South African National Essential Medicine List
Adult Hospital Level Medication Review Process
Component: Emergencies and injuries

Medicine review update
Update of October 2015 review: Ringer lactate for resuscitation in patients with hypovolaemia (see appendix I)

Executive Summary

Date: August 2019
Medicine (INN): Ringer lactate
Medicine (ATC): B05BB01
Indication (ICD10 code): Initial fluid therapy in patients admitted to hospital
Patient population: Adults with hypovalaemia
Prevalence of condition: n/a
Level of Care: Secondary hospitals
Prescriber Level: Doctor
Current standard of Care: Sodium chloride 0.9% (normal saline)
Efficacy estimates: (preferably NNT) 94 (critically ill), 111 (non-critical)
Motivator/reviewer name(s): Andrew Black; Simba Takuva; Geraldine Timothy
PTC affiliation: n/a

Name of author(s)/motivator(s): Andrew Black; Simba Takuva; Geraldine Timothy

Author affiliation and conflict of interest details:
Primary reviewer(s)

- Andrew Black: Helen Joseph Hospital, Gauteng, Adult Hospital Level Expert Review Committee (2017-2019); No applicable conflicts of interest.
- Simba Takuva: Perinatal HIV Research Unit, University of the Witwatersrand and School of Health Systems and Public Health, University of Pretoria, Adult Hospital Level Expert Review Committee (2017-2020); No applicable conflicts of interest.

Secondary reviewer

- Geraldine Timothy: Discovery Health Medical Aid, Adult Hospital Level Expert Review Committee (2017-2020); No applicable conflicts of interest.

Executive summary: Normal Saline (NS) is the only fluid recommended in the Adult Hospital Level EML 2012 for resuscitation of patients. The KwaZulu-Natal Pharmacy Therapeutics Committee (KZN PTC) commented that Ringer's Lactate (RL) should replace NS as the recommended fluid in these patients on the basis of "good evidence" suggesting RL has a favorable inflammatory profile compared with NS. Furthermore, KZN PTC stated that the use of NS was no longer supported by "current resuscitation council and critical care literature". A comparison between crystalloids, specifically normal saline vs so-called "balanced" solutions such as Ringer's Lactate was undertaken as debate centered around the potential of NS to cause hyperchloraemic metabolic acidosis and potential adverse outcomes. The literature tends to group the various balanced crystalloids and this approach was followed in this review.
The previous National Essential Medicine List Adult Hospital Level Committee reviewed this topic in October 2018 and concluded that the data available at that time was limited to small RCTs and

observational studies and was not sufficient to select one treatment over the other.
Since the previous review several large studies and systematic reviews have been published and the committee elected to update the previous review.

Introduction:

Often referred to as 'normal saline', isotonic saline (0.9% saline) contains sodium and chloride in supraphysiological concentrations. Balanced solutions, in contrast, contain lower concentrations of sodium and chloride, making them in closer in composition to plasma than 0.9 % saline. However, isotonic saline is often the preferred resuscitation fluid because of its nature and compatibility with blood transfusion. (1,2)

Despite its widespread use, isotonic saline has been linked to hyperchloraemic metabolic acidosis, immune suppression, and decreased renal perfusion. Isotonic saline has been shown to cause a metabolic acidosis in healthy volunteers and in patients undergoing elective surgical procedures. Relative to a balanced isotonic crystalloid, in which electrolyte composition is closer to plasma, isotonic saline infusion during resuscitation after trauma delays normalization of the pH and base deficit after injury. Furthermore, metabolic acidosis has been implicated in the development of coagulopathy, though its specific role has not been fully characterized. (3–7) Consequently, some guidelines recommend the use of balanced solutions as a default during resuscitation. The National Institute for Health Care Excellence (England and Wales) and Scottish Intercollegiate Guidelines Network (Scotland) guidelines do not recommend one fluid over another. (8,9)

Given the potential adverse physiologic (ie, strong ion difference) effects of normal saline solution, the need for additional evidence comparing normal saline solution and balanced crystalloids needs to be investigated.

Objective: To update the review of the evidence comparing the use of 0.9% Normal Saline (NS) with Lactated Ringer's solution (RL) (and other balanced or buffered crystalloids) in order to establish if RL should replace NS as a resuscitation fluid.

PICO Framework:

Population	Hospitalized adult patients receiving intra venous fluid therapy
Intervention	0.9% Normal Saline
Comparison	Balanced / buffered crystalloid solutions eg Ringers Lactate
Outcomes	Mortality, Acute Kidney Injury, Need for Renal Replacement Therapy, Length of hospital stay

Initial review: The initial review of October 2015 review is attached as appendix I.

Literature added post-initial review:

Since the initial 2015 review, a 2019 Cochrane review was added which reviewed studies up to July 2018 in critically ill patients. We further searched for RCTs and systematic reviews published from 2018 to date:

(((((((Normal Saline) OR Saline) OR isotonic saline) OR 0.9% saline) OR unbalanced crystalloids) OR unbuffered crystalloids) AND Clinical Trial[ptyp] AND Humans[Mesh])) AND (((((((buffered

crystalloid) OR balanced crystalloid) OR lactated ringer) OR ringer's lactate) OR Plasma-Lyte) OR Hartmann) AND Clinical Trial[ptyp] AND Humans[Mesh]) Filters: Publication date from 2018/01/01 to 2019/11/10; Humans; Adult: 19+ years

These are the key reviews and studies identified that are added to the 2015 review:

- Antequera Martin AM, et al (2019): Cochrane Systematic Review (10)
- Bampoe S, et al (2017): Cochrane Systematic Review (11)
- Brown RM, et al (2019): Secondary analysis of RCT (12)
- Kwano-Dourado, et al (2018): Systematic review (13)
- Lui C, et al (2019): Systematic Review (14)
- Rochwerg B, et al (2014): Systematic review and network-meta-analysis (15)
- Self WH, et al, (2018): Randomized Clinical Trial (16)

*The primary studies which included or reviewed a subgroup of the population included in the identified systematic reviews are not listed.

Summary of recommendations from Systematic Reviews

***Cochrane Review by Antequera Martin AM, et al (2019*)**: RCTs up to 2018 examining different buffered solutions versus intravenous 0.9% saline in a critical care setting (resuscitation or maintenance) were reviewed. Population was participants with critical illness (including trauma and burns) or undergoing emergency surgery during critical illness who required intravenous fluid therapy. A total of 21 RCTs (n=20,213) were included, 3 RCT contributed 94% of participants and 16 RCTs were conducted in adults (n= xx).

- The authors found no effect of buffered solutions on preventing in-hospital mortality compared to 0.9% saline solutions in critically ill patients (19,664 participants; 14 studies; high-certainty evidence).
- The effects of buffered solutions and 0.9% saline solutions on preventing acute kidney injury were similar in this setting (18,701 participants; 9 studies; low-certainty evidence).
- Eight studies involving 19,218 participants (95% of the 20,213 total participants) were rated as high methodological quality (trials with overall low risk of bias according to the domains: allocation concealment, blinding of participants/assessors, incomplete outcome data, and selective reporting), and in the remaining trials, some form of bias was introduced or could not be ruled out.
- Patients treated with buffered solutions showed lower chloride levels, higher levels of bicarbonate, and higher pH. The certainty of evidence for these findings was very low and outcomes examined here were not patient centered / hard clinical outcomes.

Of note, this systematic review compared buffered solutions vs. 0.9% normal saline. In sub-group analysis looking only at trials that compared Ringer's Lactate to 0.9% Normal Saline - The studies were of low methodological quality and inadequately powered with low sample sizes ranging from 11 to 24 per arm. Risk of bias ranged from unclear to high

- Seven RCTs looked at the mortality outcome (n=345). However only three trials were estimable, 112 participants. There was a trend towards lowers odds of mortality in the RL group though the estimates were imprecise with very wide confidence intervals (OR 0.32, 95% CI 0.05 – 2.14). Two studies assessed the acute kidney injury outcome and a similar

pattern was observed also with imprecise estimates (OR 0.45, 95% CI 0.06 – 3.21). While the evidence of benefit is uncertain, these RCTs of low methodological quality though imprecise show possible benefit of Ringer's Lactate over 0.9% Normal Saline in mortality and acute kidney injury. The need for high-quality, randomized, prospective trials is clear, that differentiate between fluids such as Ringer's Lactate and 0.9% normal saline solution.

Figure 1 and 2 below show a summary of the findings in studies examining adult participants.

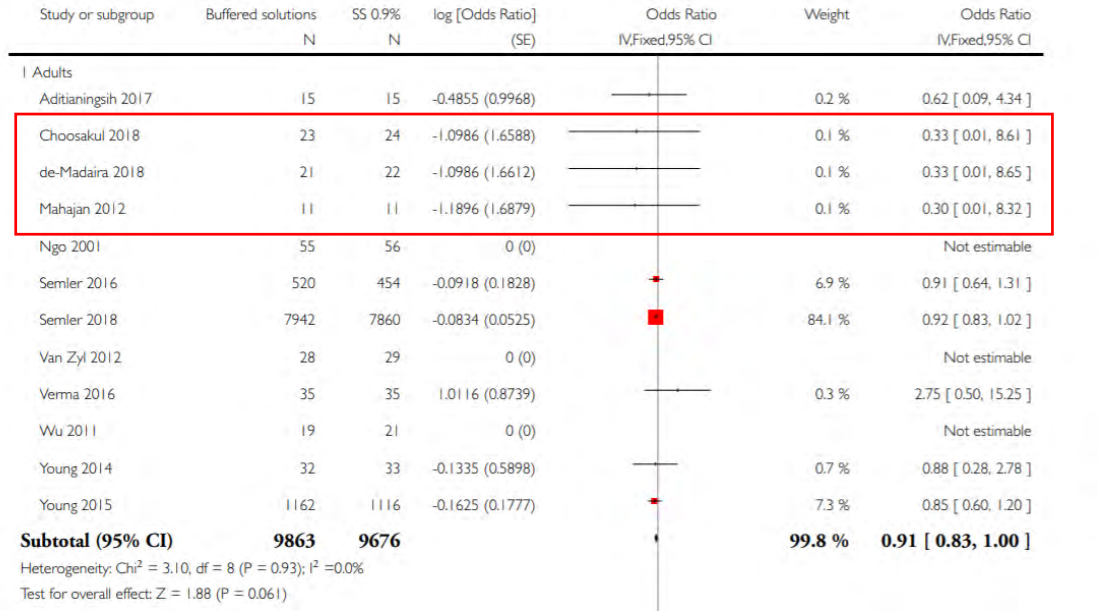

Figure 1: Buffered solutions versus 0.9% saline solution and mortality risk

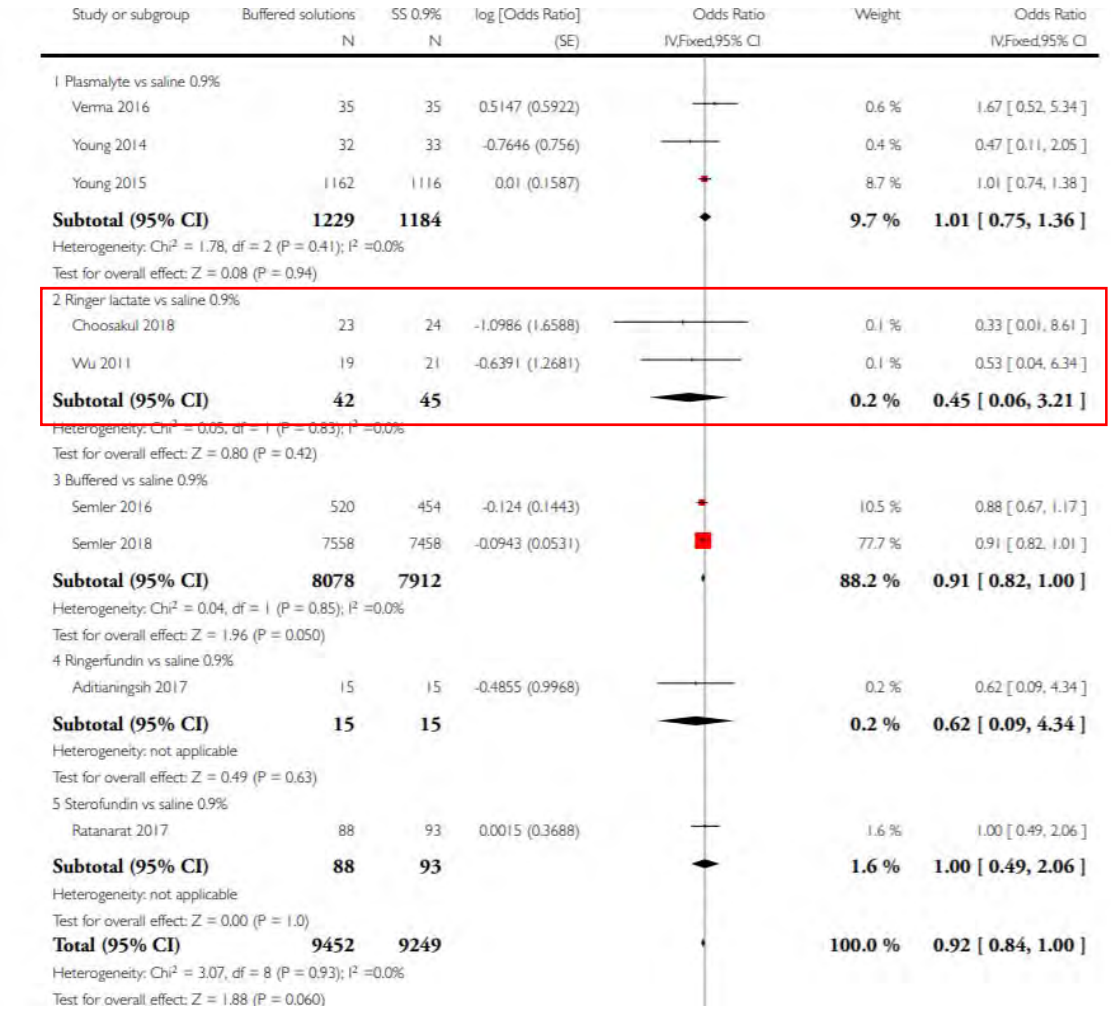

Figure 2: Buffered solutions versus 0.9% saline solution and acute renal injury

***Cochrane Review by Bampoe, et al (2017)*:** The authors reviewed the effects of perioperative intravenous administration of buffered versus non-buffered fluids for plasma volume expansion or maintenance, or both, on clinical outcomes in adults undergoing all types of surgery rather than in resuscitation. Only randomized controlled trials that compared buffered versus non-buffered intravenous fluids for surgical patients were eligible for inclusion. The review included, in total, 19 publications of 18 randomized controlled trials with a total of 1,096 participants. Outcome measures in the included studies were thematically similar, covering perioperative electrolyte status, renal function, and acid-base status; however, there was significant clinical and statistical heterogeneity among the included studies.

- The authors found insufficient evidence on effects of fluid therapies on mortality and postoperative organ dysfunction (defined as renal insufficiency leading to renal replacement therapy); confidence intervals were wide and included both clinically relevant benefit and harm: mortality (Peto OR 1.85, 95% CI 0.37 to 9.33; I^2 = 0%; 3 trials, 6 deaths, 276 participants; low-quality evidence); renal insufficiency (OR 0.82, 95% CI 0.34 to 1.98; I^2 = 0%; 4 trials, 22 events, 276 participants; low-quality evidence).

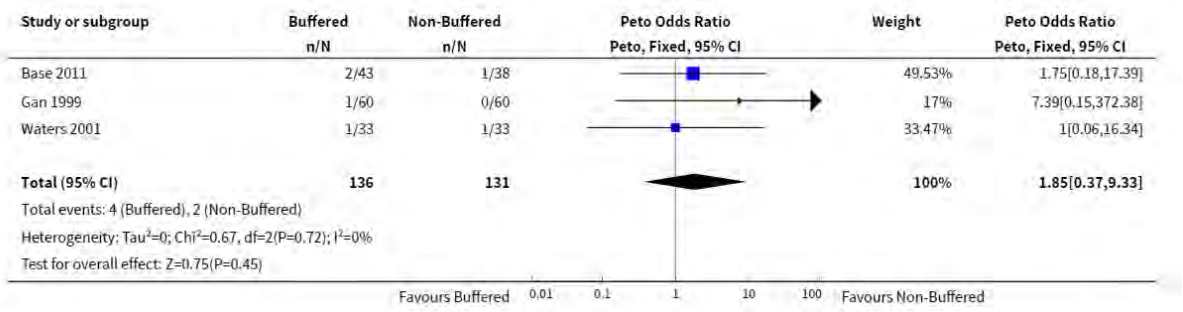

Figure 3: Comparison of buffered versus non-buffered with mortality outcome

- There were several metabolic differences noted, including a difference in postoperative pH measured at end of surgery of 0.05 units - lower in the non-buffered fluid group (12 studies with a total of 720 participants; 95% CI 0.04 to 0.07; I^2 = 61%). However, this difference was not maintained on postoperative day one. The quality of evidence for this outcome was rated as moderate
- The authors concluded that the evidence was insufficient to show effects of perioperative administration of buffered versus non-buffered crystalloid fluids on mortality and organ system function in adult patients following surgery. Benefits of buffered fluid were measurable in biochemical terms, particularly a significant reduction in postoperative hyperchloraemia and metabolic acidosis. Small effect sizes for biochemical outcomes and lack of correlated clinical follow-up data mean that robust conclusions on major morbidity and mortality associated with buffered versus non-buffered perioperative fluid choices are still lacking.
- The Cochrane reviews looked at peri-operative differences in the use of normal saline versus balanced crystalloid solutions, rather than the use of these fluids in resuscitation. No significant differences in clinically relevant outcomes were found that could support the use of one fluid over the other.

Lui C, et al (2019): This systematic review and meta-analysis of nine RCTs evaluated the efficacy and safety of balanced crystalloids versus normal saline for fluid resuscitation in critically ill patients.

- The pooled analyses showed that there were no significant differences in mortality (relative risk (RR) = 0.93, 95% CI = 0.86, 1.01), incidence of AKI (RR 0.94, 95% CI 0.88, 1.00) or RRT use rate (RR 0.94, 95% CI 0.69, 1.27) between balanced crystalloids and normal saline groups.
- Seven studies reported the incidence of AKI. There was no significant difference between the two groups (RR 0.94, 95% CI 0.88, 1.00, P = 0.06, I2=0%)
- Only five studies reported the RRT use rate, and no significant difference was found between the two groups (RR 0.94, 95% CI 0.69, 1.27, P =0.67, I2=39%)
- Six studies reported the results for ICU length of stay, and no significant difference was found between the two groups (RR -0.31 95% CI-1.60,0.97, P = 0.47, I2=100%)

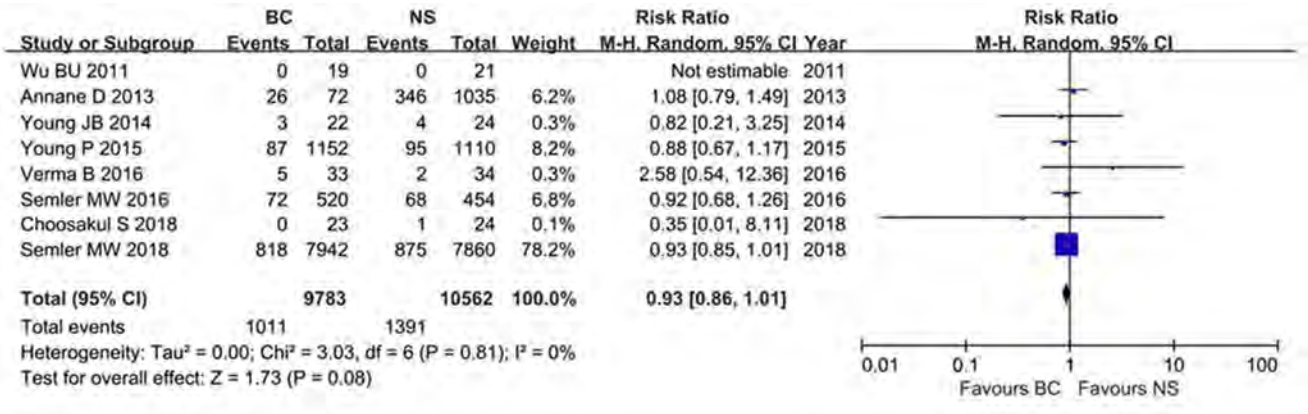

Figure 4: Effect of balanced crystalloids versus normal saline on mortality

Sensitivity analyses were performed to compare Plasma-Lyte with normal saline and compare Lactated Ringer's with normal saline across the above outcomes. Similarly, no differences were found.

Brown RM, et al (2019): This was a secondary analysis of patients from the Isotonic Solutions and Major Adverse Renal Events Trial (SMART) which investigated the effect of balanced crystalloids versus saline on 30-day in-hospital mortality among critically ill adults with sepsis. 1,641 patients were admitted to the medical intensive care unit with a diagnosis of sepsis.

- A total of 217 patients (26.3%) in the balanced crystalloids group experienced 30-day in-hospital morality, compared with 255 patients (31.2%) in the saline group (adjusted OR, 0.74; 95% CI, 0.59 - 0.93). Patients in the balanced group experienced a lower incidence of major adverse kidney events within 30 days (35.4% vs 40.1%; aOR 0.78; 95% CI 0.63 - 0.97) and a greater number of vasopressor-free days (20 ± 12 vs 19 ± 13; aOR 1.25; 95% CI 1.02 - 1.54) and renal replacement therapy-free days (20 ± 12 vs 19 ± 13; aOR 1.35 [1.08 - 1.69]), compared to the saline group.
- The conclusion was that among patients with sepsis in a large randomized trial, use of balanced crystalloids was associated with a lower 30-day in-hospital mortality compared to use of saline.

Rochwerg B, et al (2014)**:** In this systematic review and network-meta-analysis, fourteen randomized controlled trials involving 18,916 adults were available for analysis; in 4 included trials, septic patients were a subgroup of all patients enrolled. Normal saline solution, albumin, Ringer's Lactate, hydroxyethyl starch, and PlasmLyte were examined as resuscitation fluids in the setting of sepsis.

- From the 6-node analysis, balanced crystalloids showed potential benefit to saline solution (OR 0.78, 95% CI 0.58 to 1.06) in the setting of sepsis. See Table 1 below. This was evidence with low GRADE confidence, reflecting potential bias, inconsistency, and indirectness. Using indirect comparisons, this study potentially supports the use of balanced crystalloids in lieu of 0.9% normal saline solution in sepsis.

Table 1: RCT results of the 6-node analysis

Comparison	Trials With Direct Comparisons, n	Direct Estimate (95% CI); Quality of Evidence	Indirect Estimate (95% CrI); Quality of Evidence	NMA Estimate (95% CrI); Quality of Evidence
Albumin vs saline solution	2	0.81 (0.64–1.03); moderate	0.96 (0.14–6.31); very low	0.82 (0.65–1.04); moderate
Balanced crystalloid vs saline solution	0	—	0.78 (0.58–1.05); low	0.78 (0.58–1.05); low
Balanced crystalloid vs albumin	0	—	0.95 (0.65–1.38); very low	0.95 (0.65–1.38); very low

—, no direct comparisons available between two fluids.

Kwano-Dourado, et al (2018): The review tested if the use of low-chloride solutions in unselected critically ill or perioperative adult patients for maintenance or resuscitation reduces mortality and renal replacement therapy (RRT) use when compared to high-chloride fluids.

- Fifteen trials with 4067 patients, most at low risk of bias, were identified. Of those, only 11 and 10 trials had data on mortality and RRT use, respectively. A total of 3710 patients were included in the mortality analysis and 3724 in the RRT analysis.
- No statistically significant impact on mortality (OR, 0.90; 95% CI, 0.69-1.17; P = .44; I = 0%) or renal replacement therapy use (OR, 1.12; 95% CI, 0.80-1.58; P = .52; I = 0%) was found. Overall quality of evidence was low for both primary outcomes.
- The systematic review demonstrated no benefit on low- versus high-chloride solutions for unselected critically ill or perioperative adult patients with regards to mortality and renal replacement. The effect estimates had considerable imprecision. There was limited exposure volume for study fluids, a relatively low risk of the populations in each study and relatively small pooled sample size, may have obscured clinically relevant effects.

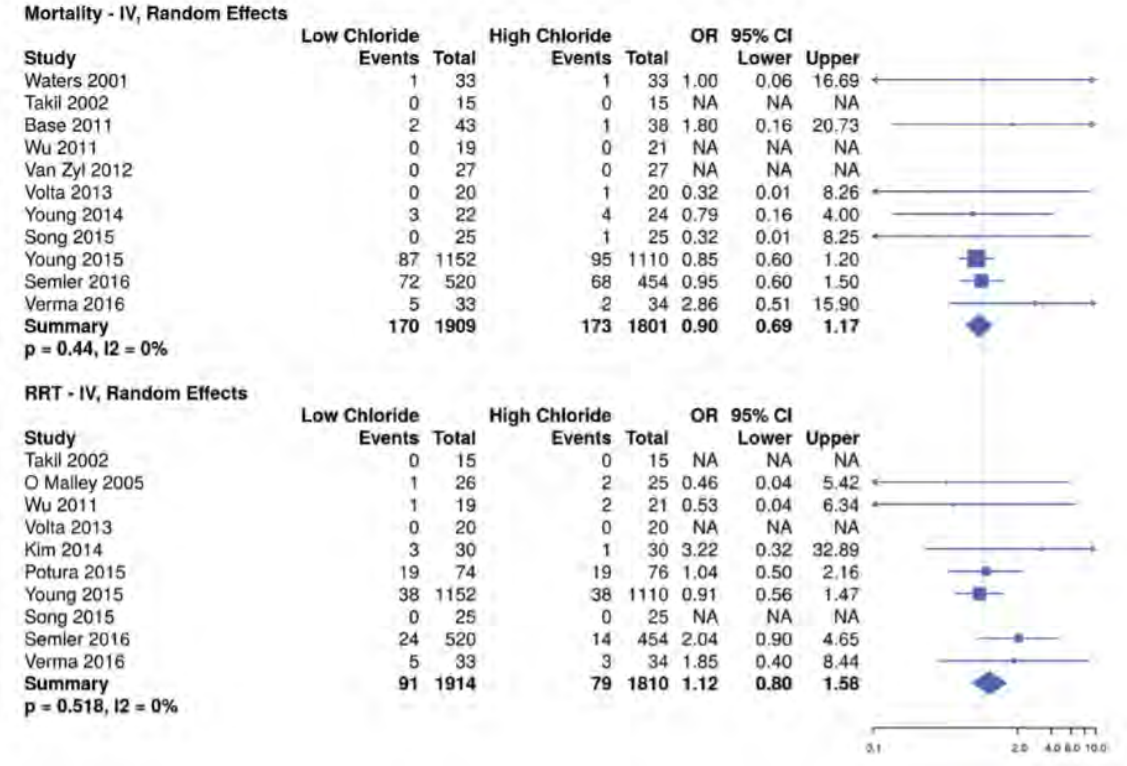

Figure 5: Impact of low- versus high-chloride solutions on mortality and need for renal replacement therapy

Eligible primary studies not included in the systematic reviews

***Self et al, (2018*)** looked at non critically patients across disciplines and was a single center multiple - crossover trial comparing balanced crystalloids with normal saline in patients treated with IV crystalloids in the Emergency department and subsequently hospitalized outside of an ICU. The primary outcome was hospital-free days (days alive after discharge before day 28). Secondary outcomes included major adverse kidney events within 30 days — a composite of death from any cause, new renal-replacement therapy, or persistent renal dysfunction (defined as an elevation of the creatinine level to ≥200% of baseline) — all censored at hospital discharge or 30 days, whichever occurred first. A total of 13,347 patients were enrolled.

- The number of hospital-free days did not differ between the balanced-crystalloids and saline groups (median, 25 days in each group; adjusted odds ratio with balanced crystalloids, 0.98; 95% confidence interval [CI], 0.92 to 1.04; P=0.41).
- Balanced crystalloids resulted in a lower incidence of major adverse kidney events within 30 days than saline (4.7% vs. 5.6%; adjusted odds ratio, 0.82; 95% CI, 0.70 to 0.95; P=0.01). There was an absolute difference of 0.9 percentage points in the risk of major adverse kidney events within 30 days in favor of the balanced-crystalloids group, corresponding to a number needed to treat of 111. Patients who showed the greatest benefit from balanced crystalloids were those who had an ED creatinine >1.5mg/dl (133 umol/L) or an ED chloride >110 as shown in the Forest plot below.

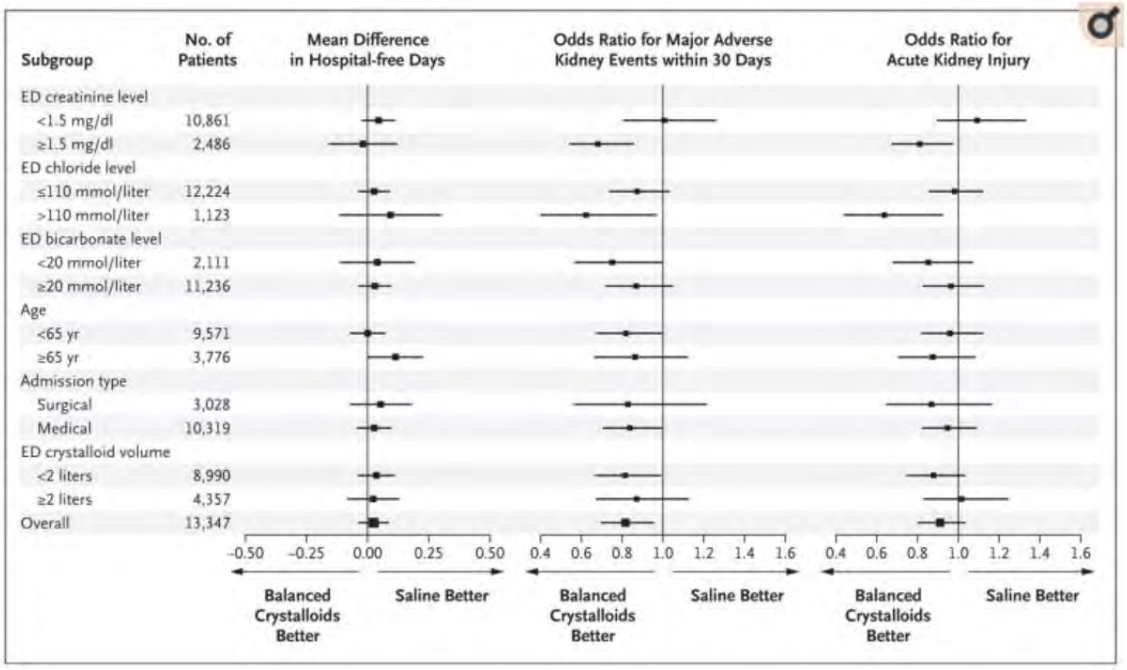

Figure 6: Forest plots for hospital-free days to day 28, major adverse kidney events within 30 days, and acute kidney injury of stage 2 or higher

- Overall the authors concluded that among noncritically ill adults treated with intravenous fluids in the emergency department, there was no difference in hospital-free days between treatment with balanced crystalloids and treatment with saline.

Ongoing adult studies

- *FLUID trial:* a protocol for a hospital-wide open-label cluster crossover pragmatic comparative effectiveness randomised pilot trial. 0.9% Normal Saline versus Ringers Lactate. Setting is hospitalized patients in Canada. N about 12,000.(17)
- *BaSICS trial:* Balanced solution versus 0.9% saline in intensive care study. Severe patients admitted to the ICU at moderate to high risk for death or acute kidney injury. Plasma-Lyte vs. 0.9% saline solution. Setting is Brazil. (18)
- *PLUS trial:* Comparison of Plasmalyte 148® and Saline for Fluid Resuscitation and Intravenous Fluid Therapy in Critically Ill Adults; 8800 participants in Australia and New Zealand. (clinicaltrials.gov)
- *CLOVERS trial:* Multicentre RCT in USA, comparing restrictive fluids strategy (vasopressors first followed by rescue fluids) vs liberal fluid strategy (fluids first followed by rescue vasopressors) on 90-day in-hospital mortality in patients with sepsis-induced hypotension. (clinicaltrials.gov)

Conclusions

- Overall, evidence from systematic reviews suggests that buffered solutions made little or no difference to overall mortality and probably may make little or no difference in reducing the number of patients with worsening kidney function. It is also uncertain if the reported impact of buffered solutions on electrolyte disturbances translates to hard core clinical outcomes.
- Sub-analysis of systematic review (low powered) and sub-analysis of RCT data show that balanced solutions may be appropriate in certain critically ill patients (including critically ill patients presenting with hyperchloraemia, previous renal replacement therapy).
- There is uncertainty of the evidence to strongly recommend balanced solutions for septic shock.

The current data might not be considered robust enough to select one treatment over the other in the peri operative or ICU setting. Fluid therapy is complex and often needs to be individualized while the data does not support replacing normal saline with a balanced solution it does indicate benefit of balanced solution in certain circumstances.

Emerging evidence suggests that rapid large-volume fluid boluses has the potential for adverse effects, and that giving up to 2L results in no increased risk of kidney injury (16, 19-25). In an analysis of 23,513 septic adults, each additional litre of intravenous fluid up to 5 L on the first day of treatment was associated with a small decrease in mortality (–0.7% absolute change per litre; 95% CI –1.0% to –0.4%); however, each additional liter beyond 5 L was associated with an increase in mortality (2.3% absolute change per litre of intravenous fluid; 95% CI 2.0% to 2.5%). (26) An adult trial in Africa, the Simplified Severe Sepsis Protocol Trial and a recent small pilot trial in Northern Europe (Conservative Versus Liberal Approach to Fluid Therapy of Septic Shock in Intensive Care [CLASSIC]) suggested potential benefit from an early restrictive approach. (20, 25) A trial in African children (FEAST) showed similar findings with this approach. (27) Further research is required to determine the volume of fluid administered and associated effects on morbidity and mortality and the possibility of a "de-escalation" protocol. However, the CLOVERS trial that is currently underway that compares liberal vs restrictive fluids strategy for early septic shock management should further inform clinical practice.

Normal saline should be the initial resuscitation fluid (2L) and the secondary fluids be informed by patient chemistry, volume of resuscitation and potential adverse events (hypo/hypernatremia and hyperchloremic acidosis with regular fluid replacement evaluation based on patient response).

Four large well designed RCTs are ongoing studies. Once published and assessed the results of these studies would further inform recommendations.

EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE	**What is the overall confidence in the evidence of effectiveness?** Confident [X] Not confident [ ] Uncertain [ ]	Meta-analyses showed that among critically ill patients receiving crystalloid fluid therapy, use of a balanced crystalloid compared with normal saline did not reduce the mortality, risk of severe AKI or RRT use rate. Evidence is limited regarding the effects of hyperchloraemic acidosis on hard clinical outcomes. However, RCT and sub-analysis of a RCT have shown benefit in a composite end point – Major adverse kidney events when balanced solution is used as the initial fluid in both critically ill and non-critically ill patients.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Benefits outweigh harms [X] Harms outweigh benefits [ ] Benefits = harms or Uncertain [ ]	No harms were identified with the use of balanced solutions.
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes [X] No [ ] List the members of the group. Ringer Lactate Balsol Plasmalyte B List specific exclusion from the group: n/a	The literature examined the difference between balanced solutions and Normal Saline. As the deleterious effects of saline are thought to be due to its hypertonicity relative to plasma the literature has placed all balanced solutions in a single group. No studies were found comparing one balanced solution to another and thus they can at present be considered a class. The most studied balanced solution is Ringers Lactate. Rationale for exclusion from the group: n/a References: n/a
VALUES & PREFERENCES / ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor [ ] Major [ ] Uncertain [X] **Is the option acceptable to key stakeholders?** Yes [X] No [ ] Uncertain [ ]	
RESOURCE USE	**How large are the resource requirements?** More intensive [X] Less intensive [ ] Uncertain [ ]	**Cost of medicines:** Medicine / Cost (ZAR) Sodium chloride 0.9%, IV, 1L / 8.59* Plasmalyte B 130/4/110/1.5/27mmol, IV, 1L / 10.63 to 21.26** Ringer lactate, IV, 1L / 8.67* Balsol, IV, IL / 9.84 to 19.68** * Contract circular RT299-2017, accessed 1 August 2019. ** 30% to 60% of SEP. SEP database 21 August 2019. *Note:* Despite the price of Ringers lactate being relatively comparable to sodium chloride 0.9%, the volume of units consumed per annum would make Ringers lactate cost

		prohibitive if recommended as an alternative option to sodium chloride 0.9%. Modelled budget impact, based on tender estimates: **Medicines** / **Annual estimate (Qty)** / **Annual estimate (ZAR)** Sodium chloride 0.9%, IV, 1L / 4,972,628 / 42,731,641 Ringer lactate, IV, 1L / 4,972,628 / 43,112,685 The estimated incremental budget expenditure is **R381,043.77.** **Additional resources:** n/a
EQUITY	**Would there be an impact on health inequity?** Yes [ ] No [X] Uncertain [ ]	
FEASIBILITY	**Is the implementation of this recommendation feasible?** Yes [X] No [ ] Uncertain [ ]	

Type of recommendation	We recommend against the option and for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
	[ ]	[ ]	[X]	[ ]	[ ]

Recommendations

- Based on this evidence review, the National Essential Medicines List Committee ***(Ref: Minutes of the NEMLC meeting of 26 September 2019)*** reccomends that normal saline should be the primary resuscitation fluid (including for septic shock).
  Rationale: Meta-analyses showed that among critically ill patients receiving crystalloid fluid therapy, use of a balanced crystalloid compared with normal saline did not reduce the mortality, risk of severe AKI or RRT use rate. Evidence is limited regarding the effects of hyperchloraemic acidosis on hard clinical outcomes.

Level of Evidence: I Systematic reviews and meta-analyses [10, 14]

- A caveat be included that balanced solutions (Ringers Lactate, balsol/ Plasmalyte) may be appropriate in some patients.
  Rationale: Limited evidence (including RCT sub-analysis) shows that balanced solutions may be appropriate in certain patients (including critically ill patients presenting with hyperchloraemia, previous renal replacement therapy).

Level of Evidence: III RCT Sub-analysis[12], Disease-oriented RCTs of low methodological quality[15]

Review indicator:

Evidence of efficacy	Evidence of harm	Price reduction
[ ]	[X]	[ ]

VEN status:

Vital	Essential	Necessary
[X]	[ ]	[ ]

Monitoring and evaluation considerations

As the use of balanced solutions for certain groups of patients has been recommended, a large increase in the use of balanced fluids is not expected. Hospitals should monitor their consumption of Balanced solutions relative to Normal saline and ensure that Normal Saline remains the primary fluid used.

Research priorities

A clearer definition of the patient population who will benefit from Balanced Solutions.
Comparison between the Balanced Solutions
The compatibility of Balanced solutions with blood products and intravenous medications.

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National Essential Medicine List Adult Hospital Level
Medication Review Process
Component: Emergencies and injuries

Date of Review: October 2015

Medication: Ringer lactate

Indication: Resuscitation in patients with hypovolaemia

Executive summary: Normal Saline (NS) is recommended in the Adult Hospital Level EML 2012 for resuscitation in patients with hypovolaemia. The KwaZulu-Natal Pharmacy Therapeutics Committee (KZN PTC) commented that Ringer's Lactate (RL) should replace NS as the recommended fluid in these patients on the basis of "good evidence" suggesting RL has a favorable inflammatory profile compared with NS. Furthermore, KZN PTC stated that the use of NS was no longer supported by "current resuscitation council and critical care literature". A comparison between crystalloids, specifically normal saline vs so-called "balanced" solutions such as Ringer's Lactate was undertaken as debate centered around the potential of NS to cause hyperchloraemic metabolic acidosis.

Introduction:

Often referred to as 'normal saline', 0.9% saline contains sodium and chloride in supraphysiological concentrations. Balanced solutions, in contrast, contain significantly lower concentrations of sodium and chloride, making them closer in composition to plasma than 0.9 % saline. However, isotonic saline is often the preferred resuscitation fluid because of its nature and compatibility with blood transfusion. (Smith *et al*., 2015)

Despite its widespread use, isotonic saline has been linked to metabolic acidosis, immune suppression, and decreased renal perfusion. Isotonic saline has been shown to cause a metabolic acidosis in healthy volunteers and in patients undergoing elective surgical procedures. Relative to a balanced isotonic crystalloid, in which electrolyte composition is similar to plasma, isotonic saline infusion during resuscitation after trauma delays normalization of the pH and base deficit after injury. Furthermore, metabolic acidosis has been implicated in the development of coagulopathy, though its specific role has not been fully characterized. Consequently some guidelines recommend the use of balanced solutions as a default during resuscitation. (Smith *et al*., 2015)

A recent narrative review on the use of IV fluids in sepsis, published in 2013, showed that there is no strong evidence showing differences in the outcomes of using balanced or unbalanced crystalloids during resuscitation. The choice of intravenous fluid should be based on the underlying pathophysiology and should not be a 'one size fits all' approach. Given the available data, the authors recommended that balanced fluids should be considered in patients who have persistent hyperchloremic acidosis after receiving chloride-rich fluids. Furthermore, it was stated that type of crystalloids may not influence the clinical outcome. (Karakala *et al*., 2013)

Objective: To review the evidence comparing the use of NS with RL (and other crystalloids) in order to establish if RL should replace NS.

Results

One Cochrane Review was summarized: The Cochrane review undertaken by Burdett *et al*,. (2012) compared perioperative buffered versus non-buffered (normal saline) fluid administration for surgery in adults; in order to review the safety and efficacy of perioperative administration of buffered versus non-buffered (normal saline) fluids for plasma volume expansion or maintenance in adult patients undergoing surgery. Publications from Cochrane Central Register of Controlled Trials (CENTRAL) (2011, Issue 4), MEDLINE (1966 to May 2011), EMBASE (1980 to May 2011), and CINAHL (1982 to May 2011) were included. The reviewers also hand searched conference abstracts and where possible, contacted leaders in the field. Only RCTs of buffered versus non-buffered intravenous fluids for perioperative fluid resuscitation were included. The trials with other forms of comparisons such as crystalloids versus colloids and colloids versus different colloids were excluded. Trials using hypertonic fluids and dextrose-based fluids were excluded. Fourteen publications reporting 13 trials or comparisons with a total of 706 participants were included. The primary outcome of mortality at any time was reported in only three studies (n=267). The mortality rate was 2.9% for the buffered fluids group and 1.5% for the non-buffered fluids group but this difference was not statistically significant. Organ dysfunction was only presented for renal impairment. There was no difference in renal insufficiency leading to renal replacement therapy between the buffered and non-buffered groups (OR 0.61, 95% CI 0.23 to 1.63, P = 0.32, I^2 = 0%). Markers of organ system failure as assessed by urine output, creatinine and its variables (for renal function), $PaC0_2$ (respiratory function) and postoperative nausea and vomiting (gastro-intestinal function) showed a statistically significant difference only in $PaC0_2$ levels. The mean difference was 1.18 with lower $PaC0_2$ levels in the non-buffered fluid group (95% CI 0.09 to 2.28, P = 0.03, I^2 = 0%) compared to the buffered fluid group. There was no difference in intraoperative blood loss nor the volumes of intraoperative red cell or fresh frozen plasma transfused between groups. There was an increase in platelet transfusion in the non-buffered group which was statistically significant after analysing the transformed data (log transformation because the data were highly skewed). A number of metabolic differences were noted. There was a difference in postoperative pH of 0.06 units, lower in the non-buffered fluid group (95% CI 0.04 to 0.08, P < 0.00001, I2 = 74%). However, this difference was not maintained on postoperative day one. There was no difference demonstrated in length of hospital stay and no data were reported on cost or quality of life. ***The reviewers concluded that the administration of buffered fluids to adult patients during surgery is equally safe and effective as the administration of non-buffered saline-based fluids.*** The use of buffered fluids is associated with less metabolic derangement, in particular hyperchloraemia and metabolic acidosis. (Burdett *et al., 2012)*

The following three randomized control trails (one being an exploratory study within an RCT), one meta-analysis and one retrospective outcome study were submitted and reviewed. The Young et al study was published in October 2015 during the write up of this review.

Young *et al*., 2015 conducted a double-blind, cluster randomized, double-crossover trial conducted in 4 ICUs in New Zealand from April 2014 through October 2014 to determine the effect of a buffered crystalloid compared with saline on renal complications in patients. Three ICUs were general medical and surgical ICUs; 1 ICU had a predominance of cardiothoracic and vascular surgical patients. All patients admitted to the ICU requiring crystalloid fluid therapy were considered for inclusion. Patients with

established acute kidney injury (AKI) requiring renal replacement therapy (RRT) were excluded. All 2278 eligible patients were enrolled; 1152 of 1162 patients (99.1%) receiving buffered crystalloid and 1110 of 1116 patients (99.5%) receiving saline were analysed. Participating ICUs were assigned a masked study fluid, either saline or a buffered crystalloid, for alternating 7-week treatment blocks. Two ICUs commenced using 1 fluid and the other 2 commenced using the alternative fluid. Two crossovers occurred so that each ICU used each fluid twice over the 28 weeks of the study. The treating clinician determined the rate and frequency of fluid administration. The primary outcome was proportion of patients with AKI (defined as a rise in serum creatinine level of at least 2-fold or a serum creatinine level of≥3.96mg/dL with an increase of≥0.5mg/dL); main secondary outcomes were incidence of RRT use and in-hospital mortality. In the buffered crystalloid group, 102 of 1067 patients (9.6%) developed AKI within 90 days after enrollment compared with 94 of 1025 patients (9.2%) in the saline group (absolute difference, 0.4%[95%CI, −2.1%to 2.9%]; relative risk [RR], 1.04 [95%CI, 0.80 to 1.36]; P = .77). In the buffered crystalloid group, RRT was used in 38 of 1152 patients (3.3%) compared with 38 of 1110 patients (3.4%) in the saline group (absolute difference, −0.1% [95%CI, −1.6%to 1.4%]; RR, 0.96 [95%CI, 0.62 to 1.50]; P = .91). Overall, 87 of 1152 patients (7.6%) in the buffered crystalloid group and 95 of 1110 patients (8.6%) in the saline group died in the hospital (absolute difference, −1.0% [95%CI, −3.3%to 1.2%]; RR, 0.88 [95%CI, 0.67 to 1.17]; P = .40). ***Among patients receiving crystalloid fluid therapy in the ICU, use of a buffered crystalloid compared with saline did not reduce the risk of AKI.***

Smith *et al.,* (2015) conducted an exploratory analysis in a subset of participants from a larger RCT, comparing the effect of resuscitation with normal saline (NS) versus Plasma-Lyte A (PLA) on acidosis and electrolyte abnormalities. Since metabolic acidosis has been associated with coagulopathy, the study sought to explore whether resuscitation of injured patients with a balanced crystalloid solution affects coagulation, as measured by endogenous thrombin potential (ETP) and thromboelastography (TEG). Among 18 evaluated subjects, at 6 h, subjects receiving NS were more acidaemic. At 6 h, there were no differences in ETP parameters between groups; however, TEG results showed the time from initial clot formation to an amplitude of 20 mm (K) was shorter (3.8 ± 2.1 vs. 7.2 ± 2.8 s) and the rapidity of fibrin build-up and cross-linking (α angle) was significantly greater (41 ± 8 vs. 24 ± 15 deg) for the PLA group than in the isotonic saline group. ***The conclusion was that relative to PLA, NS does not alter thrombin generation, but isotonic saline and PLA may differentially impact clotting factor availability. "The results suggest that resuscitation with saline may impair the clotting process and perhaps contribute obliquely to post injury coagulopathy."***

Krawjewski *et al*., (2014) conducted a meta-analysis on 21 studies (n= 6253) to assess the relationship between the chloride content of intravenous resuscitation fluids and patient outcomes in the perioperative or intensive care setting. The primary outcomes of interest were mortality, measures of kidney function, serum chloride, hyperchloraemia/metabolic acidosis, blood transfusion volume, mechanical ventilation time, and length of hospital and intensive care unit stay, high-chloride fluids did not affect mortality but were associated with a significantly higher risk of acute kidney injury (RR 1.64, 95 per cent c.i. 1.27 to 2.13; P <0.001) and hyperchloraemia/metabolic acidosis (RR 2.87, 1.95 to 4.21;P *<0.001).* High-chloride fluids were also associated with greater serum chloride (Mean Difference 3.70 (95 per cent c.i. 3.36 to 4.04) mmol/l; P <0.001), blood transfusion volume (Standardized Mean Difference 0.35, 0.07 to 0.63; P =0.014) and mechanical ventilation time (SMD 0.15, 0.08 to 0.23; P <0.001). ***The authors concluded that a weak but significant association between higher chloride content fluids and unfavorable outcomes was found, but mortality was unaffected by chloride content.***

Gunnerson et al., 2006 conducted a retrospective outcome evaluation of critically ill patients in an ICU environment (n=9799). They concluded that not all metabolic acidosis are the same. Through the cohort study, the researchers showed that each type of metabolic acidosis had a different mortality associated with it. There was increased mortality associated with lactate and unidentified anions (SIG). Metabolic acidosis (both lactic and non-lactic) was associated with high mortality and increased length of stay in hospital and in the ICU. This study did not compare specific IV fluids and its relation to metabolic acidosis. A total of 548 patients (64%) had a metabolic acidosis (standard base excess < -2 mEq/l) and these patients had a 45% mortality, compared with 25% for those with no metabolic acidosis ($p < 0.001$). Metabolic acidosis cases were sub classified on the basis of the predominant anion present (lactate, chloride, or all other anions). The mortality rate was highest for lactic acidosis (56%); for strong ion gap (SIG) acidosis it was 39% and for hyperchloremic acidosis 29% ($p < 0.001$). Of relevance was that hyperchloraemic acidosis was associated with mortality similar to that of the non-acidotic group (29% versus 26%; p = NS), despite many cases of hyperchloremic acidosis occurring in the NS group (that can mostly be avoided by resuscitating with a more balanced solution such as RL). ***This study was not a direct comparison of RL to NS but reviewed more the "condition" of metabolic acidosis and it's outcomes.***

Waters et al., (2001) sought to determine if metabolic acidosis and changes in serum osmolarity are consequences of 0.9% normal saline (NS) solution and if administration influences patient outcome. In a double blinded study patients undergoing aortic reconstructive surgery were randomly assigned to receive lactated Ringer's (LR) solution (n =33) or NS (n= 33). Anesthetic and fluid management were standardized. Multiple measures of outcome were monitored. ***The NS patients developed a hyperchloremic acidosis and received more bicarbonate therapy (30±62mLin the NS group versus 4±16mLin the LR group; mean±sd), which was given if the base deficit was greater than 5 mEq/L. The NS patients also received a larger volume of platelet transfusion (478 ± 302 mL in the NS group versus 223±24 mL in the LR group; mean ± sd). When all blood products were summed, the NS group received significantly more blood products (P=0.02). No difference in the postoperative complications nor death was seen. No difference was seen in the ventilator time (45.6 ± 147.2 h in the LR group versus 29.7 ± 61.8 h in the NS group), ICU time (4.1 ± 7.6 days in the LR group versus 2.8 ± 3.8 days in the NS group), nor hospital stay (10.1 ± 8.3 days in the LR group versus8.9 ± 4.7 h in the NS group). A significant difference in the volume of bicarbonate (3.8 ± 15.5 mL in the LR group versus 40.2 ± 64.0 mL in the NS group) used during the operative period was seen but there was no difference in the postoperative period. These changes should be considered when choosing fluids for surgical procedures involving extensive blood loss and requiring extensive fluid administration.***

Table 1: Evidence table of RCTs identified for this review

Study (year)	Study design	Participants (studies) Follow up	Study comparators	Summary of findings					Quality of study	Risk of bias
				Study event rates (%)		Absolute risk reduction (95% CI)	NNT/NNH:	Relative risk: (95% CI)		
				Intervention	Comparator					
Smith et al., 2013	Prospectively planned exploratory sub study within an RCT	n=18	Isotonic saline vs. Plasma-Lyte A (PLA)	***Primary outcome:*** Endogenous thrombin potential (ETP) or thrombogram, which correlates with both hypercoagulable and hypocoagulable states. Thromboelastography (TEG), a whole blood-based examination of global hemostasis. "There were no significant differences between the isotonic saline and PLA groups for any of the ETP parameters (t-lag, t-max, C-max, or AUC) measured at 0 or 6 h. Baseline values on admission for R, K, α angle, maximum amplitude were similar between the isotonic saline and PLA groups. At 6 h, the α angle was significantly greater and there was a trend toward K being shorter in the PLA group vs. the isotonic saline group [41_8 vs. 24_15 degrees (P=0.008) and 3.7±2.1 vs. 7.2±2.8 s (p=0.06), respectively]."					Study groups were similar at baseline Small number of participants Patients were randomized in the parent study and parent study was powered to determine differences in acidosis and base deficit, however it was not designed to detect differences in coagulation parameters. TEG analysis performed on frozen plasma.	n/a

Krajewski et al., 2014	Systematic searches of PubMed/MEDLINE, Embase and Cochrane Library (CENTRAL) databases in accordance with PRISMA guidelines. RCTs and observational studies included	21 studies involving 6253 patients		***Primary outcome:*** Mortality, measures of kidney function, serum chloride, hyperchloraemia/metabolic acidosis, blood transfusion volume, mechanical ventilation time, and length of hospital and intensive care unit stay High-chloride fluids did not affect mortality but were associated with a significantly higher risk of acute kidney injury (RR 1.64, 95 per cent c.i. 1.27 to 2.13; P <0.001) and hyperchloraemia/metabolic acidosis (RR 2.87, 1.95 to 4.21;P <0.001). High-chloride fluids were also associated with greater serum chloride (MD 3.70 (95 per cent c.i. 3.36 to 4.04) mmol/l; P <0.001), blood transfusion volume (SMD 0.35, 0.07 to 0.63; P =0.014) and mechanical ventilation time (SMD 0.15, 0.08 to 0.23; P <0.001). MD = mean difference and SMD – standardized mean difference.	Conducted sensitivity analyses Risk of bias was assessed using for RCTs, the seven-category Review Manager risk of bias tool and for non-RCTs, the Newcastle–Ottawa Scale (NOS) was used	
Gunnerson et al., 2006	Retrospective outcome evaluation	Cohort of patients in which lactic acidosis was suspected but, other acid–base abnormalities might be present. Resulted in 9,799 ICU admissions being identified. 548 patients (64%) had a metabolic acidosis (standard base excess < -2 mEq/l)		***Primary outcome:*** Mortality in metabolic acidosis patients 45% mortality, compared with 25% for those with no metabolic acidosis (p < 0.001). Metabolic acidosis cases were sub classified on the basis of the predominant anion present (lactate, chloride, or all other anions). The mortality rate was highest for lactic acidosis (56%); for strong ion gap (SIG) acidosis it was 39% and for hyperchloremic acidosis 29% (p < 0.001).	Retrospective study which means some patients data might have not have been included if variables were missing. Unable to control for severity of illness between groups. The classification scheme used might have resulted in a combined lactic/SIG acidosis being misclassified as hyperchloremic. Hyperchloremic cases could have been misclassified as either SIG or lactic acidosis if pre-existing or concomitant metabolic alkalosis was also present, decreasing the apparent impact of chloride.	Attrition: 1 pt in each group lost to follow up.

Waters *et al*., 2001	Double blinded study	Sixty-six patients (33 patients in the Ringers Lactate group, 33 patients in the NS group)	Ringers Lactate vs Normal Saline	***Primary outcome:*** Metabolic Acidosis NS resulted in significantly more acidosis on completion of surgery. This acidosis resulted in no apparent change in outcome but required larger amounts of bicarbonate to achieve predetermined measurements of base deficit and was associated with the use of larger amounts of blood products. ***Secondary outcome(s):*** Duration of mechanical ventilation, intensive care unit stay, hospital stay, and incidence of complications *No differences noted*	Sample size might not have been powered enough to find differences in the sub group analyses/multiple outcomes	
Young et al., 2015	Double-blind, cluster randomized, double-crossover trial	3 ICUs. All 2278 eligible patients were enrolled; 1152 of 1162 patients (99.1%) receiving buffered crystalloid and 1110 of 1116 patients (99.5%) receiving saline were analysed	Buffered crystalloid compared with saline on renal complications in patients	***Primary outcome:*** The primary outcome was proportion of patients with Acute Kidney Injury defined as a rise in serum creatinine level of at least 2-fold or a serum creatinine level of≥3.96mg/dL with an increase of≥0.5mg/dL); In the buffered crystalloid group, 102 of 1067 patients (9.6%) developed AKI within 90 days after enrollment compared with 94 of 1025 patients (9.2%) in the saline group (absolute difference, 0.4%[95%CI, −2.1%to 2.9%]; relative risk [RR], 1.04 [95%CI, 0.80 to 1.36]; P = .77). ***Secondary outcome(s):*** Incidence of RRT use and in-hospital mortality. In the buffered crystalloid group, RRT was used in 38 of 1152 patients (3.3%) compared with 38 of 1110 patients (3.4%) in the saline group (absolute difference, −0.1% [95%CI, −1.6%to 1.4%]; RR, 0.96 [95%CI, 0.62 to 1.50]; P = .91). Overall, 87 of 1152 patients (7.6%) in the buffered crystalloid group and 95 of 1110 patients (8.6%) in the saline group died in the hospital (absolute difference, −1.0% [95%CI, −3.3%to 1.2%]; RR, 0.88 [95%CI, 0.67 to 1.17]; P = .40).	Saline use is associated with the development of hyperchloremia and metabolic acidosis and the occurrence of these phenomena may have led clinicians to correctly deduce which fluid was which over the course of a block of treatment. Sample size calculations not performed 90% of patients might have recievd fluids before ICU admission.	n/a

Evidence Quality

Young et al.,(2015) did not perform sample size calculations. Dealing with a critically ill population more than 90% of patients were exposed to intravenous fluids before enrolment and the majority of pre-enrollment fluid was buffered crystalloid.

The Smith et al., (2015) study was limited by it being exploratory on a small sample size of RCT patients (n=18). Study groups were similar at baseline. The TEG analysis was conducted on frozen plasma and not on whole blood. Although groups were similar at baseline, the small number of participants limited the study's power to detect differences in coagulation parameters.

The Krawjewski et al., (2014) meta-analysis prompted caution with the intravenous administration of supraphysiological concentrations of chloride (above 111 mmol/l). However, most of the studies included in the meta analysis were small in size, thereby preventing firm conclusions from being drawn.

The Gunnerson et al., study (2006) has several limitations. The researchers conducted a retrospective study which means some patients data might have not have been included if variables were missing. Secondly, the researchers were unable to control for severity of illness between groups. The classification scheme used might have resulted in a combined lactic/SIG acidosis being misclassified as hyperchloremic. Conversely, some hyperchloremic cases could have been misclassified as either SIG or lactic acidosis if pre-existing or concomitant metabolic alkalosis was also present, decreasing the apparent impact of chloride.

A limitation of the Waters et al., study (2001) is that the sample size was not large enough to detect a meaningful difference on the various outcomes discussed.

Safety Information

In a review, Prough and Bidani (1999) indicated that most literature indicates that hyperchloraemic acidosis is not hazardous. However, correct treatment is dependent on differentiating between hyperchloraemic acidosis vs lactic acidosis.

Summary

No studies were found directly comparing NS and RL in haemorrhagic shock and in critically ill patients. However, the recent SPLIT Trial, conducted in critically ill patients, assessed effect of a buffered crystalloid compared with saline on renal complications in patients in New Zealand and concluded that use of a buffered crystalloid compared with saline did not reduce the risk of Acute Kidney Injury." (Young *et al*.,2015) . Other studies outlined above showed that that the administration of buffered fluids to adult patients during surgery is equally safe and effective as the administration of non-buffered saline-based fluids. One study did show that isotonic saline and PLA may differentially impact clotting

factor availability (Smith *et al*., 2015). Krawjewski *et al*. (2014) showed that there was a weak but significant association between higher chloride content fluids and unfavorable outcomes, but mortality was unaffected by chloride content. Waters *et al*. (2001) raise the point that because NS causes hyperchloremic acidosis and a significant difference in the volume of bicarbonate required during the operative period with NS was noted; such changes should be considered when choosing fluids for surgical procedures involving extensive blood loss and requiring extensive fluid administration.

Overall, the majority of current data might not be considered robust to select one treatment over the otehr, and limited to small RCTs and observational studies. The recent study in New Zealand did not show reduced risk in negative renal outcomes in using a buffered solution.

Further large randomized clinical trials are needed to assess efficacy in higher-risk populations and to measure clinical outcomes such as mortality. Evidence is limited regarding the effects of hyperchloraemic acidosis on hard clinical outcomes.

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