[365]	Abstract
Varadhan et al. 2010[366]	Review of perioperative regimens
Veroli et al. 1992[378]	Incorrect intervention (Prespinal anaesthesia loading)
Wenkui et al. 2010[394]	Incorrect intervention (Perioperative serum lactate monitoring to adjust IV fluid)
Wiedemann et al. 2008[398]	Incorrect intervention and population - not IV fluids; Acute lung injury
Williamson et al. 2009[401]	Incorrect population and Intervention (Prespinal anaesthesia loading in C-Section)
Yan et al. 2008[410]	Abstract

H.5 Replacement and redistribution

Table 26: Studies excluded from the clinical review for replacement and redistribution

Reference	Reason for exclusion
Freedman et al. 2011[125]	Population does not match protocol (paediatric population)
Rahman et al. 1988[310]	Population does not match protocol (paediatric population)

H.6 Training and education

Table 27: Studies excluded from the clinical review for training and education

Reference	Reason for exclusion
Anon et al. 1993[1]	Abstract
Aker et al. 1995 [10]	Editorial/opinion piece
Alexander 2011[12]	Commentary/Opinion piece
Banerjee et al. 2010[17]	Abstract
Borm et al. 2011[43]	Abstract
Boswort et al. 2011[44]	Before and after study for an educational intervention; not relevant to review protocol
Brazier et al. 1996[51]	Editorial/opinion piece
Campbell et al. 2006[60]	Introduction to a nursing competency assessment package
Cheron et al. 2011[67]	Study conducted in children; not related to IV fluid therapy.
Czaplewski et al. 1997[94]	Comment/opinion piece
Davidson et al. 2007[97]	Audit; specific to management in patients with fractured neck of femur
Delorenzo et al. 2007[98]	Assessed resucitaion and IV line insertion skills; not relavant to review question.
Dougal 2010[102]	Narrative paper
Eastwood et al. 2006[109]	Evaluates association of fluid balance to body weight; not relevant to review protocol
Fecher 2012[121]	Describes framework to improve nurse competencies
Froman et al. 1993[129]	Not specific to IV fluid therapy

Geyer et al. 1998[135]	Editorial/ Opinion piece
Herrod et al. 2010[174]	Evaluates presence of of hypo natraemia/hypernatraemia in patients on IV fluid therapy; not relevant to protocol
Jilek et al. 1999[197]	Comment/ opinion piece
Junaid2012[201]	Abstract
Prough et al. 1998[305]	Not relevant to protocol
Rutledge et al. 2005[317]	Review on effectiveness of Intravenous therapy teams to decrease catheter related complications
Salazar et al. 2009[318]	Abstract
Steen et al. 2010[341]	Evaluated quality of care of acutely ill patient; IV fluids not mentioned.
Turner2012[359]	Abstract
Warburton 2011[389]	Evaluates numeracy skills of healthcare professionals- not related to IV fluids
Workman et al. 2000[406]	Educational article

Appendix I: Excluded economic studies

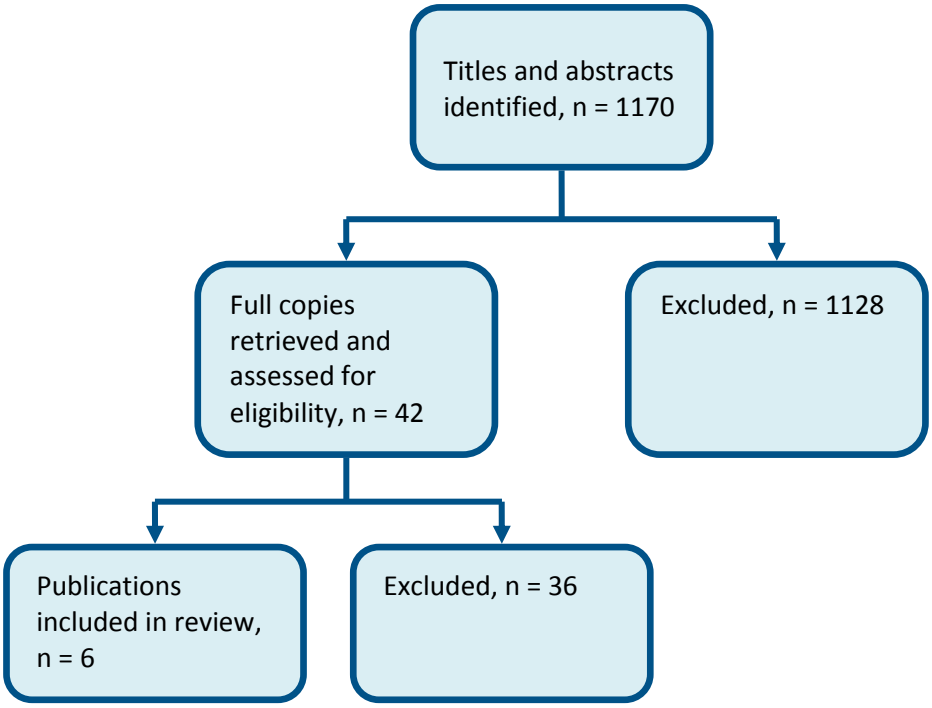
I.1.1 Studies excluded from economic review on fluid resuscitation

Reference	Reason for exclusion
Bisonni et al. 1991[30]	Interventions compared were not applicable – crystalloids vs colloids; Colloids included hetastarch
Boldt et al. 2001[37]	Author discredited - Boldt
Boldt et al. 2000[38]	Author discredited – Boldt
NICE 2004[274]	Pre- hospital setting not applicable.
Vogt et al. 1999[381]	Interventions compared not applicable – blood replacement strategies.

Appendix J: Adapted PRISMA diagrams for clinical studies

J.1 Standard principles

Figure 66: Flow diagram of clinical article selection for algorithm review



J.2 Assessment and monitoring

Figure 67: Flow diagram for serial measurement of body weight

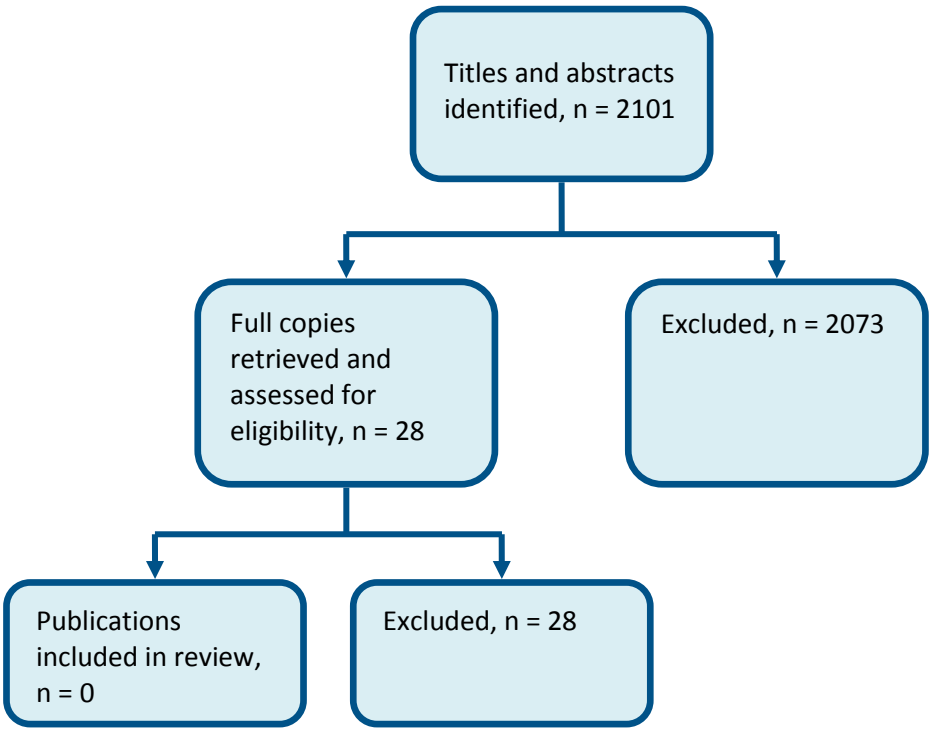


Figure 68: Flow diagram for measurement of urinary output

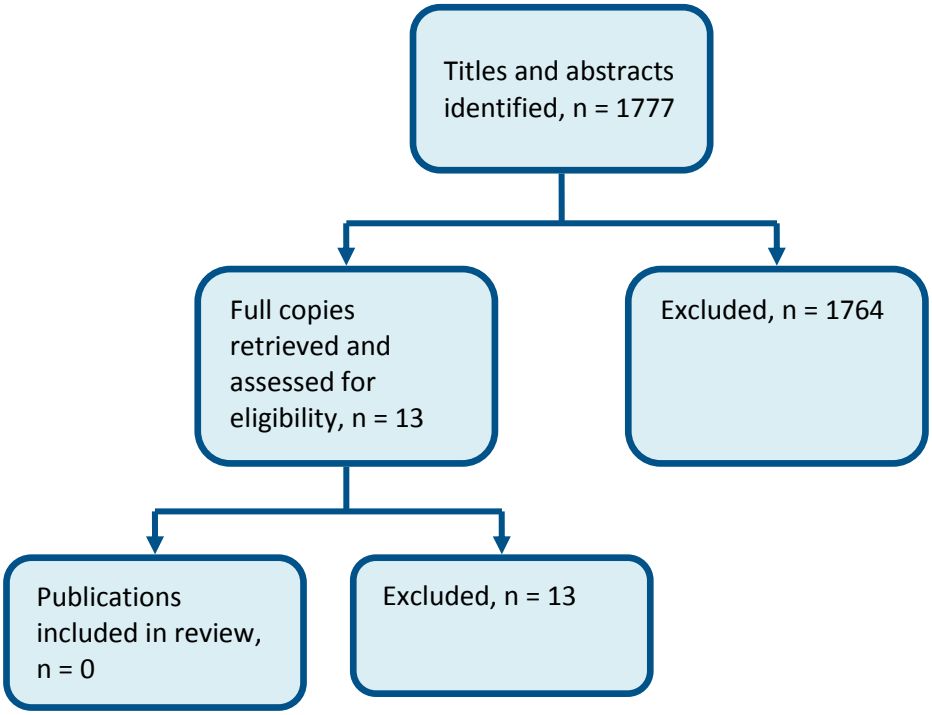
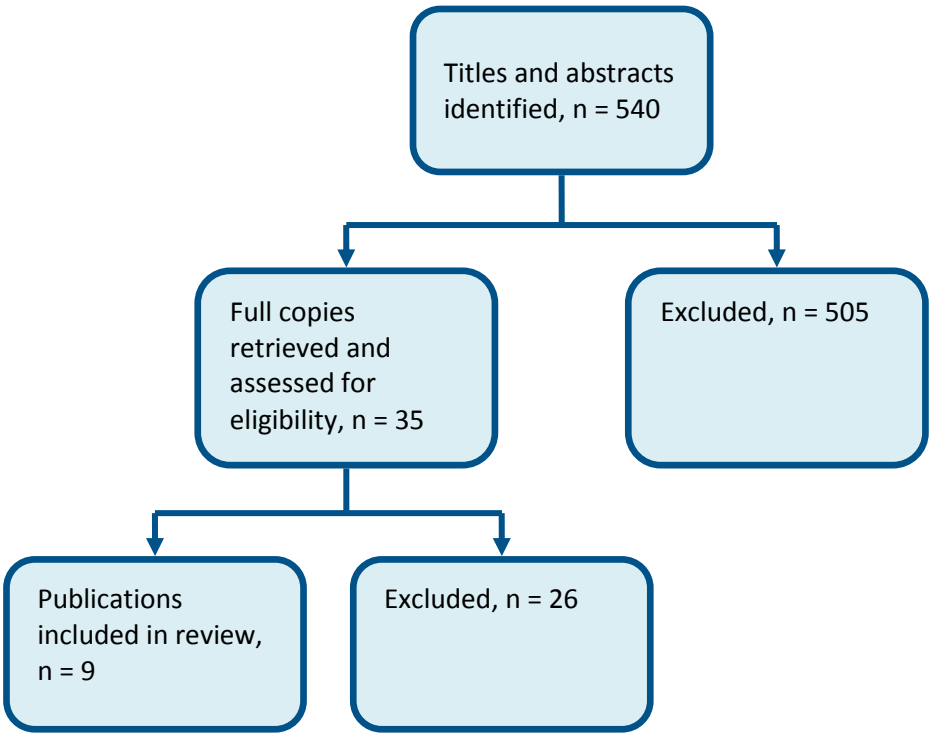
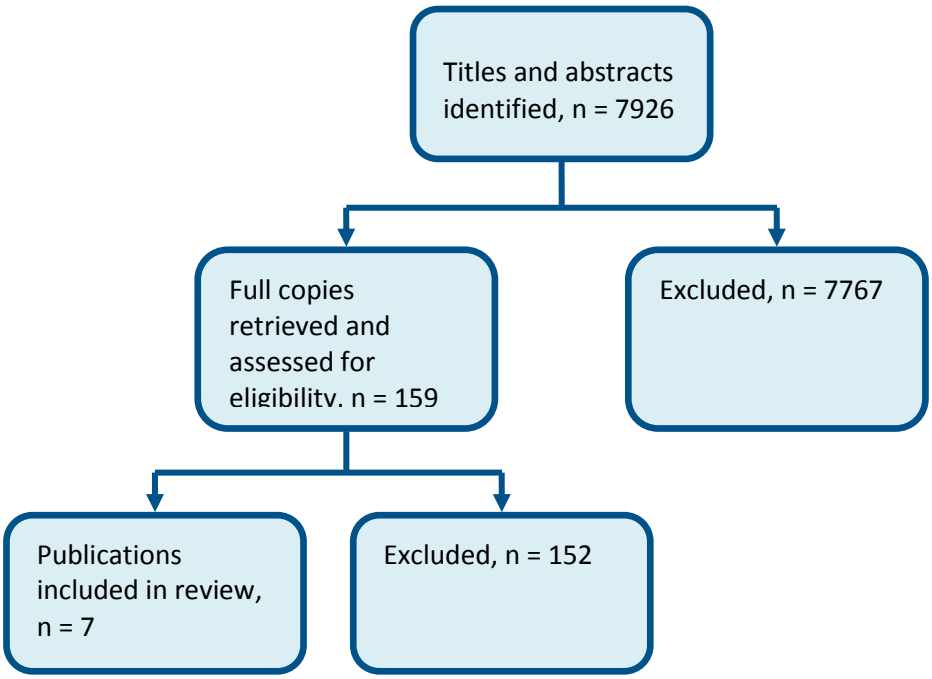


Figure 69: Flow diagram for measurement of serum chloride



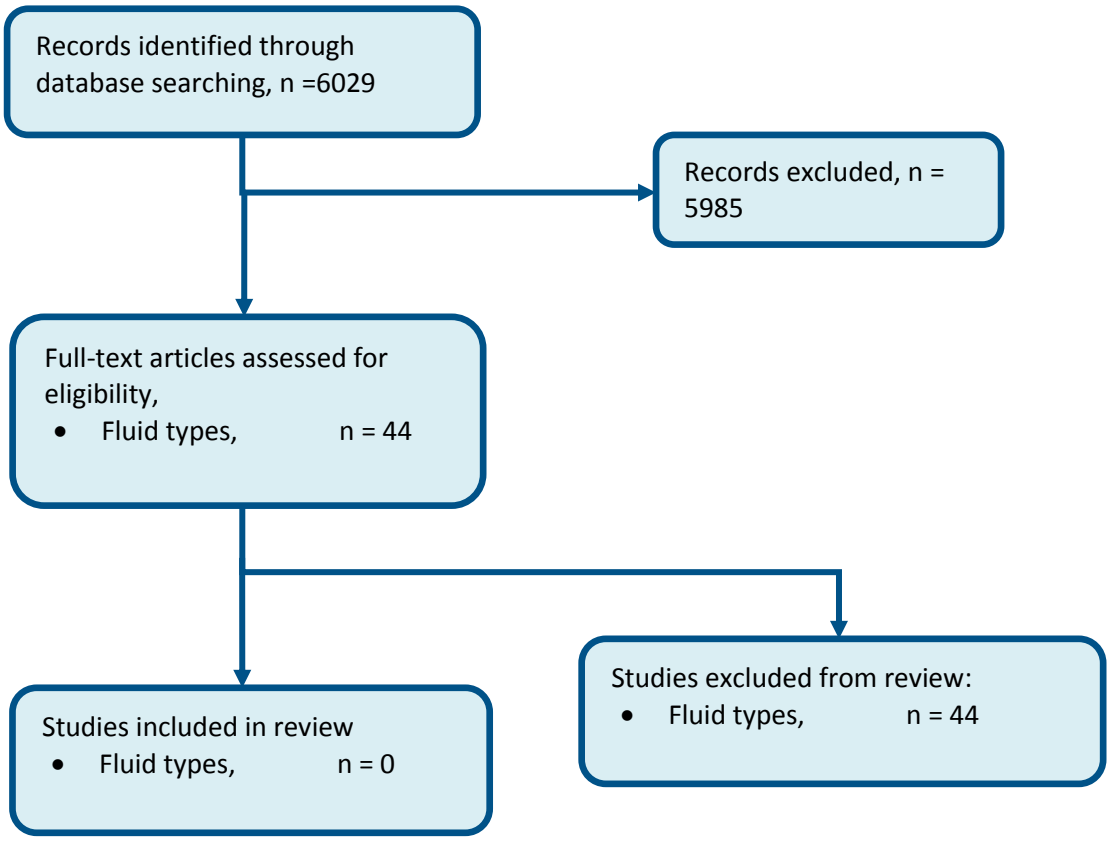
J.3 Resuscitation

Figure 70: Flow diagram for type of fluid resuscitation



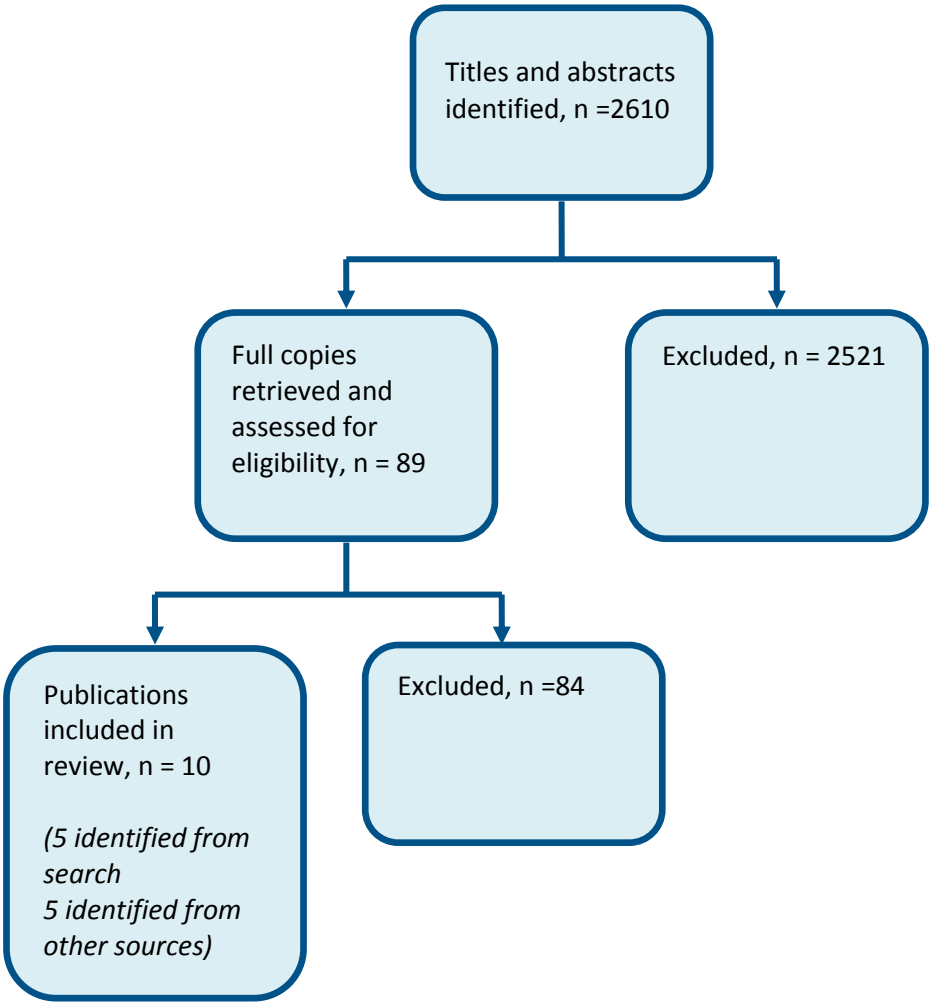
J.4 Routine maintenance

Figure 71: Flow diagram of article selection for routine maintenance fluid type review



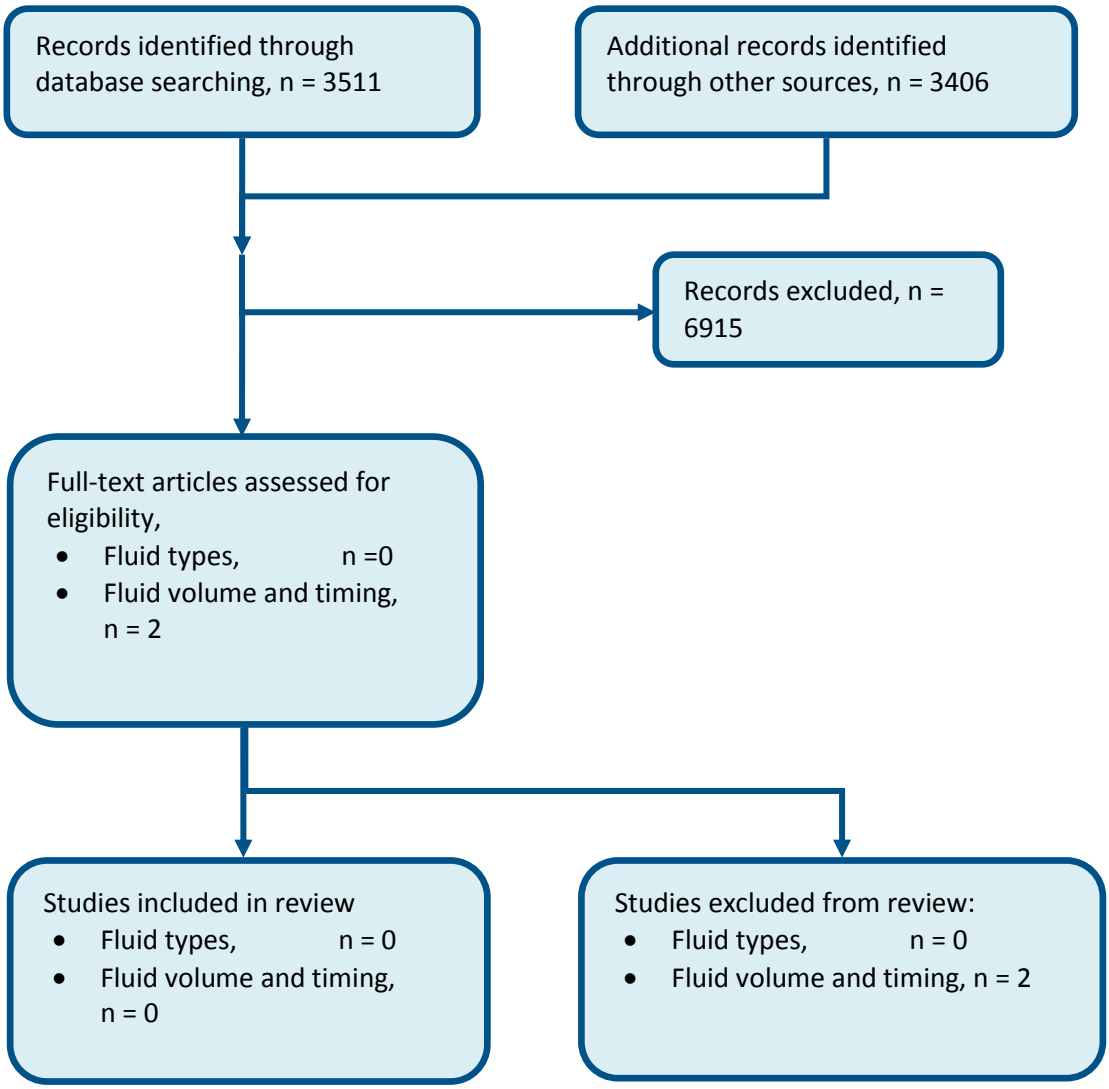
J.5 Volume and timing (Resuscitation and Routine maintenance)

Figure 72: Flow diagram of article selection for resuscitation and routine maintenance volume and timing review



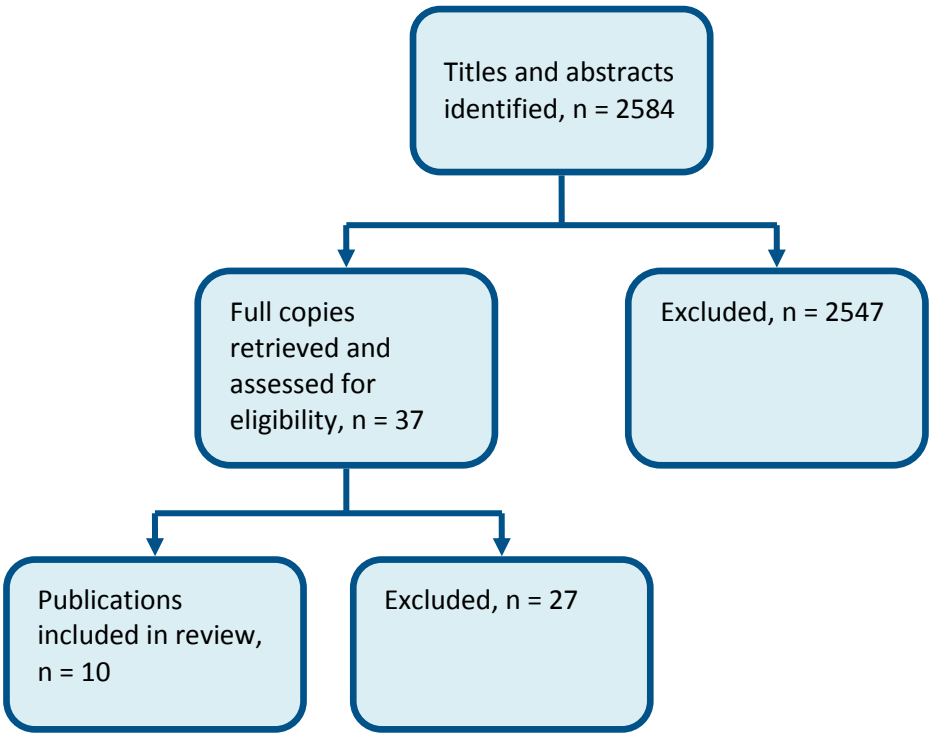
J.6 Replacement and redistribution

Figure 73: Flow diagram of article selection for IV fluid therapy for replacement of ongoing losses



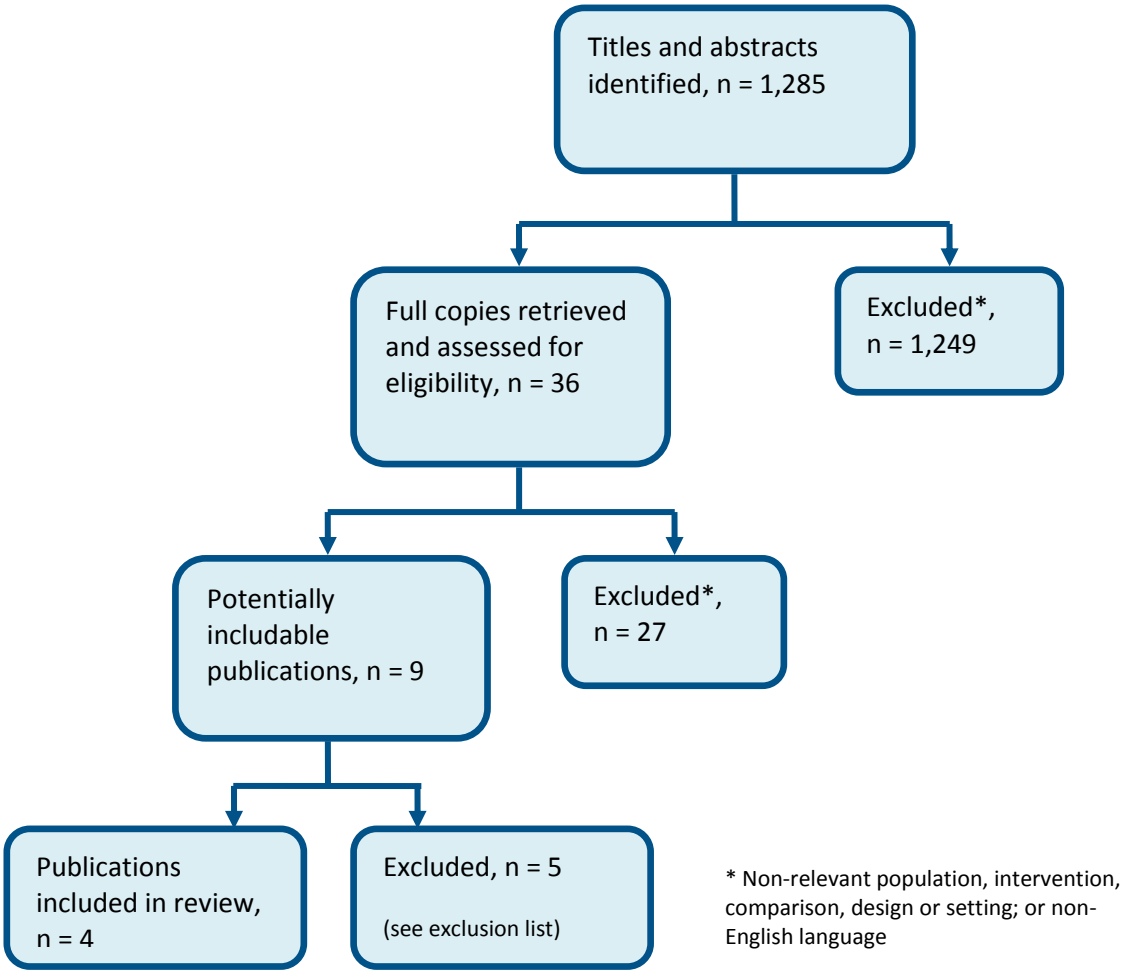
J.7 Training and education

Figure 74: Flow diagram of clinical article selection for training and education review



Appendix K: Adapted PRISMA diagrams for economic studies

Figure 75: Flow diagram of economic article selection



Appendix L: Cost-sensitivity analysis: Monitoring and Assessment Strategies for Intravenous Fluid Therapy

L.1 Introduction

The clinical assessment of a monitoring strategy includes:

- weight measurement and recording, and
- fluid balance chart recording, which includes urine output measurement.

Monitoring strategies are important as they can prevent the occurrence of fluid related complications. But excessive monitoring might increase costs unnecessarily and provide little additional health benefit.

The systematic clinical review did not identify any evidence for the optimal monitoring strategy for intravenous fluid therapy in hospitalised patients. Also, no studies were identified from published literature that assessed the cost effectiveness of different monitoring frequencies and strategies. Thus, the GDG judged that an economic analysis would be useful to help inform recommendations on optimal monitoring.

A cost effectiveness analysis was not possible due to the lack of effectiveness data identified from the systematic clinical review. The GDG decided that a cost-sensitivity analysis was the only feasible approach.

L.2 Methods

L.2.1 Overview

A threshold analysis was undertaken to identify the number of fluid associated complications that would need to be prevented in order for 2 monitoring strategies consisting of different frequencies of weight measurement and fluid balance chart recording to be cost neutral.

The GDG identified 8 monitoring strategies for comparison, ranging from no weight measurement or fluid chart recording (Strategy 1), to weight measurement twice a day and fluid balance chart recording (Strategy 8).

Table 28: Monitoring strategies

		Fluid balance chart	
Weight		**None**	**Fluid balance chart completed**
	None	Strategy 1	Strategy 5
	Twice weekly	Strategy 2	Strategy 6
	Daily	Strategy 3	Strategy 7
	Twice a day	Strategy 4	Strategy 8

The population included for the analysis was adults in the hospital requiring intravenous fluid therapy except those receiving intravenous fluid therapy for resuscitation. Monitoring and assessment strategies described here are not suitable for patients undergoing fluid resuscitation

because of their unique fluid and electrolyte requirements. For these patients, care algorithms set out in the Standard Principles, (section 4.2.1 in full guideline) will be more applicable.

We calculated the cost of each monitoring strategy. Then we estimated the number of adverse events that would need to be prevented so that a monitoring strategy would be cost neutral compared to

1. the monitoring strategy with the lowest cost (strategy 1), and
2. the monitoring strategy which the GDG judged best represented current practice (Strategy 6).

Key assumptions:

- Weight measurement
  - All weighing scales and equipment for weight measurement of mobile, partially mobile, and immobile patients were available in hospital.
  - Sanitisation costs for equipment were assumed to be negligible for all weight measurement equipment and as such were excluded from analysis.
- Fluid Balance Chart completion
  - Costs of additional stationary (fluid balance charts and pen) required across monitoring strategies was judged to be negligible and as such was excluded from the analysis.
- Nurses, Band 2, and Band 3 Health Care Assistants (HCA) were responsible for performing weight measurement and fluid balance chart completion.
- The duration of IV fluid therapy on a general ward would be 5 days.
- The estimated cost of a major intravenous fluid associated complication was based on an extended hospital length of stay (with the cost of critical care included in a sensitivity analysis).

L.2.2 Inputs

L.2.2.1 Summary table of model inputs

Resource inputs were based on the experience of the GDG. The unit costs for staff are provided in Table 1) below. These were used to cost each episode of of weight measurement and fluid balance chart recording as summarised in Table 15. Details are in the following section.

Table 29: Summary table of model inputs

Health Care Professional	Cost (£)/ hr	Cost (£)/minute	Source
HCA Band 2	£20	£0.33	PSSRU 2011[92]
HCA Band 3	£24	£0.40	
Nurse	£40	£0.67	
Average cost for HCA 2 &3		£0.37	

Table 30: Summary table for cost of clinical assessment components

Clinical Assessment	
Cost for fluid chart recording and adding up per 24 hour day	£20.36
Cost per weight measurement of a hospitalised patient	£11.10

L.2.2.2 Resource use and cost

The cost of each monitoring strategy was the sum of the costs of both assessment components and reflected the frequency of weight measurement and presence/absence fluid balance chart recording over a period of five days.

The cost of fluid balance chart recording was based on manpower costs only as stationary costs were estimated to be negligible. A fluid balance chart contains intravenous input/output and urine output components and the GDG considered that a nurse and a HCA 2 or 3 would complete 70% and 30% of the fluid chart respectively. The GDG estimated that the physical act of fluid chart recording for any hospitalised patient would take hospital staff 1 minute per hour (24 minutes per day). The adding up of fluid inputs and outputs would take 5 minutes per calculation. This calculation is completed twice every 24 hour period and is usually undertaken by a nurse (95% of the time). In the remaining 5% of cases, a HCA takes this responsibility. Using these estimates and unit costs for health care professionals **Table 31** a total of 34 minutes was required for filling and adding up a fluid balance chart every 24 hours and the resulting cost was £20.36.

Table 31: Inputs for Cost of Fluid Balance Completion (FBC)

Health Care Professional	% filling out FBC (IV input and output and urine output) undertaken by staff member	Minutes required for filling out FBC per 24 hours (Base case Estimate)	Cost
Nurse	70%	24	£11.20
HCA 2 or 3	30%	24	£2.64
Total for filling up	100%		£13.84
Health Care Professional	**% of adding up FBC undertaken by staff member**	**Minutes required for adding up FBC per 24 hours (Base case Estimate)**	**Cost**
Nurse	95%	10	£6.33
HCA 2 or 3	5%	10	£0.18
Total for adding up	100%		£6.52
Total Cost for FBC per 24 hours		34	£20.36

The cost of weight measurement was based on the amount of time required to weigh a patient and the number of staff members required for the process. The GDG considered staff time would differ according to the condition of a patient. The process of weight measurement would range from 5 to 15 minutes and require 1 to 3 hospital staff members (Table **32**). The GDG estimated that in each hospital ward a maximum of 2 HCAs would be available for conducting weight measurement. Thus, when measuring the weight of an immobile patient, 1 qualified nurse would be required in addition to 2 HCAs. The total cost of weight measurement for a hospitalised patient was £11.10, calculated as the weighted average of the 3 patient categories in (**Table 32**). Weights were assigned by the GDG according to the proportion of hospitalised patients expected to be in each patient category.

Table 32: Inputs for Cost of Weight Measurement

Patient category	Number of staff	Minutes required from each staff member	Proportion of hospitalised patients	Cost
Mobile Patient	1	5	30%	£1.83

Patient category	Number of staff	Minutes required from each staff member	Proportion of hospitalised patients	Cost
Partially Mobile Patient	2	10	50%	£11.00
Immobile Patient	3	18	20%	£25.20
Average cost for weight measurement of patient			100%	£11.10

The GDG judged that a major complication (for example oedema see 4.2.4 for other examples) would likely require additional hospital length of stay [330]. Thus, the cost of an intravenous fluid related major complication was taken as a weighted average of all NHS Reference costs 2010-2011 for fluid and electrolyte disorder non-elective inpatient long stay categories KC05 A-F. Each category was weighted according to the number of documented admissions. The result was £1868 for an average length of stay of 6 days. [101]

L.2.3 Computations

Since we are only considering the manpower costs of monitoring strategies and the cost of major complications we can say that the cost of strategy m is:

$C_m = C_m^{wfc} + C^{comp} N_m$

Where C_m^{wfc} is the cost associated with each monitoring strategy comprised of weight measurement and fluid balance chart recording, C^{comp} is the cost of a major complication and N_m is the number of complications associated with monitoring strategy m.

For a fluid L to be cost neutral it follows that

$C_m = C_L$ and

$C_m^{wfc} + C^{comp} N_m = C_L^{wfc} + C^{comp} N_L$

By rearrangement, the formula for the number of complications that would need to be prevented in order for monitoring strategy m to be cost neutral compared with the monitoring strategy L, is:

$N_m - N_L = (C_m^{wfc} - C_L^{wfc})/C^{comp}$

L.2.4 Sensitivity analyses

The GDG recognised that variation in a patient's condition would affect the time required for filling out and adding up the fluid balance chart. To address this uncertainty, the time estimate for filling out a fluid balance chart was changed to 2.5 minutes per hour (from 1 minute per hour in the base case). Using this estimation, the resulting time required for per 24 hour day was 70 minutes and the cost was £41.12.

The cost of a critical care episode was added to the cost of a complication in another sensitivity analysis. It was calculated as the weighted average of all NHS Reference costs 2010-2011 for Adult Critical Care 0 to 3 organs supported categories.[101] Each category was assigned a weight according to the number of documented days. GDG judged that support for more than 3 organs would be unlikely for major complications associated with intravenous fluid therapy so only costs associated with providing critical care support for 0-3 organs (XC01 -7) was included. The cost per critical care period was £1132.

L.3 Results

L.3.1 Base case and Sensitivity Analysis

Table 33 below provides the base case results for comparisons of a monitoring strategy versus Strategy 1, the lowest cost strategy and Strategy 6, the strategy most similar to current practice in the general ward.

The cost for a monitoring strategy of 5 days duration varies from £0, if there is no monitoring and assessment; to £213 if the monitoring strategy requires weight measurement twice a day including completion of a fluid balance chart.

Results in Table 33 correspond to comparisons of a monitoring strategy and Strategy 1. When the incremental cost difference is £213 is at its greatest in the comparison of Strategy 8 vs Strategy 1. The number of complications that strategy 8 would need to avert for it to be cost neutral would be 114 per 1000 patients. When critical care costs are included, the number of complications that would have to be prevented would reduce to 71 per 1000 patients.

The GDG assumed that monitoring and assessment in a general ward is most similar to Strategy 6, weight measurement twice a week including fluid balance chart completion. Current practice appears to be more costly than 4 monitoring strategies. The cost differentiation between Strategy 6 and Strategy 1 is £118 and current practice would need to prevent 63 complications (39 including critical care costs) to render it cost neutral. Of the 2 monitoring strategies that are more costly than current practice, the greatest incremental cost difference is £95, associated with Strategy 8. For this strategy to be cost neutral it would need to prevent (per 1000 patients) 51 complications more than current practice (32 including critical care costs).

If the estimated time required for fluid balance chart completion is increased to 70 minutes per day, the cost of monitoring strategies range from £0 to £316 (

Table 34). In this case, the most intensive monitoring strategy would need to avert 169 (106 including critical care costs) major complications per 1000 patients to be cost-neutral.

Table 33: Base case results

Strategy			Costs for 5 days (£)			Number of extra complications that would have to be prevented per 1000 patients[a] to make strategy cost neutral			Number of extra complications that would have to be prevented per 1000 patients[a] to make strategy cost neutral (including critical care costs)		
#	Weight	Fluid Balance Chart	Weight	Fluid Balance Chart	Total	compared to strategy 1	Compared to strategy 6	Compared to the next most costly strategy	compared to strategy 1	Compared to strategy 6	Compared to the next most costly strategy
1	none	no fluid chart	£0	£0	£0	---	---	---	----	---	----
2	twice a wk	no fluid chart	£16	£0	£16	8	---	8	5	---	5
3	daily	no fluid chart	£55	£0	£55	30	---	21	18	---	13
5	none	fluid chart	£0	£102	£102	54	---	25	34	---	15
4	twice a day	no fluid chart	£111	£0	£111	59	---	5	37	---	3
6	twice a wk	fluid chart	£16	£102	£118	63	---	4	39	---	2
7	daily	fluid chart	£55	£102	£157	84	21	21	52	13	13
8	twice a day	fluid chart	£111	£102	£213	114	51	30	71	32	18

Patients hospitalised for 5 days

Table 34: Sensitivity Analysis on longer time involved with fluid balance charts

Strategy			Costs for 5 days (£)			Number of extra complications that would have to be prevented per 1000 patients[a] to make strategy cost neutral			Number of extra complications that would have to be prevented per 1000 patients[a] to make strategy cost neutral (including critical care costs)		
#	Weight	Fluid Balance Chart	Weight	Fluid Balance Chart	Total	Compared to strategy 1	Compared to strategy 6	Compared to the next most costly strategy	Compared to strategy 1	Compared to strategy 6	Compared to the next most costly strategy
1	none	no fluid chart	£0	£0	£0	---	---	---	----	---	----
2	twice a wk	no fluid chart	£16	£0	£16	8	---	8	5	---	5
3	daily	no fluid chart	£55	£0	£55	30	---	21	18	---	13
5	none	fluid chart	£111	£0	£111	59	---	30	37	---	18
4	twice a day	no fluid chart	£0	£206	£206	110	---	51	69	---	32
6	twice a wk	fluid chart	£16	£206	£221	119	---	8	74	---	5
7	daily	fluid chart	£55	£206	£261	140	21	21	87	13	13
8	twice a day	fluid chart	£111	£206	£316	169	51	30	106	32	18

(a) Patients hospitalised for 5 days

L.4 Discussion

L.4.1 Summary of results

The cost associated with monitoring strategies varies according to the frequency of weight measurement and fluid balance chart recording. The incremental cost difference is greatest in the comparison between Strategy 8 and no monitoring (Strategy 1) at £213 where Strategy 8 would need to avoid an additional 114 complications per 1000 patients to become cost neutral compared with Strategy 1 (71 if critical care costs are included). This increases to 169 per 1000 patients if a more conservative assumption is made about the time involved with completing fluid balance charts.

L.4.2 Limitations & interpretation

This analysis has estimated the number of major complications that would need to be prevented in order for monitoring strategies to be cost neutral or cost saving. Even if fewer major complications are prevented in practice, it is possible for a monitoring strategy to be *cost effective* if there are minor complications prevented as well or if the QALY gain associated with a major complication is large. For example, if a complication is associated with a 0.2 QALY gain then it is only necessary for Strategy 8 to avoid 36 extra complications (30 including critical care) per 1000 patients to render it cost effective compared to no monitoring (Strategy 1).

The GDG thought that current monitoring and assessment was similar to Strategy 6 (weight measurement twice a week and fluid balance chart completion) in the general ward. If the introduction of more rigorous monitoring strategies is able to reduce the incidence of fluid associated complications, then additional manpower costs could be justified. However, the number of complications that each monitoring strategy can prevent and the proportion of patients who would require critical care because of intravenous fluid therapy related complications remain unclear from our evidence review and further research is required.

Appendix M: Cost sensitivity analysis: Types of intravenous fluids for resuscitation

M.1 Introduction

One study was identified from published literature which assessed the cost effectiveness of albumin versus 0.9% sodium chloride for the resuscitation of fluid and electrolyte status in patients with sepsis [153]. The study found that albumin was cost effective for the resuscitation of patients with severe sepsis. There were no other includable economic evaluations related to resuscitation.

Given the use of different intravenous fluid types for the resuscitation of fluid and electrolyte status has significant economic considerations; the GDG judged the identification of optimal types of intravenous fluid for fluid resuscitation as a high priority for original economic modelling. However, a cost effectiveness analysis was not possible because of the limited evidence for health outcome from the guideline's systematic review of clinical effectiveness evidence. Instead, the analysis was limited to a comparison of costs.

M.2 Methods

M.2.1 Overview

A threshold analysis was undertaken to identify the number of fluid associated complications that would need to be avoided to render any two different strategies to be cost neutral.

The comparators selected were different types of intravenous fluid fit for the purpose of fluid resuscitation as decided by the GDG:

- Crystalloids
  - 0.9% Sodium Chloride, Hartmann's Solution, Plasmalyte M, Ringer's Lactate,
- Gelatin
  - Gelofusine , Gelaspan, Geloplasma, Isoplex, Volplex
- Tetrastarches
  - 6% Tetraspan, 10% Tetraspan, 6% Venofundin, 6% Volulyte, 6% Voluven
- Albumin
  - 4.5% Albumin, 5% Albumin

The population included for the analysis was adults in the hospital requiring intravenous fluid therapy resuscitation.

M.2.2 Approach to Analysis

We calculated the cost of fluid resuscitation with each type of fluid for a typical patient. Then an equation was constructed to identify the number of major intravenous fluid related adverse events that would need to be averted to render an intravenous fluid cost neutral compared with the one with the lowest acquisition cost.

Key assumptions:

- The GDG considered the maximum volume of intravenous fluid prescribed for fluid resuscitation would be 2000 ml as described in the resuscitation algorithm (see section 7.4.1 in the full guideline)
- Resuscitation fluid therapy used 250 ml, 500ml and 1000ml bag sizes only. Only when the unit cost of 1000 ml bag sizes were not available would the unit cost of 500 ml bags be used. When unit costs of 1000ml and 500 ml bag sizes were not available, then the unit cost of 250 ml bags was used.
- Administration, storage and monitoring costs were similar across all intravenous fluids used for fluid and electrolyte resuscitation. Therefore manpower costs for administering and monitoring intravenous fluid therapy were not included.
- The estimated cost of a major intravenous fluid associated complication (for example oedema see 4.2.4 for other examples) was based on an extended hospital length of stay. The additional costs for critical care were included in a sensitivity analysis.

M.2.3 Resource Use and Costs

For each strategy we assumed 2000ml of fluid would be used. Where we had costs for different bag sizes, we used the largest (cheapest) bag size. The costs of the bags were provided by the Department of Health Commercial Medicines Unit (CMU) in 2012.[80] The CMU does not contract for human albumin but were able to supply a range of prices from different manufacturers. For the other products they were able to provide a single contract price (see Table 35).

The GDG judged that a major complication would likely require additional hospital length of stay[330]. Thus, the cost of an intravenous fluid related major complication was taken as a weighted average of all NHS Reference costs 2010-2011 for fluid and electrolyte disorder non-elective inpatient long stay categories KC05 A-F. Each category was weighted according to the number of documented admissions. The result was £1868 for an average hospital length of stay of 6 days. [101] This figure did not include costs for critical care.

M.2.4 Calculations

Since we are only considering the acquisition cost of fluid and the cost of major complications we can say that the cost of strategy i is:

$C_i = C_i^{fluid} + C^{comp} N_i$

Where C_i^{fluid} is the acquisition cost of the fluid, C^{comp} is the cost of a major complication (i.e. £1868 in the base case) and N_i is the number of major complications associated with fluid i.

For a fluid to be cost neutral it follows that

$C_i = C_L$ and

$C_i^{fluid} + C^{comp} N_i = C_L^{fluid} + C^{comp} N_L$

Rearranging, we derive a formula for the number of major complications that would need to be averted in order for fluid i to be cost neutral compared with the fluid with the lowest acquisition cost.

$N_L - N_i = (C_i^{fluid} - C_L^{fluid}) / C^{comp}$

M.2.5 Sensitivity Analysis

The GDG highlighted that often major adverse events can lead to need for critical care. The model was modified to consider the cost of more serious adverse events.

The cost of a Critical Care period was calculated as the weighted average of all NHS Reference costs 2010-2011 for Adult Critical Care 0 to 3 organs supported categories (XC04Z-XC07Z). [101] Each category was weighted according to the total number of days recorded. GDG judged that support for more than 3 organs would be unlikely for major complications associated with intravenous fluid therapy so only costs associated with providing critical care support for 0-3 organs was included. The cost per critical care period was £1132.

M.3 Results

The results in Table 35 show that the total acquisition cost of resuscitation intravenous fluids would range from £1.40 for 0.9% Sodium Chloride to £136.24 for 4.5% Albumin. This suggests that 4.5% Albumin would have to have 72 fewer major complications per 1000 fluid resuscitation patients than 0.9% Sodium Chloride for it to be cost neutral.

Adding the cost of critical care stay to the cost of complication reduces the number of major complications per 1000 patients that need to be avoided in order to render a fluid therapy cost neutral compared to 0.9% Sodium Chloride (Table 35). It suggests 4.5% Albumin would need to avoid 45 major complications per 1000 patients to be cost neutral compared to 0.9% Sodium Chloride.

Table 35: Cost of fluids for resuscitation

	Unit Cost for 1000ml bag	Unit Cost for 500ml bag	Unit Cost for 250ml bag	Cost of fluid for resuscitation (2000ml) (a)	Number of extra major complications per 1000 patients that must be avoided for fluid to be cost neutral (including critical care costs)	
					Compared with lowest cost fluid	Compared with next most costly fluid
0.9% Sodium Chloride	£0.70	£0.63		£1.40	-	-
Hartmann's Solution	£0.85	£0.70		£1.70	<1 (<1)	<1 (<1)
Plasmalyte M	£0.92			£1.84	<1 (<1)	<1 (<1)
Ringer's Lactate		£1.25		£5.00	2 (1)	2 (1)
Volplex	£3.80	£2.10		£7.60	3 (2)	1 (1)
Isoplex	£3.90	£2.20		£7.80	3 (2)	<1 (<1)
Gelofusine / Gelaspan	£4.80			£9.60	4 (3)	1 (1)
Geloplasma		£2.50		£10.00	5 (3)	<1 (<1)
6% Venofundin		£6.30		£25.20	13 (8)	8 (5)
6% Tetraspan		£6.50		£26.00	13 (8)	<1 (<1)
6% Voluven		£7.50		£30.00	15 (10)	2 (1)
6% Volulyte		£7.65		£30.60	16 (10)	<1 (<1)
10% Tetraspan		£9.90		£39.60	20 (13)	5 (3)
5% Albumin		£30.52		£122.08	65 (40)	44 (28)

	Unit Cost for 1000ml bag	Unit Cost for 500ml bag	Unit Cost for 250ml bag	Cost of fluid for resuscitation (2000ml) (a)	Number of extra major complications per 1000 patients that must be avoided for fluid to be cost neutral (including critical care costs)	
					Compared with lowest cost fluid	Compared with next most costly fluid
		(b)				
4.5% Albumin			£17.03 (c)	£136.24	72 (45)	8 (5)

(a)Total cost for fluid resuscitation based on unit costs of 250ml or 500ml bags only when unit costs for 1000 ml bags were not available. It is noted that on a local contract, the availability of bag size may differ. (b) Mid point of range £26.04-£35.00. (c) Mid point of range £12.50-£21.57.

M.4 Discussion

M.4.1 Summary of results

Intravenous fluids used for resuscitation range in acquisition cost. At the extremes of this range, there is a 97 fold difference between the cost of 0.9% sodium chloride (£1.40) and 4.5% Albumin (£136.24). But, on the basis of fluid resuscitation requiring 2000ml of intravenous fluid, we estimate that if 72 or more major complications are avoided per 1000 patients then 4.5% Albumin will be cost saving overall. After adding the cost of critical care 4.5% Albumin would now be cost saving if it prevented 45 major complications per 1000 patients (compared with 72 in the base case).

M.4.2 Incidence of fluid-related complications

The important question is 'Can the choice of fluid prevent these complications?' The clinical review of randomised controlled trials did not find strong evidence to suggest that using different intravenous fluid types for fluid resuscitation would lead to different incidences of fluid related complications. In the case of tetrastarches, the evidence for mortality would suggest more complications (not less) than with the cheaper crystalloids. For severe sepsis it would appear that albumin prevents enough complications to be cost-effective although not cost saving. More research is needed especially with regard to albumin and gelatin.

M.4.3 Limitations / Interpretation

We have estimated the number of major complications that would need to be averted in order for each fluid type to be cost neutral or cost saving. However, even if a fluid prevented fewer major complications it could still be cost saving if in addition it also prevented more minor complications. Furthermore, even if the fluid were not cost saving or cost neutral, it might still be cost-effective if there were a big enough QALY gain associated with preventing complications. Hypothetically, if a major complication was associated with a loss of 0.2 QALYs, then 4.5% Albumin would only have to prevent major complications 23 per 1000 patients (or 19 if we include the critical care costs), assuming a willingness to pay of £20,000 per QALY gained.

The analysis did not take account of fluid volume. In the clinical evidence there was little evidence of a difference in fluid volume, except in the case of albumin vs sodium chloride. But even here it is doubtful that this difference is large enough that a fewer number of bags could be used. Furthermore, if one less bag was required then albumin would still be the most costly fluid in terms

of acquisition cost and that's not even considering the additional costs associated with storing and administering albumin.

It is not easy to tell which fluid is most cost-effective since the number of complications associated with each fluid is unclear from our evidence review and further research is required.

Appendix N: Cost sensitivity analysis: Intravenous fluids for routine maintenance

N.1 Introduction

No studies were identified from published literature that assessed the cost effectiveness of intravenous fluids for the maintenance of fluid and electrolyte status.

The GDG found that the least costly fluid (0.9% Sodium Chloride) is the one of the most prescribed maintenance fluid therapy regimens in their experience. However, it was considered that more expensive types of intravenous fluid (including those containing potassium) may reduce the number of fluid related adverse events, and therefore represent a better use of resources if the reduction of fluid related complications outweighs the additional cost of fluid.

Given the use of different intravenous fluid types for the maintenance of fluid and electrolyte status has significant economic considerations; the GDG judged the identification of optimal types of intravenous fluid for fluid maintenance as the highest economic priority.

The evidence from the systematic review of clinical outcomes was deemed insufficient to develop a cost-effectiveness analysis and therefore a cost analysis was developed instead.

N.2 Methods

N.2.1 Overview

The comparators selected were different types of intravenous fluid fit for the purpose of fluid maintenance as decided by the GDG. In addition to comparing 10 different fluids, there were also four strategies that combine the different fluids by alternating between different types for the same patient. As with the other strategies fluid was restricted to 2L per patient per day but was prescribed in the following ratios:

- 1L 0.9% Sodium Chloride to 2L 5% Dextrose with Potassium (2G/27mmol)
- 1L Hartmann's solution to 1.5L 5% Dextrose with Potassium (3G/40mmol)
- 1L Ringer's Lactate to 1.5L 5% Dextrose with Potassium (3G/40mmol)
- 2L 0.45% Sodium Chloride in 5% Dextrose and Potassium (1.5G/20mmol) to 500ml Sodium Chloride with 5% Dextrose.

The number of bags was estimated from the daily requirement (2L for a 70kg patient) and then rounded to the nearest whole bag.

The population included for the analysis was adults in the hospital requiring intravenous fluid therapy for the maintenance of fluid and electrolyte status.

N.2.2 Approach to Analysis

We calculated the cost of maintenance with each type of fluid for a typical patient. Then we estimated the number of major intravenous fluid related adverse events that would need to be averted to render an intravenous fluid cost neutral compared with the one with the lowest acquisition cost.

Key assumptions:

- The GDG considered the correct volume of intravenous maintenance fluid prescribed per day for a person weighing 70kg to be 1750-2100ml (25-30ml/kg see 5.1, especially Table 9, and 8.5). For simplicity we assumed 2000ml per day.
- According to physiological needs of potassium (1mmol/kg/day), the GDG considered the potassium requirement per 24 hours to be in the range of 56-80 mmol for a 70kg patient (see 5.1, especially Table 9, and 8.5).
- Maintenance fluid therapy was administered for 5 days in the base case analysis.
- Maintenance fluid therapy used 500ml and 1000ml bag sizes only. Only when the unit cost of 1000 ml bag sizes were not available would the unit cost of 500 ml bags be used.
- Administration, storage and monitoring costs were similar across all intravenous fluids used for fluid and electrolyte maintenance. Therefore manpower costs for administering and monitoring intravenous fluid therapy were not included.
- The estimated cost of a major intravenous fluid associated complication (for example oedema see 4.2.4 for other examples) was based on an extended hospital length of stay (including the cost for critical care in a sensitivity analysis).
- Uncertainty around the duration of maintenance fluid therapy was examined by varying the number of days fluid was administered.

N.2.3 Resource Use and Costs

The cost of intravenous fluids therapy per 24 hours was the product of the cost per bag of fluid multiplied by the number of bags required to attain the required daily volume intake. Unit costs for 500ml and 1000ml bags of fluid were provided by the Commercial Medicines Unit (CMU) 2012.[80] In the few cases where prices were not available from the CMU, NHS Trust data was gathered by GDG members.

In the base case, the GDG assumed intravenous fluids for the maintenance of fluid and electrolyte status would be administered for 5 days.

The GDG judged that a major complication would likely require additional hospital stay. Thus, the cost of an intravenous fluid related major complication was taken as a weighted average of all NHS Reference costs 2010-2011 for fluid and electrolyte disorder non-elective inpatient long stay categories KC05 A-F. Each category was weighted according to the number of documented admissions. The result was £1868 for an average hospital length of stay of 6 days. This figure did not include costs for critical care.

N.2.4 Calculations

Since we are only considering the acquisition cost of fluid and the cost of major complications we can say that the cost of strategy i is:

$C_i = C_i^{fluid} + C^{comp} N_i$

Where C_i^{fluid} is the acquisition cost of the fluid, C^{comp} is the cost of a major complication and N_i is the number of complications associated with fluid i.

For a fluid to be cost neutral it follows that

$C_i = C_L$ and

$C_i^{fluid} + C^{comp} N_i = C_L^{fluid} + C^{comp} N_L$

Rearranging, we derive a formula for the number of complications that would need to be averted in order for fluid i to be cost neutral compared with the fluid with the lowest acquisition cost.

$N_L - N_i = (C_i^{fluid} - C_L^{fluid})/C^{comp}$

N.2.5 Sensitivity Analysis

The GDG highlighted that often major adverse events require critical care. The model was modified to consider uncertainty around the cost of an adverse event.

The cost of a Critical Care period was calculated as the weighted average of all NHS Reference costs 2010-2011 for Adult Critical Care 0 to 3 organs supported categories. 2 Each category was assigned weighted according to the number of documented days. GDG judged that support for more than 3 organs would be unlikely for major complications associated with intravenous fluid therapy so only costs associated with providing critical care support for 0-3 organs was included. The cost per critical care period was £1132.

The duration of intravenous fluid therapy was varied within a range of 1 to 10 days.

N.3 Results

The results in Table 36 show that the acquisition cost of maintenance fluid for a 70kg adult for 5 days would range from £7 up to £108. The most costly fluid would need to avert 54 major complications per 1000 maintenance patients for it to be cost neutral compared with the four fluids with the lowest acquisition costs.

Including the cost of critical care stay to the cost of a complication reduces the number of complications per 1000 patients that need to be avoided in order to render a fluid therapy cost neutral (Table 36). It suggests that the most costly fluid would need to avoid 34 complications per 1000 patients to be cost neutral compared to the cheapest fluids.

The number of complications that would be required to achieve cost neutrality or cost savings is sensitive to the duration of fluid use – see Figure 76 Effect of Length of Maintenance Intravenous Fluid Therapy on the number of complications per 1000 patients that a fluid would need to avert to be cost neutral compared with lowest cost maintenance fluid regimen.

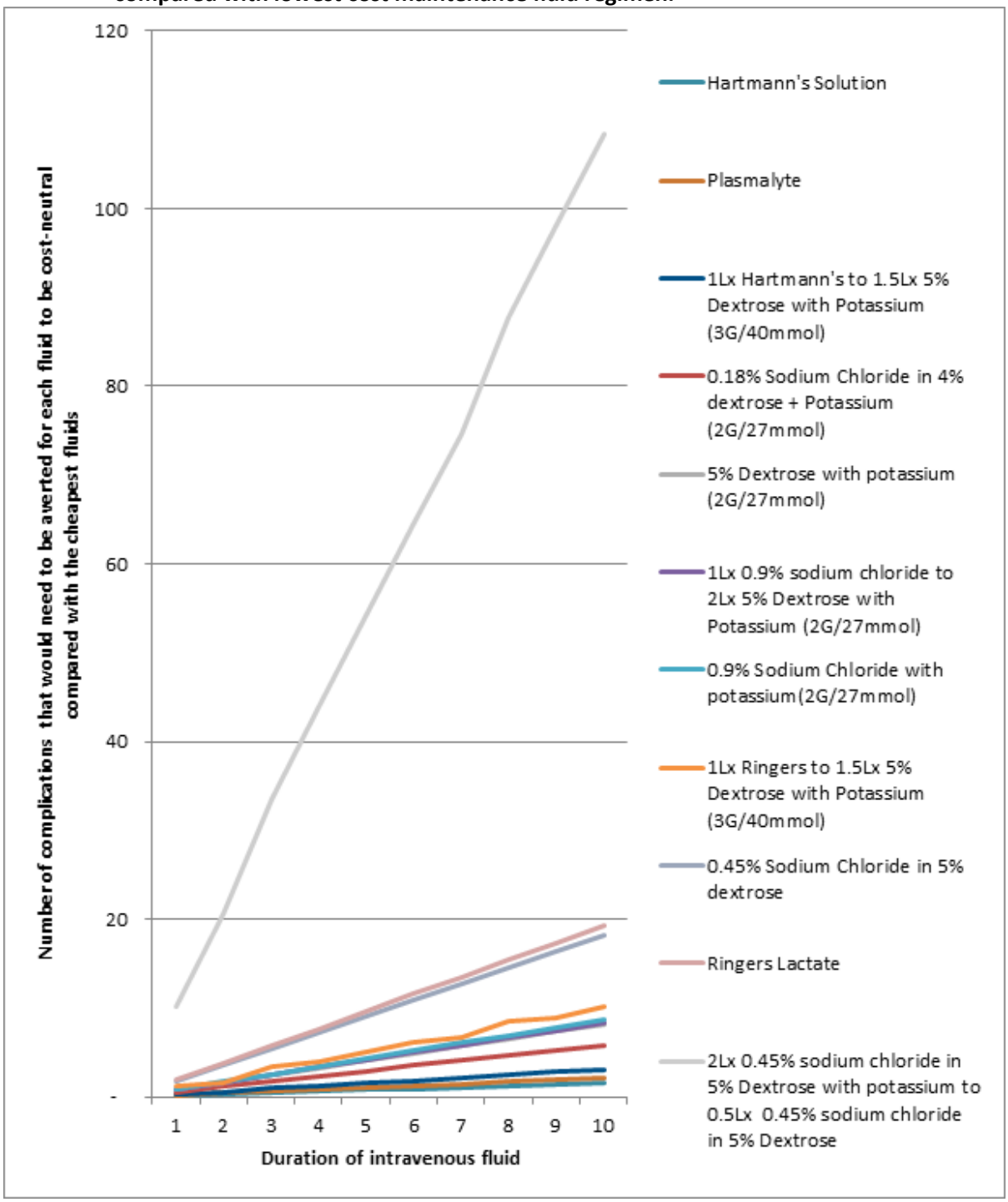
Table 36: Cost of fluids for maintenance

IV fluid type (in order of cost of fluid per patient)	Unit Cost	Cost of fluid per 70kg patient (1)		Number of extra complications per 1000 patients that that would have to be avoided for fluid to be cost neutral		Number of extra complications per 1000 patients that would have be avoided for fluid to be cost neutral including critical care costs	
	1000ml bag	500ml bag		Compared with lowest cost fluids	Compared with next most costly strategy	Compared with lowest cost fluids	Compared with next most costly strategy
0.9% sodium chloride	£0.70	£0.63	£7.00	-		-	
0.18% sodium chloride in 4% dextrose	£0.70	£0.65	£7.00	-	-	-	-
5% Dextrose	£0.70	£0.63	£7.00	-	-	-	-
1Lx 0.9% sodium chloride to 2Lx 5% dextrose	£0.70		£7.00	-	-	-	-
Hartmann's Solution	£0.85	£0.70	£8.50	1	1	1	1
Plasmalyte M	£0.90	£0.80	£9.00	1	0	1	0
1Lx Hartmann's to 1.5Lx 5% Dextrose with Potassium (3G/40mmol)	(2)		£9.88	2	0	1	0
0.18% Sodium Chloride in 4% dextrose + Potassium (2G/27mmol)	£1.25		£12.50	3	1	2	1
5% Dextrose with potassium (2G/27mmol)	£1.46*		£14.64	4	1	3	1
1Lx 0.9% sodium chloride to 2Lx 5% Dextrose with Potassium (2G/27mmol)	(3)		£14.78	4	0	3	0
0.9% Sodium Chloride with potassium(2G/27mmol)	£1.51**		£15.12	4	0	3	0

1Lx Ringers to 1.5Lx 5% Dextrose with Potassium (3G/40mmol)	(4)		£16.48	5	1	3	0
0.45% Sodium Chloride in 5% dextrose		£1.20	£24.00	9	4	6	3
Ringers Lactate		£1.25	£25.00	10	1	6	0
2Lx 0.45% sodium chloride in 5% Dextrose with potassium to 0.5Lx 0.45% NaCl in 5% Dextrose	(5)		£108.16	54	45	34	28

(1) Assumed to be 2000ml per day for 5 days based on unit costs of 500ml bags only when unit costs for 1000 ml bags were not available. It is noted that on a local contract, the availability of bag size may differ.
(2)1L Hartmann's [£0.85] to 1.5 L 5% Dextrose with Potassium (3G/40mmol) [£1.08]*
*(3)1L 0.9% Sodium Chloride [£1.51**] to 2L 5% Dextrose with Potassium (2G/27mmol)[£1.46*]*
(4)1L [2 bags of 500ml @ £1.25 each] Ringer's Lactate to 1.5L 5% Dextrose with Potassium (3G/40mmol) [£1.46]*
*(5) 2L [4 bags of 500ml@ £6.46*** each] 0.45% Sodium Chloride with 5% Dextrose and Potassium 1.5G/20mmol to 500ml Sodium Chloride with 5% Dextrose [£1.20]*
Unit costs are from the Department of Health Comercial Medicines Unit except where denoted as follows:
**Supplied by an NHS Trust which wished to remain anonymous.*
***Both the Pharmacy Department of Brighton and Sussex University Hospitals NHS Trust and an NHS Trust which wished to remain anonymous reported £1.51.*
**** Average of two prices from the Pharmacy Department of Brighton and Sussex University Hospitals NHS Trust (£6.78) and an NHS Trust which wished to remain anonymous (£6.13).*

Figure 76: Effect of Length of Maintenance Intravenous Fluid Therapy on the number of complications per 1000 patients that a fluid would need to avert to be cost neutral compared with lowest cost maintenance fluid regimen.



N.4 Discussion

N.4.1 Summary of results

Maintenance fluid regimens range in acquisition cost. At the extremes of this range, one fluid was 7 times more costly than the four cheapest fluids. But, on the basis of a 5-day therapy duration and other key assumptions, we estimate that if 54 or more complications are avoided per 1000 patients then fluid regimen 0.45% Sodium Chloride with 5% Dextrose with potassium (1.5g/20mmol) will be cost saving overall. After adding the cost of critical care, fluid regimen 0.45% Sodium Chloride with 5% Dextrose with potassium (1.5g/20mmol) would now be cost saving if it prevented 34 complications per 1000 patients (compared with 62 complications in the base case). The longer the duration of fluid, the more complications need to be averted to justify the extra cost.

The lowest cost fluids were 0.9% sodium chloride, 0.18% sodium chloride in 4% glucose and 5% glucose. However, the GDG do not believe that these fluids would effectively meet bodily requirements for electrolytes. The cheapest fluid that would meet bodily fluid and electrolyte requirements (see 5.1, especially Table 9) was 0.18% sodium chloride in 4% glucose plus porassium (2G/27mmol, 0.2% concentration) at a cost of £12.50 extra per patient over 5 days and would need to prevent 2 or 3 complications per 1000 patients to be cost neutral.

N.4.2 Incidence of fluid-related complications

Published observational evidence suggests that the incidence of intravenous fluid associated complications is high in post-operative patients. [100,386,387] It appears that fluid associated morbidity is widely observed; specifically, cardiovascular complications including tachyarrhythmia and dysrhythmia, fluid overload, and pulmonary oedema. These fluid related complications were observed in at least 7% to as many as 54% of post-operative patients in these studies. [100,386,387] Patients with complications appeared to spend an additional 2.5 days in hospital compared to patients without complications. 10 In one study, two out of three patients who developed pulmonary oedema experienced unplanned critical care admissions. [387]

But the important question is 'Can the choice of fluid prevent these complications?' The clinical review did not find evidence from randomised controlled trials to suggest that using different intravenous fluid types for fluid maintenance would lead to different incidences of fluid related complications. Future research in this area is needed to clarify and confirm whether different fluid types confer different health benefits. Given the poor quality of the evidence decided that it would be appropriate to consider the physiological requirements (see 5.1, especially Table 9).

N.4.3 Limitations / Interpretation

We have estimated the number of major complications that would need to be averted in order for each fluid type to be cost neutral or cost saving. However, even if a fluid prevented fewer major complications it could still be cost saving if it prevented more minor complications or otherwise improved the patient's health. Furthermore, even if the fluid were not cost saving or cost neutral, it might still be cost-effective if there were a big enough QALY gain associated with preventing complications. Hypothetically, if a major complication was associated with a loss of 0.2 QALYs, then fluid regimen 0.45% Sodium Chloride with 5% Dextrose with potassium (1.5g/20mmol) would only have to prevent complications 20 per 1000 patients or 17 if we include the critical care costs), assuming a willingness to pay of £20,000 per QALY gained.

The results should be taken as indicative. However, the cost of fluids varies considerably according to local contracts. Furthermore prices are dependent on the quantity ordered, such that if the NHS were to invest significantly in one of the fluids that appear more costly in this analysis, that could potentially bring the price down close to that of one of the cheaper fluids.

Appendix O: Research recommendations

1. Research question: What is the incidence of complications during, and as a consequence of, IV fluid therapy?

Why this is important?

This is almost certainly under-reported in the ward setting with significant implications for patients, predominantly morbidity through to mortality. It is probable that complications of fluid therapy are frequent and may be associated with increased clinical needs, such as critical care and, on occasion, may necessitate resuscitation. Lack of a set of clearly defined features of the complications of fluid mismanagement compounds the problem. It is important to define these features and then undertake an observational study in a hospital setting to determine the epidemiology of these complications. Such a study would highlight the prevalence of fluid related complications and inform the development of preventive measures.

Criteria for selecting high-priority research recommendations

PICO question	Primary: What is the frequency of a series of complications during, or as a consequence of, IV fluid management? Secondary: Using these criteria, can we identify the morbidity and long-term consequences of these complications in terms of escalated care, length of stay and other secondary complications?
Importance to patients or the population	By defining the prevalence of the problem, risk factors can then be identified and mechanisms can be put in place to identify and prevent these complications occurring. This would have a significant impact on patient safety in a relatively large hospital-patient population.
Relevance to NICE guidance	It would provide the currently unavailable information about the iatrogenic issues surrounding fluid management, create a monitoring and audit system , identify risk factors and facilitate preventive measures. It might also provide a research tool to investigate fluid management in the ward and other environments.
Relevance to the NHS	We perceive this to be a common set of problems. Each has an immediate impact on patients themselves and results in a range of seriousness of complications, all of which will need lesser or greater intervention. We think it will identify problems that prolong patient stays and may also impact on mortality either directly or indirectly.
National priorities	This is a major patient safety issue, which to date has not been recognised.
Current evidence base	There is no current evidence base but hospital doctors will confirm that the problem exists. It has never been studied and as stated, there are no basic definitions of what constitutes a fluid management problem. There are no epidemiological data and no trials, observational or otherwise.
Equality	It is for all hospital patients in ward environments that need IV fluids, but it also applies in other areas, such as critical care units and theatres.
Study design	Because this has no obvious data base, it requires an initial observational study to establish the epidemiology of the problem. The results from this study can be used to try to identify risk factors and causative issues. The study could then be followed through to assess outcomes from these problems in the intermediate and long term, focusing on requirements for escalation of treatment, treatment other than for the primary problem, that is, treatment of the iatrogenic problem, other secondary issues and length of stay. It should then be developed into a national audit system and eventually become a quality indicator.

Feasibility	The study is observational – it will have a potential immediate benefit to patients being observed. It is an assessment of current management and a form of quality assurance, so ethically it should pose few problems. It should be relatively simple to implement across wards and will have relatively modest costs. A pilot study could be performed in a matter of months and provide a rich source of information on how to expand the system, which should eventually evolve into a useful hospital audit tool. Issues will include educating doctors and nurses to identify and record these 'new' episodes. It will require a robust recording system.
Other comments	Potential funding – not known. Not previously examined systematically but anecdotal reports suggest t is a relatively common problem.
Importance	This is a very important question to the overall guideline as the information provided will underpin the necessity of the guideline and provide an ongoing method to ensure improvement in fluid management at the bedside, while providing valuable, educational information that can be used to develop a robust audit tool. High: the research is essential to inform future updates of key recommendations in the guideline.

2. Research question: Are balanced solutions superior to sodium chloride 0.9% for the resuscitation of patients with acute shock?

Why this is important?

Physiological studies, large cohort studies and small randomised studies have shown that balanced crystalloids may be superior to sodium chloride 0.9% for the treatment of surgical patients. However, the quality of the evidence is poor. These studies have shown that, when compared with sodium chloride 0.9%, there is less disturbance in acid–base balance (hyperchloraemic acidosis), acute kidney injury, the need for renal replacement therapy, blood loss and overall complication rates with balanced crystalloids. However, large randomised trials have shown that crystalloids are superior to colloids for resuscitation. In these studies colloids were given for prolonged periods of time and the groups of patients included were heterogenous. The proposed trial will help validate whether the data gathered from physiological studies and cohort studies that compared sodium chloride 0.9% with balanced crystalloids translate into relevant clinical benefit in patients needing acute fluid resuscitation, and will be a valuable guide to clinical practice.

Criteria for selecting high-priority research recommendations

PICO question	Population: Acutely shocked patients presenting to the Accident and Emergency Department Intervention: Resuscitation with 0.9% saline OR a balanced crystalloid (e.g. Hartmann's/Ringer's Lactate/Plasmalyte – Fluids to be given in the first 6 hours of resuscitation Comparison: Resuscitation with 0.9% saline compared to a balanced crystalloid Outcomes: Post-resuscitation complications (Clavien-Dindo classification) Incidence of acute kidney injury/need for renal replacement therapy Length of hospital stay Mortality Incidence of acidosis/need for bicarbonate to correct acidosis Volume of fluid needed to complete acute resuscitation

Importance to patients or the population	Balanced crystalloids may help reduce complications and length of hospital stay, resulting in better patient outcomes.
Relevance to NICE guidance	If the hypothesis is proven, this study could generate Grade A evidence for the use of balanced crystalloids for resuscitation of the acutely shocked patient.
Relevance to the NHS	Would help improve patient outcomes, reduce hospital stay and reduce NHS costs.
National priorities	NICE Intravenous fluid therapy Guidance.
Current evidence base	NICE Intravenous fluid therapy Guidance. Physiological studies, large cohort studies and small randomised studies have shown that balanced crystalloids may be superior to 0.9% saline for the management of surgical patients, however, the quality of the evidence is poor and there are no large randomised trials. On the other hand, large randomised trials have shown that crystalloids are superior to colloids for resuscitation. However, in these studies colloids were given for prolonged periods of time and the groups of patients included were heterogenous. Hence, the proposed trial will be timely and a valuable addition to the knowledge base.
Equality	None identified.
Study design	RCT. Power calculations should be conducted to establish the required sample size of the trial. It is important that the study is adequately powered to detect a clinically important effect size.
Feasibility	Can the proposed research be carried out in a realistic timescale and at an acceptable cost? Yes Are there any ethical or technical issues? No
Other comments	This issue has not been addressed previously. It could be undertaken as a partnership between National Funding Bodies (e.g. Research Councils and Industry.
Importance	High: the research is essential to inform future updates of key recommendations in the guideline

3. Research question: Are balanced crystalloids superior to a combination of a balanced crystalloid and a gelatin suspended in a balanced solution for the resuscitation of patients with acute shock?

Why this is important?

Recent large randomised controlled trials suggest that crystalloids (sodium chloride 0.9% or balanced solutions) are superior to 6% hydroxyethyl starch for resuscitation. Mortality and complication rates, especially renal complications, may be increased with 6% hydroxyethyl starch. However, there is a lack of good-quality evidence on the use of gelatin for resuscitation. Some randomised controlled trials have shown that when colloids are used for resuscitation, volumes of fluid required may be less than with crystalloids. It must be remembered that colloids cannot be used exclusively for resuscitation and that some free water must be provided, and there are limited data on the use of gelatins for resuscitation. The proposed trial will help inform whether a combination of gelatin and crystalloid is superior to crystalloid alone for the resuscitation of patients with acute shock.

Criteria for selecting high-priority research recommendations

PICO question	Population: Acutely shocked patients presenting to the Accident and Emergency Department Intervention: Resuscitation with a balanced crystalloid (e.g. Hartmann's/Ringer's Lactate/Plasmalyte and a combination of a gelatin in a balanced crystalloid and a balanced crystalloid – Fluids to be given in the first 6 hours of resuscitation Comparison: Each other Outcomes: Post-resuscitation complications (Clavien-Dindo classification) Incidence of acute kidney injury/need for renal replacement therapy Length of hospital stay 7-day, 30-day and 90-day Mortality Volume of fluid needed to complete acute resuscitation Post-resuscitation fluid requirements
Importance to patients or the population	A combination of a gelatin with a balanced crystalloid may help reduce complications and length of hospital stay, resulting in better patient outcomes.
Relevance to NICE guidance	If the hypothesis is proven, this study could generate Grade A evidence for the use of a combination of a gelatin with a balanced crystalloid for resuscitation of the acutely shocked patient.
Relevance to the NHS	Would help improve patient outcomes, reduce hospital stay and reduce NHS costs.
National priorities	NICE Intravenous fluid therapy Guidance.
Current evidence base	NICE Intravenous fluid therapy Guidance. Recent large randomised controlled trials suggest that crystalloids (0.9% saline or balanced solutions) are superior to 6% hydroxyethyl starch for resuscitation. Mortality and complication rates, especially renal complications, may be increased with the latter. However, patient groups were heterogenous and patients in both arms of the trials received similar volumes of fluid. This has led, somewhat prematurely, to the recommendation that colloids should not be used for resuscitation. It has been shown in randomised controlled trials that when colloids are used for resuscitation, volumes of fluid are less and that physiological endpoints are achieved sooner than with crystalloids. It must be remembered that colloid cannot be used exclusively for resuscitation and that some free water must be provided, and there are limited data on the utility of gelatins for resuscitation. Hence, the proposed trial will be timely and a valuable addition to the knowledge base.
Equality	No issues identified.
Study design	RCT. Power calculations should be conducted to establish the required sample size of the trial. It is important that the study is adequately powered to detect a clinically important effect size.
Feasibility	Can the proposed research be carried out in a realistic timescale and at an acceptable cost? Yes Are there any ethical or technical issues? No
Other comments	This issue has not been addressed previously. It could be undertaken as a partnership between National Funding Bodies (e.g. Research Councils and Industry.
Importance	High: the research is essential to inform future updates of key recommendations in the guideline

4. Research question: When undertaking perioperative goal-directed fluid therapy, does the choice of fluid affect complications and hospital length of stay?

Why is this important?

Several studies have shown reduced lengths of stay and reduced complications after a variety of surgical procedures when fluid therapy is optimised by targeting various haemodynamic goals (goal-directed therapy [GDT]). The most common haemodynamic goal has been optimal stroke volume, as measured by oesophageal doppler or an alternative non-invasive technique. Most studies have used colloids (hydroxyethyl starch or gelatin), although some have used crystalloid.

Colloids are more expensive than crystalloids and recent data indicate that hydroxyethyl starch is associated with an increased risk of acute kidney injury in patients with sepsis. If colloids are to be used as the default fluid for perioperative GDT, there should be clear evidence for their benefit over crystalloids.

There is evidence showing benefit of physiological (or balanced) fluids compared with saline-based fluids; therefore, it would seem appropriate to undertake a blinded, randomised controlled trial of colloid in balanced solution compared with a balanced crystalloid solution for perioperative GDT. If mortality is to be the primary end point for such a study, then prohibitively large numbers of patients would need to be enrolled. Other achievable outcomes include hospital length of stay, recovery of gut function (for gastrointestinal surgery) and complications such as renal impairment, infection, pulmonary oedema and myocardial infarction. Such a study should be designed to show non-inferiority for crystalloid versus colloid.

Criteria for selecting high-priority research recommendations

PICO question	Population: Patients undergoing major surgery (elective and emergency) Intervention: Goal-directed fluid therapy targeted at optimising stroke volume Comparison: Colloid (gelatin or hydroxyethyl starch) in balanced solution versus a balanced solution of crystalloid (for example, Plasma-Lyte 148) Outcomes: Length of hospital stay, time to recovery of bowel function (if gastrointestinal surgery); complications: renal impairment, infection, pulmonary oedema and myocardial infarction
Importance to patients or the population	Optimising outcome and reducing length of stay after major surgery
Relevance to NICE guidance	Enabling guidance of choice of fluid based on high-quality evidence
Relevance to the NHS	A study showing non-inferiority for crystalloid for perioperative GDT would enable considerable cost savings
National priorities	No relevant national priorities
Current evidence base	A recent double-blinded pilot study (50 patients undergoing surgery for ovarian cancer) compared balanced crystalloid with balanced hydroxyethyl starch solution using a goal-directed haemodynamic algorithm. The colloid was associated with better haemodynamic stability. (Feldheiser A et al. [2013] British Journal of Anaesthesia 110: 231–40)
Equality	None identified
Study design	Double-blinded, RCT powered to show non-inferiority of crystalloid compared with colloid
Feasibility	The proposed research should be carried out within a realistic timescale and cost. A pilot study involving 50 patients has already been published
Other comments	None
Importance	High: the research is essential to ensure cost-effective perioperative fluid

	therapy

5. Research question: Does a higher sodium content IV fluid regimen for maintenance reduce the risk of developing hyponatraemia and volume depletion without increasing risk of volume overload in hospitalised adults?

Why is it important?

Patients who cannot meet their daily needs of fluids and electrolytes through oral or enteral routes but are otherwise euvolaemic often need IV fluid therapy for maintenance. The most common complications of this therapy are hyponatraemia (if excessive IV water is administered), volume overload (if excessive sodium and water are administered) and volume depletion and/or acute kidney injury (if inadequate sodium and water are administered). There are no published trials considering what the optimal IV fluid regimen for maintenance is.

A randomised controlled trial is needed to compare IV fluid maintenance regimens with different sodium concentrations (for example, comparison between sodium chloride 0.18% in glucose 4% and sodium chloride 0.45% in glucose 4% solutions) in terms of the above detailed complication rates, cost and other clinical outcomes (for example, length of stay). The patient group will be heterogeneous, and analysis should consider both 'medical' and 'surgical' patients.

Criteria for selecting high-priority research recommendations

PICO question	Population: Adult hospitalised patients needing IV fluids for maintenance (as defined by the NICE guidance) Intervention: Administration of IV fluids Comparison: Sodium chloride 0.18% in glucose 4% and sodium chloride 0.45% in glucose 4% solutions with 1 mmol/kg/day potassium. (For simplicity, suggest using 1.5 litres if weight is under 50 kg, 2 litres if weight is 51–70 kg and 2.5 litres if weight is above 70 kg with 1 mmol/kg/day of potassium) Outcomes: Development of fluid-related complications (volume overload, including peripheral oedema and pulmonary oedema attributable to IV fluids, hyponatraemia, volume depletion and dehydration), length of stay and 28-day mortality Economic analysis
Importance to patients or the population	Reducing fluid-related complications by optimising fluid regimens would reduce morbidity, mortality and costs of treatment of adult hospitalised patients needing IV fluid therapy. Moreover, addressing this research question will increase awareness of the importance of encouraging rapid return to the use of enteral route for hydration to reduce complications from IV fluid therapy.
Relevance to NICE guidance	May inform guidance on the solution of choice in this clinical context May have more general relevance to the wider population of patients receiving IV fluids
Relevance to the NHS	May demonstrate the potential for significant bed-day savings and reduce the length and cost of hospital stays, reducing complication and use of resources
National priorities	N/A
Current evidence base	There is no published evidence addressing this question. There is a large variability in practice across the NHS
Equality	N/A
Study design	Prospective randomised controlled trial is proposed. Blinding is feasible for the first 24 hours. Prescribing after the first 24 hours will be based on a pre-designed protocol guided by changes in patients' fluid status and electrolyte

	measurements.
Feasibility	No ethical or technical issues. A multicentre approach will be essential because using the strict definition of patients needing IV fluid for maintenance will result in numbers being small and the patient group will be heterogeneous.
Other comments	N/A
Importance	High: the research is essential to inform future updates of key recommendations in the guideline

6. Research question: Does the introduction of hospital systems that ensure:

- **all hospital healthcare professionals involved in prescribing and delivering IV fluid therapy are appropriately trained in the principles of fluid prescribing; and**
- **all IV fluid therapy related complications are reported;**

lead to a reduction in fluid related complications and associated healthcare costs?

Why is this important?

Despite the fact that assessment of a patient's IV fluid needs and prescription of an appropriate IV fluid regimen can be complex, the job is often delegated to healthcare professionals with limited experience and little or no relevant training. Errors in prescribing IV fluids and electrolytes are thought to be common and associated with unnecessary morbidity, mortality and increased healthcare costs. The problems are most likely to occur in emergency departments, acute admission units and medical and surgical wards rather than operating theatres and critical care units, since the staff in more general hospital areas have less relevant expertise, and standards of recording and monitoring of IV fluid and electrolyte therapy can be poor. In addition, the consequences of IV fluid mismanagement are not widely reported. It would be useful to undertake this study to evaluate and audit the effects of introducing training and governance initiatives in the NHS.

Criteria for selecting high priority research recommendations

PICO question	Population: Adult hospital patients in emergency departments, acute admission units and medical and surgical wards, who need IV fluid therapy. Intervention: Introduction of clinical governance systems to ensure that: a. all healthcare professionals involved in prescribing and delivering IV fluid therapy in hospitals are appropriately trained on the principles of IV fluid prescription; b. all patients on IV fluids are appropriately monitored and reassessed on a regular basis; and c. all Comparison: Current standards of care. Outcomes: Morbidity, mortality, length of stay and full financial costs of clinical problems related to the under- or over-provision of fluid or electrolytes in IV fluid therapy.
Importance to patients or the population	It is anticipated that the introduction of proper systems to ensure higher standards of IV fluid prescribing and administration will significantly reduce risks and cost related to under-hydration, over-hydration and electrolyte abnormalities currently caused by inapprorpiate IV fluid therapy, with consequent reductions in morbidity, mortality, length of stay and financial costs.
Relevance to NICE guidance	Research in this area would support or appropriately modify the many NICE recommendations on IV fluid therapy which have had to be based on

	physiological and clinical principles due to the lack of direct evidence.
Relevance to the NHS	Research in this area would clarify the costs and benefits of investing in clinical governance systems to ensure optimal IV Fluid prescribing with probable significant reduction in overall costs.
National priorities	No relevant national priorities
Current evidence base	Although there is some audit evidence that standards of knowledge and training in the area of IV fluid prescribing are very poor, there is little or no evidence that improving those standards will be effective in reducing clinical problems and costs.
Equality	None identified.
Study design	Details of methodology would need careful consideration but these questions could be addressed by either a cluster-randomized RCT with interventions at whole ward level or a step-wedge design.
Feasibility	This proposed research should be able to be carried out within a realistic timescale and cost.
Other comments	None
Importance	High: the research is essential to confirm that investments in improving standards of IV fluid therapy are worthwhile.

Appendix P: Useful information

P.1 Composition of commonly used crystalloids

Table 37: Composition of electrolytes in commonly used crystalloids (fluids reviewed as part of clinical evidence)

Content	Plasma	Sodium chloride 0.9%*	Sodium chloride 0.18%/ 4% glucose(a)	0.45% NaCl/ 4% glucose(a)	5% glucose(a)	Hartmann's	Lactated Ringer's (USP)	Ringer's acetate	Alternative balanced solutions for resucitation**	Alternative balanced solutions for maintenance**
Na+ (mmol/l)	135-145	154	31	77	0	131	130	130	140	40
Cl– (mmol/l)	95-105	154	31	77	0	111	109	112	98	40
[Na+]:[Cl–] ratio	1.28 - 1.45:1	1:1	1:1	1:1	-	1.18:1	1.19:1	1.16:1	1.43:1	1:1
K+ (mmol/l)	3.5-5.3	*	*	*	*	5	4	5	5	13
HCO3 – / Bicarbonate	24-32	0	0	0	0	29 (lactate)	28 (lactate)	27 (acetate)	27(acetate) 23(gluconate)	16(acetate)
Ca2+ (mmol/l)	2.2-2.6	0	0	0	0	2	1.4	1	0	0
Mg2+ (mmol/l)	0.8-1.2	0		0		0	0	1	1.5	1.5
Glucose (mmol/ l)	3.5-5.5	0	222(40 g)	0	278(50 g)	0	0	0	0	0
pH	7.35-7.45	4.5-7.0	4.5		3.5-5.5	5.0-7.0	6-7.5	6-8	4.0-8.0	4.5-7.0
Osmolarity (mOsm/l)	275-295	308	284		278	278	273	276	295	389

** These solutions are available with differing quantities of potassium already added, and the potassium containing versions are usually more appropriate for meeting maintenance needs.*

***Alternative balanced solutions are available commercially under different brand names and composition may vary by preparation*

(a) The term dextrose refers to the dextro-rotatory isomer of glucose that can be metabolised and is the only form used in IV fluids. However IV fluid bags are often labelled as glucose so only this term should be used. Traditionally hospitals bought a small range of fluids combining saline (0.18-0.9%) with glucose but several recent NICE/NPSA documents have recommended specific combinations, which are now purchased to enable guidelines to be followed. Glucose–saline combinations now come in 5 different concentrations, and the addition of variable potassium content expands the pre-mixed range to 13 different products. Prescribers must therefore specify the concentration of each component; the term dextrose-saline (or abbreviation D/S) is meaningless without these details. What is specified also impacts significantly on the cost of the product.

P.2 Composition of commonly used colloids

Table 38: Composition of electrolytes in commonly used colloids (fluids reviewed as part of clinical evidence)

Content (Values reported as ranges)	Gelatin*	Tetrastarch*	Albumin*
Sodium (mmol/l)	145-154	137-154	100-160
Chloride (mmol/l)	103-145	118-154	128
Potassium(mmol/l)	4-5.1	4	≤2mmol
Magnesium(mmol/l)	1	1-1.5	-
Acetate(mmol/l)	24	24-34	-
Malate(mmol/l)	-	5	-
Octanoate(mmol/l)	-	-	6.4
Calcium(mmol/l)	1-6.5	2.5	-
Average molecular weight	30000-35000	130000	-
Molar substitution	-	0.4-0.42	-
Weight of colloid per litre	35grams (3.5%)-40grams (4%)	60grams (6%)	-
pH	7.1-7.7	4.5-6.5	-
Theoretical osmolarity	274-301	286.5-308	274
Sodium: chloride ratio	1-1.47:1	1-1.25:1	-
Colloid osmotic pressure ay 37 degree Celsius	25.7-33.3	36	-

**Fluids are available commercially under different brand names in each class and composition may vary by preparation*

P.3 Consequences of fluid mismanagement to be reported as critical incidents

Table 39: Consequences of fluid mismanagement to reported as critical incidents

Consequence of fluid mismanagement	Identifying features	Time frame of identification
Dehydration	• Patient's fluid needs not met by oral or enteral intake and • Features of dehydration on clinical examination • Low urine output or concentrated urine • Biochemical indicators, such as more than 50% increase in urea or creatinine with no other identifiable cause	Before and during IV fluid therapy
Pulmonary oedema (breathlessness during infusion)	• No other obvious cause identified (for example, pneumonia, pulmonary embolus or asthma) • Features of pulmonary oedema on clinical examination	During IV fluid therapy or within 6 hours of stopping IV fluids

Consequence of fluid mismanagement	Identifying features	Time frame of identification
	• Features of pulmonary oedema on X-ray	
Hyponatraemia	• Serum sodium less than 130 mmol • No other likely cause of hyponatraemia identified	During IV fluid therapy or within 24 hours of stopping IV fluids
Hypernatremia	• Serum sodium 155 mmol/l or more • Baseline sodium normal or low • IV fluid regimen included 0.9% sodium chloride • No other likely cause of hypernatremia identified	During IV fluid therapy or within 24 hours of stopping IV fluids
Peripheral oedema	• Pitting oedema in extremities and/or lumbar sacral area • No other obvious cause identified (for example, nephrotic syndrome or known cardiac failure)	During IV fluid therapy or within 24 hours of stopping IV fluids
Hyperkalaemia	• Serum potassium more than 5.5 mmol	During IV fluid therapy or within 24 hours of stopping IV fluids
Hypokalaemia	• Serum potassium less than 3.0 likely to be due to infusion of fluids without adequate potassium provision • No other obvious cause (for example, potassium-wasting diuretics, re-feeding syndrome)	During IV fluid therapy or within 24 hours of stopping IV fluids
Abbreviation: IV, intravenous		

P.4 Table to calculate dose of fluid replacement by body weight

Table 40: IV fluid prescription (by body weight) for routine maintenance over a 24-hour period

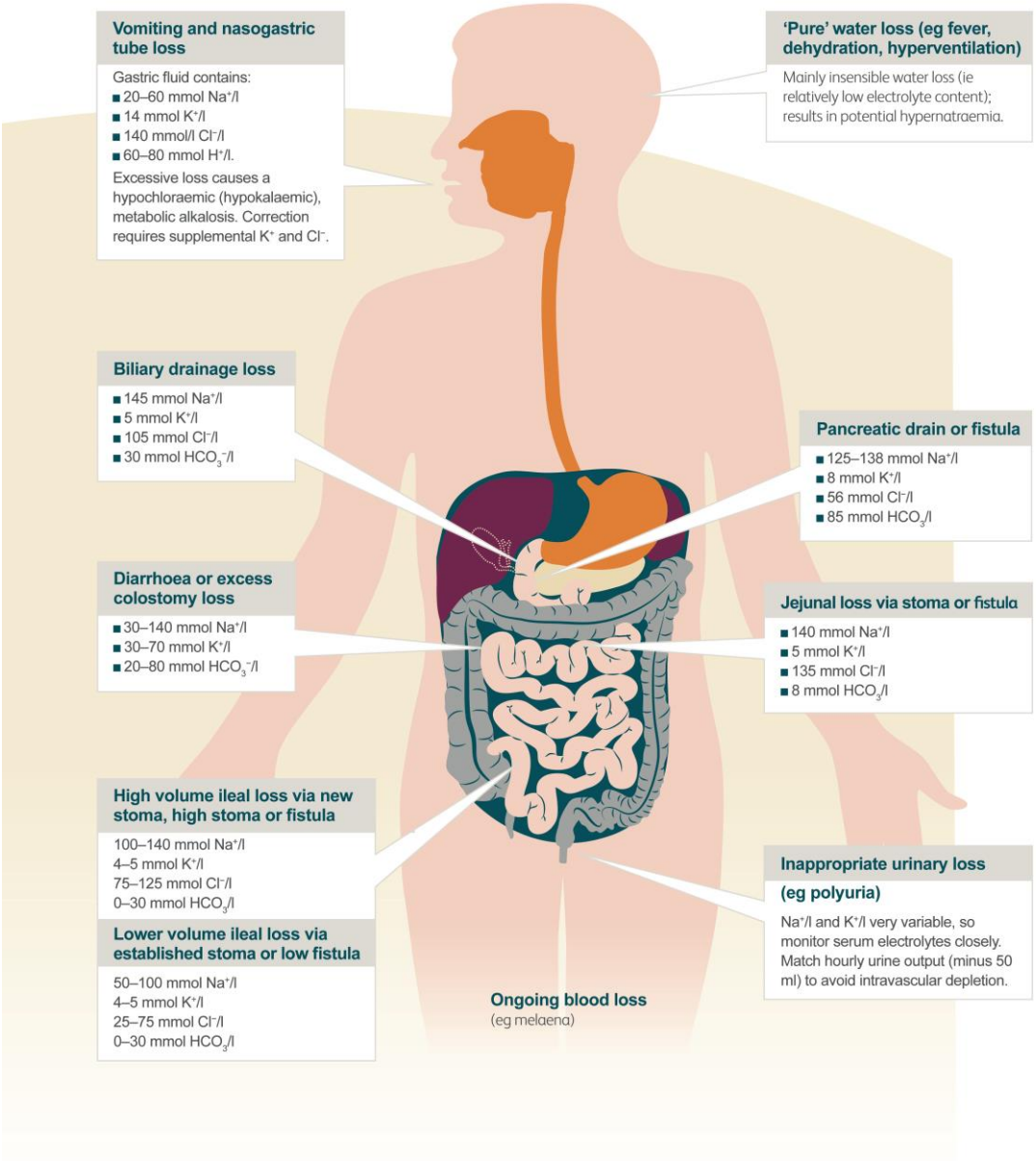
Body weight	Water	Sodium, chloride, potassium		Body weight	Water	Sodium, chloride, potassium
kg	25–30 ml/kg/day	approx. 1 mmol/kg/day of each		kg	25–30ml/kg/day	approx. 1 mmol/kg/day of each
40	1000–1200	40		71	1775–2130	71
41	1025–1230	41		72	1800–2160	72
42	1050–1260	42		73	1825–2190	73
43	1075–1290	43		74	1850–2220	74
44	1100–1320	44		75	1875–2250	75
45	1125–1350	45		76	1900–2280	76
46	1150–1380	46		77	1925–2310	77
47	1175–1410	47		78	1950–2340	78
48	1200–1440	48		79	1975–2370	79
49	1225–1470	49		80	2000–2400	80
50	1250–1500	50		81	2025–2430	81
51	1275–1530	51		82	2050–2460	82
52	1300–1560	52		83	2075–2490	83
53	1325–1590	53		84	2100–2520	84

54	1350–1620	54		85	2125–2550	85
55	1375–1650	55		86	2150–2580	86
56	1400–1680	56		87	2175–2610	87
57	1425–1710	57		88	2200–2640	88
58	1450–1740	58		89	2225–2670	89
59	1475–1770	59		90	2250–2700	90
60	1500–1800	60		91	2275–2730	91
61	1525–1830	61		92	2300–2760	92
62	1550–1860	62		93	2325–2790	93
63	1575–1890	63		94	2350–2820	94
64	1600–1920	64		95	2375–2850	95
65	1625–1950	65		96	2400–2880	96
66	1650–1980	66		97	2425–2910	97
67	1675–2010	67		98	2450–2940	98
68	1700–2040	68		99	2475–2970	99
69	1725–2070	69		100	2500–3000	100
70	1750–2100	70		>100	2500–3000	100

1. Add 50-100 grams/day glucose (e.g. glucose 5% contains 5g/100ml).

2. For special considerations refer to the recommendations for routine maintenance.

P.5 Diagram of ongoing losses



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