WHO Surgical Site Infection Prevention Guidelines
Web Appendix 16
Summary of a systematic review on the maintenance of adequate circulating volume control/normovolemia

1. Introduction

Wound healing and resistance to infection are dependent on tissue oxygen tension. Sufficient tissue oxygenation is essential for collagen synthesis and wound repair and is improved by adequate arterial oxygenation. Ideally, perioperative fluid therapy prevents tissue hypoxia by maximizing the cardiac output and thus improving arterial oxygenation. However, the optimal perioperative fluid strategy remains a subject of debate. A large variability exists between regimens in daily practice and both fluid overload (hypervolemia) and hypovolemia have been associated with increased mortality and morbidity.

Fluid overload leads to a decrease in muscular oxygen tension. Due to surgical trauma, a systemic inflammatory response arises, which leads to a fluid shift to the extravascular space. Following a large fluid shift, generalized oedema may occur, which decreases tissue oxygenation and impedes tissue healing. By contrast, hypovolemia leads to arterial and tissue hypoxia due to a decrease in cardiac output. The optimal fluid (colloid or crystalloid) or strategy of fluid management (goal-directed, liberal or restricted) remains a subject of controversy.

Goal-directed fluid therapy (GDFT) uses cardiac output or similar parameters to guide intravenous fluid and inotropic administration. The disadvantage associated with GDFT is the difficulty in adequately assessing normovolemia. Liberal and restrictive fluid strategies use standard fluid regimens not based on cardiac output and an adequate assessment of normovolemia in these strategies remains complicated. In addition, the physiological effects of any given volume of fluid may differ, depending on the magnitude of the surgical stress response and not solely on the volume of fluids administered. At present, there is no universal definition of normovolemia or standardized method to assess it. Some studies assess normovolemia by urinary output, whereas other studies use more invasive techniques, such as cardiac output or cardiac index.

A systematic review published in 2011 assessed the effect of GDFT on surgical site infection (SSI) and other infection rates in patients undergoing surgery and found that it significantly reduces the risk of infection compared with standard haemodynamic fluid therapy. Few organizations have issued recommendations regarding the maintenance of normovolemia. The United Kingdom (UK)-based National Institute for Health and Care Excellence (NICE) recommends maintaining adequate perfusion during surgery. Based on an evidence update in 2013, it is stated that haemodynamic GDFT appears to reduce SSI rates. The guidelines of the Society for Healthcare Epidemiology of America (SHEA)/Infectious Diseases Society of America (IDSA) do not formulate any specific recommendation for the maintenance of normovolemia with the purpose of preventing SSI. However, in a statement on oxygen therapy, it is indirectly recommended to maintain an appropriate volume replacement.
2. **PICO question**

Does the use of specific fluid management strategies during surgery affect the incidence of SSI?

- **Population:** inpatients and outpatients of any age undergoing surgical operation (any type of procedure)
- **Intervention:** specific fluid management strategies during surgery
- **Comparator:** standard fluid management during surgery
- **Outcomes:** SSI, SSI-attributable mortality

3. **Methods**

The following databases were searched: Medline (OvidSP); Excerpta Medica Database (EMBASE); Cumulative Index to Nursing and Allied Health Literature (CINAHL); Cochrane Central Register of Controlled Trials (CENTRAL); and WHO regional medical databases. The time limit for the review was between 1 January 1990 and 17 January 2014. Language was restricted to English, French and Spanish. A comprehensive list of search terms was used (Appendix 1).

Two independent reviewers screened the titles and abstracts of retrieved references for potentially relevant studies. The full text of all potentially eligible articles was obtained and two authors independently reviewed these for eligibility based on inclusion criteria. Duplicate studies were excluded.

The two authors extracted data in a predefined evidence table (Appendix 2) and critically appraised the retrieved studies. Quality was assessed using the Cochrane Collaboration tool to assess the risk of bias of randomized controlled studies (Appendix 3). Any disagreements were resolved through discussion or after consultation with the senior author, when necessary. Meta-analyses of available comparisons were performed using Review Manager version 5.3 as appropriate (Appendix 4). Adjusted odds ratios (OR) with 95% confidence intervals (CI) were extracted and pooled for each comparison with a random effects model. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (GRADE Pro software) was used to assess the quality of the body of retrieved evidence (Appendix 5).
4. Study selection

Flow chart of the study selection process

- Potentially relevant articles $n = 286$
  - Medline $n = 82$
  - EMBASE $n = 123$
  - CINHAL $n = 47$
  - Cochrane CENTRAL $n = 0$
  - WHO Global Library $n = 34$

Citations identified through other sources $n = 40$

Total articles after removal of duplicates $n = 213$

Total articles screened $n = 213$

Excluded after title and abstract screening $n = 148$

Full-text articles assessed for eligibility $n = 65$

Full-text articles excluded $n = 41$
  - Article type (reviews/editorials/non-randomized clinical trials) $n = 16$
  - No correlation SSI/intervention $n = 14$
  - Other intervention than fluid management $n = 6$
  - Irrelevant $n = 4$
  - Out of the time limit $n = 1$

Randomized controlled trials included in the analysis $n = 24$
5. **Summary of the findings and quality of the evidence**

A total of 24 RCTs comparing specific strategies of fluid management with standard fluid management were identified with an SSI outcome. Included patients were adults undergoing several types of surgical procedures (colorectal, abdominal, general, urology, gynaecological, cardiothoracic, vascular, orthopaedic and other surgery). No study was available in a paediatric population.

Despite the heterogeneity among the selected studies regarding the specific type of fluid management strategy used and fluid management in the perioperative period, the following comparisons of fluid management strategies were made:

1. **Preoperative period (GDF vs. standard fluid management)**
2. **Intraoperative period:**
   a. **GDFT vs. standard fluid management**
   b. restrictive fluid management vs. standard fluid management
3. **Postoperative period:**
   a. **GDFT vs. standard fluid management**
   b. restrictive fluid management vs. standard fluid management
4. **Pre- and postoperative periods combined (GDF vs. standard fluid management)**

The results of the meta-analyses and single studies based on these comparisons are summarized as follows (Appendix 4):

1. **Preoperative period**
   One randomized clinical trial (RCT) comparing GDFT vs. standard fluid management preoperatively (Appendix 4, comparison 1) demonstrated no benefit in reducing the risk of SSI (OR: 0.47; 95% CI: 0.13–1.72).

2. **Intraoperative period**
   a. 14 RCTs comparing GDFT vs. standard fluid management intraoperatively were identified. Three studies showed a decreased risk of SSI when GDFT was used. The remaining 11 trials showed no difference in risk. A meta-analysis of the 13 RCTs (Appendix 4, comparison 2a) showed that GDFT has a significant benefit compared to standard fluid maintenance in reducing the SSI rate (OR: 0.56; 95% CI: 0.35–0.88).

   b. Five RCTs compared restrictive fluid management vs. standard fluid management. All studies showed no difference in the risk of SSI. A meta-analysis of the 5 RCTs (Appendix 4, comparison 2b) showed no significant difference in the risk of SSI (OR: 0.73; 95% CI: 0.41–1.28).

   The quality of evidence for these two comparisons was low and very low, respectively, due to risk of bias and imprecision (Appendix 5).

3. **Postoperative period**
   a. Two RCTs compared GDFT vs. standard fluid management in the postoperative period. One study showed a decreased risk of SSI in the GDFT group, whereas the other showed no difference in risk. A meta-analysis of the 2 RCTs (Appendix 4,
comparison 3a) showed a decreased risk of SSI when GDFT is used postoperatively (OR: 0.24; 95% CI: 0.11–0.52).

b. One RCT \(^{28}\) comparing restrictive vs. standard fluid management postoperatively showed no difference in risk (Appendix 4, comparison 3b; OR: 6.20; 95% CI: 0.68–56.56).

4. One RCT \(^{10}\) compared GDFT vs. standard fluid management pre- and postoperatively combined and demonstrated no benefit (Appendix 4, comparison 4; OR: 0.75; 95% CI: 0.16–3.52).

Five RCTs reported that either fluid overload or hypovolemia seem to be associated with increased mortality and morbidity \(^{11,16,20,21,28}\).

In conclusion, the available evidence related to **specific strategies of intraoperative fluid management vs. standard fluid management** (comparison 2) can be summarized as follows.

Overall, a low quality of evidence from RCTs shows that intraoperative GDFT has a significant benefit in reducing the SSI rate compared to standard fluid management. This effect is also shown for GDFT in the postoperative period. Restrictive fluid management has neither benefit nor harm compared to standard fluid management in reducing the SSI rate (very low quality of evidence).

Of note, the included studies present some limitations. Definitions of SSI, methods for the measurement of normovolemia, protocols used for GDFT and restricted and standard therapy practices differed greatly. For GDF, multiple different goals were used across the studies. Thus, an adequate assessment of normovolemia in these strategies remains complicated. In addition, the physiological effects of any given volume of fluid may differ, depending on the magnitude of the surgical stress response and not solely on the volume of fluids administered. There is no universal definition of normovolemia or a standardized method of assessing normovolemia in the current literature. Some studies determine normovolemia by urinary output, whereas others use more invasive techniques by assessing the cardiac output or cardiac index. The quality of the included RCTs was moderate to low. Most studies had unclear blinding and/or an unclear risk of selective outcome reporting.

6. **Other factors considered in the review of studies**

The systematic review team identified the following other factors to be considered.

**Potential harms**

The effect of inadequate fluid management during the surgical procedure may potentially influence different organ system derangements, mainly cardiovascular, tissue healing, renal and lungs. Both fluid overload and hypovolemia are likely to increase mortality and morbidity \(^{11,16,20,21,28}\).

Adequately measuring the volume status of patients without invasive measurements may be difficult. However, when the measurement of normovolemia is inadequate, it is hardly possible to administer the optimal fluid regimen. In addition, the actual physiological effect of
administered fluids could differ also depending on several other factors, such as surgical stress, normothermia and tissue oxygenation.

Resource use

No study was found on costs and/or the cost-effectiveness of different fluid management strategies during surgery.

7. Key uncertainties and future research priorities

The systematic review team identified the following key uncertainties and future research priorities.

In particular, a widely-accepted definition for normovolemia is needed. Future studies including large well-designed RCTs with clear definitions should aim at identifying the most accurate and least invasive method of measuring normovolemia and assess its influence on tissue oxygenation and normothermia. Studies should be conducted also in low- to middle-income countries. More research is required to investigate the effectiveness of different fluid management strategies in the paediatric population.
APPENDICES

Appendix 1: Search terms

Medline (through OvidSP)

1. wound infection.mp. or exp wound infection/
2. exp surgical procedures, operative/ or exp perioperative period/ or preoperative care/ or (surger* or operat* or perioperat* or peri-operat* or pre-operat* or preoperat* or postoperat* or post-operat*).ti,ab,kw.
3. surgical wound infection/ or (surgical site infection* or SSI or SSIs or surgical wound infection* or surgical infection* or post-operative wound infection* or postoperative wound infection*).ti,ab,kw.
4. exp blood volume/ or exp fluid therapy/ or (blood volume* or normovolemia or fluid management).ti,ab,kw. or (circulat* adj2 volume*).ti,ab,kw. or (volume* adj3 blood).ti,ab,kw.
5. 1 or 3
6. 2 and 4 and 5
7. limit 6 to yr="1990 -17-1-2014"

EMBASE

1. surgical infection/ or (surgical site infection* or SSI or SSIs or surgical wound infection* or surgical infection* or post-operative wound infection* or postoperative wound infection*).ti,ab,kw.
2. exp surgery/ or perioperative period/ or preoperative care/ or (surger* or operat* or perioperat* or peri-operat* or pre-operat* or preoperat* or postoperat* or post-operat*).ti,ab,kw.
3. blood volume/ or (blood volume* or normovolemia or fluid management).ti,ab,kw. or (circulat* adj2 volume*).ti,ab,kw. or (volume* adj3 blood).ti,ab,kw.
4. 1 and 2 and 3
5. limit 4 to yr="1990 - 2014"
6. exp wound infection/
7. 1 or 6
8. 2 and 3 and 7
9. limit 8 to yr="1990 -Current"

CINAHL

("normovolemia" OR "GDFT" OR “goal directed fluid therapy” OR (MH "fluid therapy+") OR "fluid therapy" OR (MH "fluid resuscitation")).AND ("ssi" OR (MH "surgical wound infection") OR "surgical site infection" OR (MH "surgical wound infection") OR (MH "wound infection+") OR "wound infection")

Cochrane CENTRAL

1. wound infection:ti,ab,kw
2. surgical wound infection:ti,ab,kw
3. normovolemia:ti,ab,kw
4. fluid therapy:ti,ab,kw
5. 1 or 2
6. 3 or 4
7. 5 and 6

WHO Global Health Library

1. (ssi)
2. (surgical site infection)
3. (surgical site infections)
4. (wound infection)
5. (wound infections)
6. (postoperative wound infection)
7. (normovolemia)
8. (fluid therapy)
## Appendix 2: Evidence table

<table>
<thead>
<tr>
<th>Study, year, reference</th>
<th>Type of surgery</th>
<th>End point</th>
<th>Intervention</th>
<th>Control</th>
<th>Timing</th>
<th>Modality of optimization</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benes 2010 31</td>
<td>Major abdominal surgery (colorectal, pancreatic, vascular)</td>
<td>Vigileo™ (Vigileo, Nyon, Switzerland) monitor/flotrack SVV &lt;10% or CI &gt;10% to previous fluid challenge.</td>
<td>Bolus of 3 mL/kg colloids and infusion of dobutamine to maintain CI between 2.5-4 L/minute/m², ephedrine boluses 5-15 mg or norepinephrine to treat a fall in systolic arterial pressure &lt;90 mmHg or MAP &gt;70 mmHg.</td>
<td>Additional fluids or vasoactive substances to maintain blood pressure, diuresis and CVP in normal ranges (MAP &gt;65 mmHg, heart rate &lt;100 bpm, CVP 8-15 mmHg urine output &gt;0.5 mL/kg/hour).</td>
<td>Intra-operative</td>
<td>Fluids and inotropes</td>
<td>Wound infection/dehiscence I: 2/60 C: 5/60</td>
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<td>Boyd 1993 10</td>
<td>Emergency/ elective major abdominal or vascular surgery or other major operations</td>
<td>PAC: DO2&gt;600 mL/minute/m²</td>
<td>Deliberate increase of oxygen delivery index to greater than 600 mL/minutes/m² by use of dopexamine hydrochloride infusion.</td>
<td>Best standard perioperative care.</td>
<td>Pre- and post-operative</td>
<td>Fluids and inotropes</td>
<td>Wound infection (positive wound swab cultures) I: 3/53 C: 3/54</td>
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<tr>
<td>Brandstrup 2003 11</td>
<td>Elective colorectal resection</td>
<td>Haematocrit 25-35%.</td>
<td>A) Restricted= • no preloading • no replacement of</td>
<td>B) Standard= • preload: 500 mL HAES 6%</td>
<td>Intra-operative</td>
<td>Fluids</td>
<td>Superficial wound infection,</td>
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third space loss
- 500 mL glucose 5% in water less oral fluid intake during fast
- volume-to-volume with HAES 6% with allowance for maximum 500 mL extra.
Blood component therapy started at approximate loss >1500 mL dependent on hematocrit.

- Third space loss: normal saline 0.9%: 7 mL/kg/hour, first hour; 5 mL/kg/hour, second and third hours; 3 mL/kg/hour, following hours
- Loss during fast: 500 mL of normal saline 0.9% independent of oral intake

Blood loss: loss up to 500 mL: 1000-1500 mL of normal saline; loss >500 mL, additional HAES 6%.

haematoma or dehiscence
I: 9/69
C: 18/72

Anastomotic leakage (requiring operation)
I: 1/69
C: 4/72

Leakage of the rectum (drained deep abscess)
I: 2/69
(occurred following re-operation for anastomotic leakage/necrosis of stoma)
C: 2/72

Peritonitis without leakage
I: 1/69
C: 0/72

Adverse events: not specified
LF: specified
Overall complications: 21 vs. 40
P=0.003
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Type</th>
<th>Procedure</th>
<th>Fluids</th>
<th>Infection</th>
<th>Leakage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forget 2010</td>
<td>Major abdominal (upper or lower gastrointestinal, hepatic)</td>
<td>Masimo SET® (Masimo, Irvine, CA, USA) pulse oximeter PVI &gt;13% during 5 minutes.</td>
<td>Bolus of 500 mL crystalloids with 2 mL/kg/hour continuous infusion. Bolus of HAES 250 mL every 5 minutes until PVI &lt; 13%, norepinephrine to maintain MAP &gt;65 mmHg.</td>
<td>Bolus of 500 mL crystalloids with 4-8 mL/kg/hour continuous infusion. Bolus of colloids if acute blood loss &gt;50 mL or if MAP &lt;65 mmHg or CVP &lt;6 mmHg. If MAP &lt;65 mmHg was unresponsive to fluids, norepinephrine was given.</td>
<td>Intra-operative</td>
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<tr>
<td>Gan 2002</td>
<td>Elective general, urology, gynaecological</td>
<td>Oesophageal doppler: SV optimization with FTc between 0.35-0.4 seconds.</td>
<td>5 mL/kg lactated Ringer’s solution and Ringer’s solution at a rate of 5 mL/kg/hour. Protocol group= bolus of fluids administered and guided by Doppler estimations of SV and FTc.</td>
<td>5 mL/kg lactated Ringer’s solution and Ringer’s solution at a rate of 5 mL/kg/hour. Control group= bolus of 200 mL fluid given when urinary output &lt; 0.5 mL/kg/hour or an increase in heart rate &gt;20% above baseline or &gt;100 beats/minute or a decrease in mean systolic blood pressure less than</td>
<td>Intra-operative</td>
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</tbody>
</table>

Intra-operative Fluids

Infection of surgical site:
- I: 8/41
- C: 8/41
- P=1.0

Other infections (pulmonary, line-related, other abdominal)
- I: 6/41
- C: 7/41

Leakage of anastomosis
- I: 5/41
- C: 5/41

Wound infection:
- I: 4/50
- C: 5/50
- P = not significant
<table>
<thead>
<tr>
<th>Study Reference</th>
<th>Type of Surgery</th>
<th>Fluid Management</th>
<th>Intraoperative Fluids</th>
<th>Postoperative Fluids</th>
<th>Infection</th>
<th>Wound Infection</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harten 2008</td>
<td>Emergency abdominal surgery</td>
<td>LiDCO™ cardiovascular system (Lidco, London, UK): pulse pressure variation less than 10%. Fluid boluses of 250ml HAES (Voluven®) were administered over 15 minutes during the operation if the pulse pressure varied by more than 10%.</td>
<td>Fluid boluses of 250ml HAES (Voluven®)</td>
<td>Fluid boluses of 250ml HAES (Voluven®)</td>
<td>20% below baseline or less than 90 mmHg or a CVP &lt;20% baseline.</td>
<td>Standard of care by clinical team in charge.</td>
<td>Intra-operative Fluids</td>
</tr>
<tr>
<td>Holte 2007</td>
<td>Elective colonic surgery</td>
<td>None</td>
<td>Restrictive fluid = • 7 mL/kg/hour RL, first hour • 5 mL/kg/hour, subsequent hours • (Voluven®: 7 mg/kg) • Postoperative: no intravenous fluids</td>
<td>Liberal fluids = • 10 mL/kg RL preload • 18 mL/kg/hour RL • Voluven®: 7 mg/kg Postoperative: 10 mL/kg RL</td>
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<td>Intra-operative Fluids</td>
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<tr>
<td>Kabon 2005</td>
<td>Open elective colon resection with an</td>
<td>Urinary output &gt;1 mL/kg/hour or mean arterial blood pressure</td>
<td>Small fluid management = maintenance: 8-10 mL/kg/hour lactated</td>
<td>Large fluid management = • Fluid bolus of 10 mL/kg</td>
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<td>Postoperative Fluids</td>
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<tr>
<td>Lobo 2002</td>
<td>Elective hemicolectomies and sigmoid-</td>
<td>PAC: DO2&gt;600ml/minute/m²</td>
<td>Restricted treatment</td>
<td>Standard postoperative fluids as usual on surgical</td>
<td>Post-operative fluids</td>
<td>Wound infection:</td>
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</table>
| anticipated duration | >2 hours | >70% pre-induction value | Ringer’s solution intraoperatively and first hour postoperatively. | before induction of anaesthesia  
- Maintenance: 16-18 mL/kg/hour lactated Ringer’s solution intraoperatively and first hour postoperatively.  
Additional fluid given to maintain urinary output >1 mL/kg/hour or mean arterial blood pressure >70% pre-induction value. | Any CDC infection 10.5% =13/124  
Infection by pus and positive culture (5.7%) = 7/124  
Total infection by either criterion: 11.3% = 14/124  
C: n= 129  
Superficial (3.9%) = 5/129  
Deep 5.4% = 7/129  
Peritoneal 2.3% = 3/129  
Any CDC infection 7.0% = 9/129  
Infection by pus and positive culture (4.7%) = 6/129  
Total infection by either criterion: 8.5% = 11/129  

\[ P \text{(superficial)} = 0.354 \]
\[ P \text{(deep)} = 0.939 \]
\[ P \text{(peritoneal)} = 0.247 \]
\[ P \text{(any CDC infection)} = 0.322 \]
\[ P \text{(total infection)} = 0.462 \]

\( P=\text{not significant} \)
<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Surgery</th>
<th>Intraoperative Fluids</th>
<th>Postoperative Fluids</th>
<th>Wound Infections</th>
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<tbody>
<tr>
<td>Lopes 2007</td>
<td>High-risk surgery (upper/lower gastrointestinal, hepatobiliary, urology, other)</td>
<td>Variation in arterial pulse pressure (ΔPP) (IBP plus; Dixtal; Philips Healthcare, Amsterdam, the Netherlands); ΔPP ≤10%</td>
<td>Fluid at the discretion of the anaesthetist.</td>
<td>Abdominal infection: I: 3/17 C: 4/16 Anastomotic leak: I: 0/17 C: 1/16</td>
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<tr>
<td>Mayer 2010</td>
<td>Major abdominal surgery (intestine resection, gastric resection, liver resection, esophageal resection, Whipple)</td>
<td>Vigileo™ monitor/flotrac sensor: CI ≥ 2.5 L/minute/m² SVI &lt;35 mL/m²: 500 mL crystalloids or dobutamine 10/hour + 250 mL colloids, SVI &gt;35 mL/m²: dobutamine 10 mL/hour, MAP &lt;65 mmHg: norepinephrine 5 mL/hour.</td>
<td>Management at discretion of the intensive care unit. Monitoring arterial and pressure and CPV with markers of tissue perfusion, such as urine output.</td>
<td>Wound infection (clinical diagnosis): I: 3/30 C: 8/30 Abdominal infection (abdominal CT): I: 1/30 C: 4/30 OR/P values not specified</td>
</tr>
<tr>
<td>Mc Kendry 2004</td>
<td>Elective cardiac surgery</td>
<td>Oesophageal doppler: stroke volume index &gt;35 mL/m² SV &gt;35 mL/m² using repeated colloid challenges with nitrates and inotropes.</td>
<td>Management at discretion of the intensive care unit. Monitoring arterial and pressure and CPV with markers of tissue perfusion, such as urine output.</td>
<td>Chest/sterneal wound infection: I: 1/89 C: 4/85 Infected leg wound: I: 1/89 C: 1/85</td>
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<tr>
<td>Mythen 1995</td>
<td>Elective cardiac surgery</td>
<td>Oesophageal doppler: SV optimization and rise in CVP &lt;3 mmHg.</td>
<td>200 mL intravenous colloid boluses over 10 minutes until targets reached.</td>
<td>Routine administration of crystalloid or colloids.</td>
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<tr>
<td>Nisanevich 2005</td>
<td>Major elective intra-abdominal surgery (colon/rectum, small bowel resections, gastric resections, and pancreaticoduodenectomy/partial pancreas resections)</td>
<td>Restricted protocol group 4 mL/kg/h RL solution throughout intraoperative period.</td>
<td>Liberal protocol group  - bolus of 10 mL/kg RL solution before skin incision  - 12 mL/kg/hour RL solution throughout intraoperative period Fluid boluses provided when needed.</td>
<td>LIBERAL PROTOCOL</td>
</tr>
<tr>
<td>Pearse 2005</td>
<td>Elective or emergency major general surgery (vascular, upper and lower gastrointestinal,</td>
<td>LiDCO™ cardiac sensor system: DO2 &gt; 600 mL/minute/m², SV &gt;10%</td>
<td>GDFT challenge: 250 mL intravenous colloid solution until 10% rise in SV &gt;20 minutes. Dopexamine if DO2I &lt; 600 mL/minute.</td>
<td>Control fluid challenge: 250 mL intravenous colloid until 2 mmHg rise in CVP achieved &gt;20 minutes.</td>
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<tr>
<td>Description</td>
<td>Methods</td>
<td>Fluids</td>
<td>Intraoperative Fluids and Inotropes</td>
<td>Wound Infections</td>
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<td>-----------------</td>
</tr>
<tr>
<td>Pillai 2011</td>
<td>Radical cystectomy</td>
<td>Oesophageal doppler: SV optimization with FTc&gt; 0.35 seconds. Fluid challenge 3 mL/kg over 10 minutes with colloids until targets met. Standard intraoperative fluids at discretion of the anaesthetist.</td>
<td>Intra-operative Fluids</td>
<td>Wound infections: Superficial: I: 1/32 C: 8/34 Deep: I: 1/32 C: 2/34 Combined: I: 2/32 C: 10/34 P&lt;0.01</td>
</tr>
<tr>
<td>Sandham 2003</td>
<td>Urgent or elective major abdominal, thoracic, vascular, or orthopaedic surgery</td>
<td>PAC: CI &gt;3.5 and &lt;4.5 L/minute/m², 550 &lt; DO2 &lt;600 mL/minute/m², MAP &gt;70 mmHg, PCWP &lt; 18 mmHg Fluid loading, inotropic therapy, vasodilator therapy, vasopressors for hypotension and blood transfusion for a hematocrit of less than 27% (guided by the use of a pulmonary-artery catheter placed before surgery). Measurement of CVP (standard care without the use of a pulmonary artery catheter).</td>
<td>Intra-operative Fluids and Inotropes</td>
<td>Wound infections: I: 66/941 C: 83/965 P=0.23</td>
</tr>
<tr>
<td>Scheeren 2013</td>
<td>High risk surgical patients (major abdominal surgery and radical cystectomy)</td>
<td>Vigileo™ FlowTrac, SVV &gt;10% 200 mL HAES infused over 10 minutes until SVV &lt;10%. Treatment according to a standardized approach.</td>
<td>Intra-operative Fluids</td>
<td>Wound infections: I: 0/26 C: 7/26 OR/P values not specified</td>
</tr>
<tr>
<td>Author</td>
<td>Type</td>
<td>Fluid therapy/dosage</td>
<td>Evidence</td>
<td>Wound/infectious complications:</td>
</tr>
<tr>
<td>---------------</td>
<td>-----------------------------</td>
<td>-------------------------------------------------------------------------------------</td>
<td>----------</td>
<td>---------------------------------</td>
</tr>
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</table>
| Senagore 2009 | Elective laparoscopic segmental colectomy | GD-H (Hetastarch) maintenance regimen of 5 mL/kg/h RL continued during surgery
- 200 mL aliquot of HAES 6%
- bolus repeated until SV >10% increased
GD-LR
- maintenance regimen of 5 mL/kg/hour, RL continued during surgery
- 300 mL aliquot of RL
Bolus repeated until SV >10% increased. | Standard maintenance regimen of 5 mL/kg/h RL continued during surgery
- boluses given when triggered by haemodynamic variables. | Intra-operative | Fluids |
| Smetkin 2009  | Off pump cardiac bypass surgery | PiCCO Plus® (Pulsion Systems, Feldkirchen, Germany) monitor: ITBVI 850 to 1000 mL/m, ScvO2 > 60% | HAES (200kDa, 6% Hemohes®, B.Braun, Melsungen, Germany), 500 mL over 30 minutes up to max 2 g/kg stepwise. | Fluid therapy based on CVP, HR and MAP. | Intra-operative | Fluids and inotropes |
| Venn 2002     | Orthopaedic surgery         | Oesophageal doppler: SV optimization with FTc > 0.4 seconds | Repeated 200 mL gelofusine fluid challenges guided by central venous pressure (n=31) or oesophageal Doppler ultrasonography (n=30). | Intravenous fluids as thought appropriate by anaesthetist (conventional intraoperative fluid management, n=29). | Intra-operative | Fluids |
| Vermeulen 2009| Elective major abdominal     | None                                                                                 | Restricted intravenous fluid regime = | Hospital standard intravenous fluid | Post-operative | Fluids |

GD-H: 6/21
GD LR: 4/21
C: 1/22
OR/P values not specified

GD-H: 6/21
GD LR: 4/21
C: 1/22
P=not significant

OR/P values not specified
<table>
<thead>
<tr>
<th>Study</th>
<th>Procedure</th>
<th>Fluid Regime</th>
<th>Complication</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Oesophageal Doppler: SV optimization and rise in CVP &lt;3 mmHg</td>
<td>1.5 L/24 hour RL + 2.5 L/24 hour RL</td>
<td>Wound dehiscence I: 1/30 C: 0/32</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Routine cardiovascular monitoring and CVP measurements. CVP was used to guide intravenous fluid administration and kept between 12-15 mmHg.</td>
<td></td>
<td>OR/P values not specified</td>
<td></td>
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Intra-operative Fluids

“Complication type”: “Infectious” (unclear): I: 14/64 C: 11/64 P=0.532

“Wound”: I: 5/64 C: 4/64 P=0.748

Anastamotic leakage: I: 1/64 C: 2/64
| Wilson 1999 | Elective major surgery (repair of aortic or common iliac aneurysm, resection of upper gastrointestinal malignancy, anterior resection, cystectomy) | PAC: DO2 > 600 mL/minute/m² | 1 L Hartmann’s solution bolus, human albumin solution 4.5% until pulmonary artery occlusion pressure >12 mmHg achieved. Haemoglobin concentration <110 g/L red blood cell transfusion instead of albumin. Inotrope suppletion 0.025 microg/kg/minute for adrenaline and 0.125 microg/kg/minute for dopexamine. | No standardized protocol | Pre-operative fluids and inotropes | Wound sepsis: adrenaline 3/46, dopexamine 0/46 C: 3/46
Abdominal sepsis: adrenaline 2/46, dopexamine 0/46 C: 2/46
Anastomotic breakdown: adrenaline 0/46, dopexamine 0/46 C: 3/46
OR/P values not specified |

SVV: stroke volume variation; CI: cardiac index; CVP: central venous pressure; MAP: mean arterial pressure; I: intervention; C: control; OR: odds ratio; SSI: surgical site infection; PAC: premature atrial contraction; HAES: hydroxyethyl starch; LF: lost to follow-up PVI: Pleth variability index; SV: stroke volume; FTc: corrected flow time; CDC: Centers for Disease Prevention and Control; RL: Ringer’s lactate; GD-H: goal-directed therapy with hetastarch; GD-LR: goal-directed therapy with lactated Ringer’s solution; PCWP: pulmonary capillary wedge pressure; DOP: Doppler ultrasonography
Appendix 3: Risk of bias assessment of the included randomized controlled trials (Cochrane Collaboration tool)

<table>
<thead>
<tr>
<th>Author, year, reference</th>
<th>Sequence generation</th>
<th>Allocation concealment</th>
<th>Participants blinded</th>
<th>Care providers blinded</th>
<th>Outcome assessors blinded</th>
<th>Incomplete outcome data</th>
<th>Selective outcome reporting</th>
<th>Other sources of bias</th>
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<tbody>
<tr>
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<td>Scheeren 2013 24</td>
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<td>Patient Selection</td>
<td>Blinding</td>
<td>Randomization</td>
<td>Analysis</td>
<td>Findings</td>
<td>Conclusion</td>
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<td>Vermeulen 2009</td>
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<td>Wakeling 2005</td>
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### Appendix 4: Comparisons

#### Comparison 1: GDFT vs. standard fluid management (preoperative), outcome SSI

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>GDFT Events</th>
<th>Total</th>
<th>Standard fluid management Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
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</thead>
<tbody>
<tr>
<td>Wilson 1991</td>
<td>5</td>
<td>92</td>
<td>5</td>
<td>46</td>
<td>100.0%</td>
<td>0.47 [0.13, 1.72]</td>
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<tr>
<td>Total (95% CI)</td>
<td>92</td>
<td>100.0%</td>
<td>46</td>
<td>100.0%</td>
<td>0.47 [0.13, 1.72]</td>
<td></td>
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</tbody>
</table>

Total events: 5

Heterogeneity: Not applicable

Test for overall effect: Z = 1.14 (P = 0.25)

GDT: goal-directed fluid therapy; SSI: surgical site infection; M-H: Mantel-Haenszel (test); CI: confidence interval
Comparison 2a: GDFT vs. standard fluid management (intraoperative), outcome SSI

GDFT: goal-directed fluid therapy; SSI: surgical site infection; M-H: Mantel-Haenszel (test); CI: confidence interval
Funnel plot 2a: GDFT vs. standard fluid management (intraoperative), outcome SSI

GDFM: goal-directed fluid therapy; M-H: Mantel-Haenszel (test); CI: confidence interval
Comparison 2b: Restrictive vs. standard fluid management (intraoperative), outcome SSI

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Restrictive</th>
<th>Standard</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
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<tbody>
<tr>
<td>Brandstrup 2003</td>
<td>10</td>
<td>20</td>
<td>72</td>
<td>0.44 [0.19, 1.03]</td>
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<tr>
<td>Holte 2007</td>
<td>1</td>
<td>0</td>
<td>16</td>
<td>3.19 [0.12, 84.43]</td>
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<tr>
<td>Kabon 2005</td>
<td>14</td>
<td>124</td>
<td>11</td>
<td>1.37 [0.59, 3.14]</td>
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<tr>
<td>Lobo 2002</td>
<td>0</td>
<td>10</td>
<td>1</td>
<td>0.30 [0.01, 8.33]</td>
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<tr>
<td>Nisanovich 2005</td>
<td>9</td>
<td>77</td>
<td>14</td>
<td>0.58 [0.23, 1.43]</td>
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</table>

Total events: 296
Total (95% CI): 302

Heterogeneity: Tau^2 = 0.03; Chi^2 = 4.06, df = 4 (P = 0.30); I^2 = 10%

Test for overall effect: Z = 1.11 (P = 0.27)

SSI: surgical site infection; M-H: Mantel-Haenszel (test); CI: confidence interval

Funnel plot 2b: Restrictive vs. standard fluid management (intraoperative), outcome SSI
Comparison 3a: GDFT vs. standard fluid management (postoperative), outcome SSI

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>GDFT Events</th>
<th>GDFT Total</th>
<th>Standard fluid management Events</th>
<th>Standard fluid management Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
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</thead>
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<tr>
<td>Mc Kendry 2004</td>
<td>2</td>
<td>89</td>
<td>5</td>
<td>85</td>
<td>22.7%</td>
<td>0.37 [0.07, 1.95]</td>
<td></td>
</tr>
<tr>
<td>Pearson 2005</td>
<td>8</td>
<td>62</td>
<td>25</td>
<td>60</td>
<td>77.3%</td>
<td>0.21 [0.08, 0.51]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>10</td>
<td>30</td>
<td>145</td>
<td>151</td>
<td>100.0%</td>
<td>0.24 [0.11, 0.52]</td>
<td></td>
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</tbody>
</table>

Total events: 10, 30
Heterogeneity: Tau² = 0.00; Chi² = 0.35, df = 1 (P = 0.55); I² = 0%
Test for overall effect: Z = 3.56 (P = 0.0004)

GDFT: goal-directed fluid therapy; SSI: surgical site infection; M-H: Mantel-Haenszel (test); CI: confidence interval

Funnel plot 3a: GDFT vs. standard fluid management (postoperative), outcome SSI
Comparison 3b: Restrictive vs. standard fluid management (postoperative), outcome SSI

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Restrictive</th>
<th>Standard</th>
<th>Odds Ratio</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>Vermeulen 2009</td>
<td>5</td>
<td>30</td>
<td>1</td>
<td>100.0%</td>
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<tr>
<td>Total (95% CI)</td>
<td>30</td>
<td>32</td>
<td>1</td>
<td>100.0%</td>
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</table>

Total events: 5
Heterogeneity: Not applicable
Test for overall effect: Z = 1.52 (P = 0.11)
SSI: surgical site infection; M-H: Mantel-Haenszel (test); CI: confidence interval

Comparison 4: GDFT vs. standard fluid management (pre- and postoperative), outcome SSI

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>GDFT</th>
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<th>Odds Ratio</th>
<th>Odds Ratio</th>
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<tr>
<td></td>
<td>Events</td>
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<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Boyd 1993</td>
<td>3</td>
<td>53</td>
<td>4</td>
<td>54</td>
</tr>
<tr>
<td>Total (95% CI)</td>
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<td>54</td>
<td>4</td>
<td>54</td>
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</tbody>
</table>

Total events: 3
Heterogeneity: Not applicable
Test for overall effect: Z = 0.36 (P = 0.72)
GDFT: goal-directed fluid therapy; SSI: surgical site infection; M-H: Mantel-Haenszel (test); CI: confidence interval
Appendix 5: GRADE tables

Comparison 2a: GDTF vs. standard fluid management (intraoperative), outcome SSI

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>№ of patients</th>
<th>Effect</th>
<th>Quality</th>
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</thead>
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<tr>
<td></td>
<td>№ of studies</td>
<td>Study design</td>
<td>Risk of bias</td>
</tr>
<tr>
<td>Surgical site infection</td>
<td>14</td>
<td>RCTs</td>
<td>Serious ¹</td>
</tr>
</tbody>
</table>

1. Risk of performance bias, detection bias, reporting bias and other bias (different definitions of how to measure normovolemia, protocols for GDTF and standard therapy practices and SSI).
2. Optimal information size not met.

GDFT: goal-directed fluid therapy; RCT: randomized clinical trial; OR: odds ratio; CI: confidence interval

Comparison 2b: Restrictive vs. standard fluid management (intraoperative), outcome SSI

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>№ of patients</th>
<th>Effect</th>
<th>Quality</th>
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</thead>
<tbody>
<tr>
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<td>Risk of bias</td>
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<tr>
<td>Surgical site infection</td>
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<td>RCTs</td>
<td>Serious ¹</td>
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</tbody>
</table>

1. Risk of performance bias, detection bias, reporting bias and other bias (different definitions of how to measure normovolemia, protocols for GDTF and standard therapy practices and SSI).
2. Optimal information size not met and CI fails to exclude both appreciable benefit and harm (RR and RRR of 25%).

GDFT: goal-directed fluid therapy; RCT: randomized clinical trial; OR: odds ratio; CI: confidence interval; RR: relative risk; RRR: relative risk reduction
References


