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N. E. Hammond
C. Taylor
M. Saxena
B. Liu
S. Finfer
P. Glass
I. Seppelt
L. Willenberg
J. Myburgh

Resuscitation fluid use in Australian and New Zealand Intensive Care Units between 2007 and 2013

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For the George Institute for Global Health and the Australian and New Zealand Intensive Care Society Clinical Trials Group.

Take-home message: Fluid resuscitation in Australian and New Zealand ICUs changed over a 6-year period with an increased use of crystalloids, primarily due to increased use of buffered salt solutions. Albumin is the most commonly used colloid solution, although the overall use of colloids has decreased, associated with a decrease in the use of gelatin solutions and negligible use of HES.

Electronic supplementary material
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N. E. Hammond (✉) · C. Taylor · M. Saxena · B. Liu · S. Finfer · P. Glass · I. Seppelt · L. Willenberg · J. Myburgh
Division of Critical Care and Trauma, The George Institute for Global Health, University of Sydney, Sydney, Australia
e-mail: nhammond@georgeinstitute.org.au

N. E. Hammond · S. Finfer
Malcolm Fisher Department of Intensive Care Medicine, Royal North Shore Hospital, St Leonards, Australia

N. E. Hammond · C. Taylor · S. Finfer · P. Glass · I. Seppelt
Sydney Medical School, University of Sydney, Sydney, Australia

M. Saxena · J. Myburgh
Department of Intensive Care Medicine, St George Hospital, Kogarah, Australia

B. Liu
School of Public Health and Community Medicine, The University of New South Wales, Sydney, Australia

I. Seppelt
Department of Intensive Care Medicine, Nepean Hospital, Kingswood, Australia

N. E. Hammond · M. Saxena · J. Myburgh
St George Clinical School, University of New South Wales, Sydney, Australia

Abstract *Introduction:* Recent evidence indicates that the choice of intravenous fluids may affect outcomes in critically ill patients. *Methods:* We recorded the administration of resuscitation fluids in patients admitted to Australian and New Zealand adult intensive care units (ICUs) for a 24-h period at 6 time points between 2007 and 2013. Changes in patterns of fluid use over this period were determined using regression analyses. *Results:* Of the 2825 patients admitted to the 61 ICUs on the 6 study days, 754 (26.7 %) patients received fluid resuscitation. Of those receiving fluid resuscitation, the proportion of patients receiving crystalloid significantly increased from 28.9 % (41/142) in 2007 to 50.5 % (48/95) in 2013 (adjusted odds ratio (OR) 2.93; 95 % confidence intervals (CI) 1.35–6.33; $p = 0.006$); of these, the proportion of patients receiving buffered salt solutions significantly increased from 4.9 % (7/142) in 2007 to 31.6 % (30/95) in 2013 (OR 7.00; 95 % CI 2.14–22.92; $p = 0.001$). The use of colloids significantly decreased from 59.9 % (85/142) in 2007 to 42.1 % (40/95) in 2013 (adjusted OR 0.34; 95 % CI 0.16–0.74; $p = 0.007$) due to a significant decrease in the proportion of patients receiving gelatin; 28.9 % (41/142) to 2.1 % (2/95) (OR 0.10; 95 % CI 0.03–0.29; $p \leq 0.001$). *Conclusion:* Fluid resuscitation practice in Australia and New Zealand adult ICUs has changed over the 6-year study period. Crystalloid use increased primarily due to an increase in the use of buffered salt solutions while overall the use of colloid has decreased.

Keywords Intensive care · Fluid resuscitation · Colloid · Crystalloid · Point prevalence · Time trend

Introduction

The intravenous administration of colloids or crystalloids for fluid resuscitation is one of the most common interventions in intensive care medicine [1]. In the last decade, a number of pivotal randomised controlled trials (RCTs) have demonstrated that the type of fluid used for resuscitation, particularly colloids such as albumin and hydroxyethyl starch (HES), may affect patient-centred outcomes [2–8].

In 2004 the saline versus albumin fluid evaluation (SAFE) study compared resuscitation with 4 % albumin to 0.9 % saline in 6997 intensive care unit (ICU) patients [2]. No significant difference in 28-day mortality between the two groups was observed, although albumin was associated with increased long-term mortality in patients with severe traumatic brain injury [6].

In 2008, the volume substitution and insulin therapy in severe sepsis (VISEP) trial compared resuscitation with 10 % hydroxyethyl starch (HES) 200/0.5 to Ringer's lactate in 537 patients with severe sepsis [3]. Although no significant difference in the primary outcome of 28-day mortality was observed, HES was associated with a significant increase in the risk of developing acute renal failure and use of renal replacement therapy.

In 2012, three fluid resuscitation trials were completed. The scandinavian starch in severe sepsis/septic shock (6-S) trial compared resuscitation with 6 % HES 130/0.42 to Ringer's acetate in 804 intensive care patients with severe sepsis [5]. Resuscitation with HES was associated with an increase in 90-day mortality and use of renal replacement therapy. The CRYSTMAS study [9] compared the effects of 6 % HES 130/0.4 to 0.9 % saline in 196 patients with severe sepsis on attainment of haemodynamic stability; no difference in 90-day mortality was reported. The Crystalloid versus Hydroxyethyl Starch Trial (CHEST) compared resuscitation with 6 % HES 130/0.4 to 0.9 % saline in 7000 intensive care patients [4] and reported no difference in 90-day mortality but an increase in the use of renal replacement therapy in patients assigned to receive HES.

The results of these trials and subsequent high-quality systematic reviews [10–14] were influential to amendments to clinical practice guidelines [15, 16] and to licencing approvals for these fluids by International Medical Regulatory Authorities [17–22].

Emerging evidence, primarily from observational studies have raised concerns about the safety and efficacy of crystalloid solutions, particularly the use of 0.9 % saline, suggesting that solutions containing high chloride concentrations may be associated with the development of acute kidney injury compared to solutions with lower chloride concentrations such as compound sodium lactate or 'buffered'/'balanced' salt solutions [23–25].

In light of these developments, our objective was to determine trends and patterns of the use of resuscitation fluids in Australia and New Zealand.

Methods

Between 2007 and 2013, we conducted six cross-sectional point prevalence studies on the use of resuscitation fluids in Australian and New Zealand ICUs. The first of these studies was an international cross-sectional study conducted in 2007 following the completion of the SAFE study (the SAFE-Translation of Research Into Practice Study (SAFE-TRIPS) [1]). Subsequent studies from 2009 to 2013 were conducted through the Point Prevalence Program established by the Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group and The George Institute for Global Health, Sydney, Australia.

Australian and New Zealand data were extracted from the SAFE-TRIPS database. For each subsequent point prevalence study, participating ICUs from the ANZICS Clinical Trials Group network collected data on all patients present in the ICU at a 10 am census point on a prespecified day in December 2009, September 2011, May 2012, November 2012, and November 2013 (Supplementary Appendix 1). Data were entered into an electronic data capture system (REDCap; Vanderbilt University, Tennessee, USA) hosted at The George Institute for Global Health [26].

Participants and data collection

Human Research Ethics Committee approval was obtained at each participating hospital for each point prevalence day; the need for individual patient consent was waived at all sites. Data were included if patients were 16 years or older on the study day and required intravascular volume expansion at any time on the study day defined as a bolus of crystalloid or colloid, a crystalloid infusion of 5 ml/kg/h (or 400 ml/h) or greater for one or more hours and any colloid infusion. Patients were excluded if they did not require intravascular volume expansion on the study day.

Data collected included demographics (age and sex) and clinical characteristics [Acute Physiological And Chronic Health Evaluation (APACHE) II score [27]]; number of days in the ICU; admission diagnosis; predefined subgroup characteristics (sepsis and traumatic brain injury), and information on the type of fluid administered for resuscitation. The type of fluid given for resuscitation was classified into categories of crystalloid or colloid (Supplementary Appendix 2).

Statistical analysis

Analyses were carried out using SAS software v.9.2 (Cary, NC, USA). Patient demographics, clinical characteristics and fluid type received were described using proportions for categorical data and means ± standard deviations (SD) for continuous data. Differences in fluid types administered over the time points were determined using a generalised linear model adjusting for potential confounders and for sites that participated in more than one study day. Predetermined confounders were age, illness severity (APACHE II), admission source, post-operative versus non-operative admission, an admission diagnosis of trauma or sepsis, and time from ICU admission in days. Associations between fluid type (crystalloid or colloid) and individual confounders, with time retained as a constant covariate, were determined; those meeting a pre-defined level of statistical significance ($p < 0.1$) were included in the final model (Supplementary Appendix 3). Patterns in crystalloid and colloid use are reported as unadjusted proportions over time and unadjusted, and where indicated adjusted odds ratios (OR). Patients with sepsis and traumatic brain injury were analysed separately using the same methods. Patterns of selected individual fluid use were reported as proportions over time and as unadjusted odds ratios.

Sensitivity analysis

A pre-defined sensitivity analysis including the sites that participated for ≥5 time points was conducted.

Results

Patient and ICU characteristics

Over the six study days, data were collected on 2825 patients admitted to 61 ICUs of whom 754 (26.7 %) patients received fluid for resuscitation. The number of patients, sites and patient characteristics at each data collection time point are shown in Table 1. Across the six time points, the numbers of participating sites ranged from 23 to 44 and the total number of patients from 399 to 596. The proportion of patients receiving resuscitation fluid across the six time points ranged between 19.6 and 35.1 %.

Type of resuscitation fluid use in patients receiving fluids

Among patients receiving resuscitation fluids, the proportion receiving crystalloids significantly increased from 28.9 % (41/142) in 2007 to 50.5 % (48/95) in 2013 (Fig. 1) (OR 2.59; 95 % confidence intervals (CI) 1.30–5.18; $p = 0.007$).

Of the predetermined confounders, illness severity, admission source, post-operative admission, trauma, days in ICU, and sepsis were associated with the use of crystalloid fluid and time ($p < 0.1$) and included in the regression model (Supplementary Appendix 3). Compared to 2007, the adjusted odds of receiving a crystalloid at each subsequent time point were 1.34 (95 % CI 0.50–3.60; $p = 0.566$), 1.50 (95 % CI 0.64–3.56; $p = 0.353$), 3.24 (95 % CI 1.38–7.54; $p = 0.007$), 5.11 (95 % CI 2.00–13.07; $p \leq 0.001$), and 2.93 (95 % CI 1.35–6.33; $p = 0.006$) across 2009–2013 respectively (Fig. 2).

Regarding specific crystalloids, the proportion of patients receiving buffered salt solutions significantly increased from 4.9 % (7/142) in 2007 to 31.6 % (30/95) in 2013 (Fig. 3a) (OR 7.00; 95 % CI 2.14–22.92; $p = 0.001$) (Supplementary Appendix 4). The proportion receiving 0.9 % saline did not significantly change over the time: 18.3 % (26/142) in 2007 and 15.8 % (15/95) in 2013 (Fig. 3a) (OR 1.12; 95 % CI 0.45–2.79; $p = 0.803$) (Supplementary Appendix 4).

The proportion of patients receiving colloid significantly decreased from 2007 (59.9 %; 85/142) to 2013 [(42.1 %; 40/95) (Fig. 1); OR 0.42; 95 % CI 0.20–0.88; $p = 0.021$] compared to the odds of receiving colloid in 2007.

Age, admission source, post-operative admission, trauma, days in ICU, and sepsis were included in the regression model (Supplementary Appendix 3). Compared to 2007, the adjusted odds of receiving a colloid was 0.58 (95 % CI 0.32–1.08; $p = 0.088$), 0.43 (95 % CI 0.22–0.82; $p = 0.011$), 0.52 (95 % CI 0.25–1.05; $p = 0.067$), 0.29 (95 % CI 0.15–0.56; $p \leq 0.001$), and 0.34 (95 % CI 0.16–0.74; $p = 0.007$) across 2009 to 2013 respectively (Fig. 2).

Regarding specific colloids, the proportion of patients who received 4–5 % albumin did not change significantly over the time points: 36.6 % (52/142) in 2007 compared to 31.6 % (30/95) in 2013 (Fig. 3b) (OR 0.57; 95 % CI 0.27–1.22; $p = 0.150$) (Supplementary Appendix 4). Similarly, the proportion of patients receiving concentrated albumin did not significantly change from 4.2 % (6/142) in 2007 to 11.6 % (11/95) in 2013 (Fig. 3b) (OR 3.02; 95 % CI 0.93–9.78; $p = 0.065$) (Supplementary Appendix 4). There was a significant decrease in the proportion of patients receiving gelatin for fluid resuscitation over the time points: 28.9 % (41/142) in 2007 compared to 2.1 % (2/95) in 2013 (Fig. 3b) (OR 0.10; 95 % CI 0.03–0.29; $p \leq 0.001$) (Supplementary Appendix 4). The proportion of patients receiving HES did not change from 2007 to 2013 (0–3.6 %) (Fig. 3b).

Table 1 Patient characteristics

	Month year (time point)						Total *n* (all study days)
	April–July 2007 (1)	December–February 2009/10 (2)	September–October 2011 (3)	May–June 2012 (4)	November–December 2012 (5)	November–December 2013 (6)	
Participating sites, *n* (%)	23 (37.7)	33 (54.1)	39 (63.9)	44 (72.1)	33 (54.1)	30 (49.2)	61
All patients, *n* (%)	404 (14.3)	455 (16.1)	511 (18.1)	596 (21.1)	460 (16.3)	399 (14.1)	2825
Patients receiving fluid, *n* (%)	142 (35.1)	128 (28.1)	131 (25.6)	168 (28.2)	90 (19.6)	95 (23.8)	754
Fluid patient characteristics							
Age in years, mean (±SD)	59.2 ± 18.1	60.7 ± 16.4	60.3 ± 17.8	62.7 ± 16.5	61.6 ± 18.6	60.2 ± 16.4	
Male sex, *n* (%)	96 (67.6)	81 (64.8)	80 (61.1)	103 (61.3)	46 (51.1)	55 (57.9)	461
APACHE II, mean (±SD)	16.5 ± 7.3	20.2 ± 7.8	20.5 ± 7.7	19.7 ± 8.1	19.7 ± 7.1	20.2 ± 7.3	
Reason for admission to ICU							
Surgical, *n* (%)	75 (52.8)	61 (48.8)	47 (36.2)	73 (43.5)	31 (34.4)	41 (43.2)	328
Medical, *n* (%)	67 (47.2)	64 (51.2)	83 (63.8)	95 (56.5)	59 (65.6)	54 (56.8)	422
Source of admission to ICU							
Emergency room, *n* (%)	17 (12.0)	27 (21.1)	36 (27.5)	47 (28.0)	23 (25.6)	21 (22.1)	171
Hospital floor, *n* (%)	27 (19.0)	13 (10.2)	25 (19.1)	26 (15.5)	13 (14.4)	12 (12.6)	116
Transfer from other ICU, *n* (%)	1 (0.7)	3 (2.3)	5 (3.8)	2 (1.2)	2 (2.2)	8 (8.4)	21
Transfer from other hospital, *n* (%)	11 (7.8)	13 (10.2)	12 (9.2)	12 (7.1)	12 (13.3)	12 (12.6)	72
Operating room (emergency surgery), *n* (%)	24 (16.9)	20 (15.6)	20 (15.3)	28 (16.7)	14 (15.6)	9 (9.5)	115
Operating room (elective surgery), *n* (%)	46 (32.4)	37 (28.9)	23 (17.6)	41 (24.4)	16 (17.8)	29 (30.5)	192
Predefined subgroups							
Trauma, *n* (%)	14 (10.0)	18 (14.9)	25 (19.1)	14 (8.3)	12 (13.6)	6 (6.3)	89
Traumatic brain injury, *n* (%)	7 (4.9)	7 (5.5)	8 (6.1)	5 (3.0)	4 (4.4)	1 (1.1)	32
Number of days in ICU at study day, median (IQR)	1.5 (1, 6)	1 (1, 9)	2 (1, 6)	2 (1, 3)	3 (1, 10)	1 (1, 3)	
Sepsis patients receiving fluid characteristics							
Sepsis patients receiving fluid, *n* (%)	32 (22.5)	46 (35.9)	53 (40.5)	59 (35.1)	23 (25.6)	34 (35.8)	247
Age years, mean (±SD)	59.2 ± 16.6	59.5 ± 15.9	62.3 ± 15.8	62.8 ± 15.6	56.7 ± 20.1	58.3 ± 16.1	
Male sex, *n* (%)	21 (65.6)	28 (62.2)	34 (64.2)	33 (55.9)	9 (39.1)	24 (70.6)	149
APACHE II, mean (±SD)	18.2 ± 7	23.4 ± 7.7	22.4 ± 7.5	22 ± 7.5	21.5 ± 7.2	24.3 ± 8.2	
Reason for admission to ICU							
Surgical, *n* (%)	8 (25.0)	15 (33.3)	12 (23.1)	16 (27.1)	4 (17.4)	7 (20.6)	62
Medical, *n* (%)	24 (75.0)	30 (66.7)	40 (76.9)	43 (72.9)	19 (82.6)	27 (79.4)	183
Source of admission to ICU							
Emergency room, *n* (%)	5 (15.6)	14 (30.4)	12 (22.6)	22 (37.3)	7 (30.4)	10 (29.4)	70
Hospital floor, *n* (%)	9 (28.1)	4 (8.7)	18 (34.0)	12 (20.3)	4 (17.4)	7 (20.6)	54
Transfer from other ICU, *n* (%)	0 (0)	3 (6.5)	3 (5.7)	1 (1.7)	1 (4.4)	5 (14.7)	13
Transfer from other hospital, *n* (%)	5 (15.6)	5 (10.9)	4 (7.6)	4 (6.8)	5 (21.7)	5 (14.7)	28
Operating room (emergency surgery), *n* (%)	6 (18.8)	6 (13.0)	7 (13.2)	10 (17.0)	3 (13.0)	1 (2.9)	33
Operating room (elective surgery), *n* (%)	0 (0)	8 (17.4)	3 (5.7)	4 (6.8)	1 (4.4)	4 (11.8)	20
Predefined subgroup							
Trauma, *n* (%)	2 (6.3 %)	4 (9.3)	8 (15.1)	4 (6.8)	4 (17.4)	2 (5.9)	24
Number of days in ICU at study day, median (IQR)	4 (1.5, 8)	9 (1, 15)	4 (2, 12)	3 (1, 9)	3 (1, 16)	2 (1, 4)	

Resuscitation fluid use in patients with sepsis

Of the patients that received fluid, 33 % had an admission diagnosis of sepsis (247/754) (Table 1).

The proportion of sepsis patients receiving crystalloids significantly increased from 15.6 % (5/32) in 2007 to 44.1 % (15/34) in 2013 (Fig. 4a) (adjusted OR 3.18; 95 % CI 1.01–10.00; $p = 0.048$).

The proportion of sepsis patients receiving colloids did not significantly change from 59.4 % (19/32) in 2007 to 52.9 % (18/34) in 2013 (Fig. 4b) (adjusted OR 0.79; 95 % CI 0.25–2.46; $p = 0.683$).

Resuscitation fluid use in patients with traumatic brain injury

Of all the patients that received fluid over the 6 study days, 32/754 (4.2 %) had traumatic brain injury (Table 1). The small numbers of this patient population precluded any analyses.

Sensitivity analysis

A sensitivity analysis was conducted using data from 15 sites ($n = 15/61$; 24.6 %) that participated in five or more time points: 329/1334 (24.7 %) patients were included. There was no difference in trends in this analysis compared to those in the main analysis (Supplementary Appendix 5).

Discussion

Key findings

Between 2007 and 2013, fluid resuscitation practices in Australian and New Zealand ICUs changed substantially. Our results demonstrated a significant increase in the use of crystalloid solutions, specifically buffered salt solutions and a decrease in the use of colloids, specifically gelatin.

Relationship to previous work

Prior studies on the use of resuscitation fluids are primarily based on clinician surveys rather than studies reporting actual fluid use. International surveys suggest variability in preferences for crystalloid or colloid use [28–30]. Our study conducted in Australian and New Zealand ICUs demonstrated temporal changes in fluid use that may reflect a change in clinical practice following the publication of landmark fluid resuscitation research [2–7].

Clinical implications/significance

Although 0.9 % saline remains the most commonly used resuscitation fluid and crystalloid both in Australia and New Zealand and worldwide [1], the increased use of buffered salt solutions observed in our study may have been influenced by emerging evidence about potential nephrotoxicity with the use of 0.9 % saline, particularly in patients with sepsis [23, 24, 31–33]. In addition, factors such as institutional preferences and cost may also have had an influence.

Factors potentially influencing the overall reduction in the use of colloid solutions may include consistent conclusions from high-quality RCTs [3–5] and systematic reviews [10–14] reporting the lack of benefit associated with colloids on patient-centred outcomes such as mortality and an increased risk of acute kidney injury requiring renal replacement therapy. In addition, there is no clinically

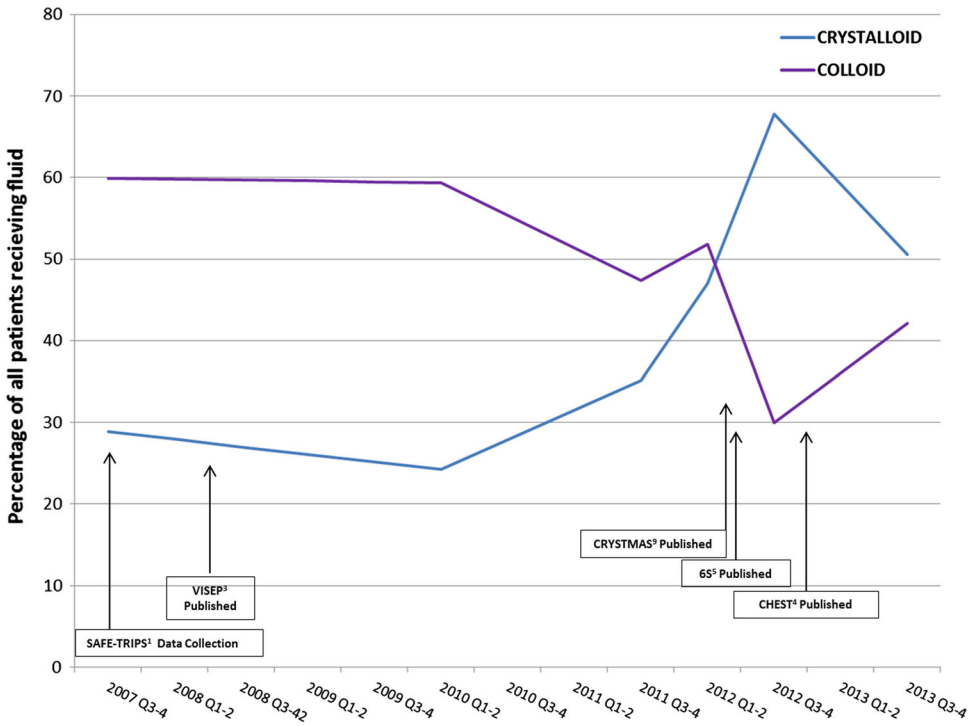

Fig. 1 Time trend of crystalloid and colloid administered between 2007 and 2013 in relation to key published research

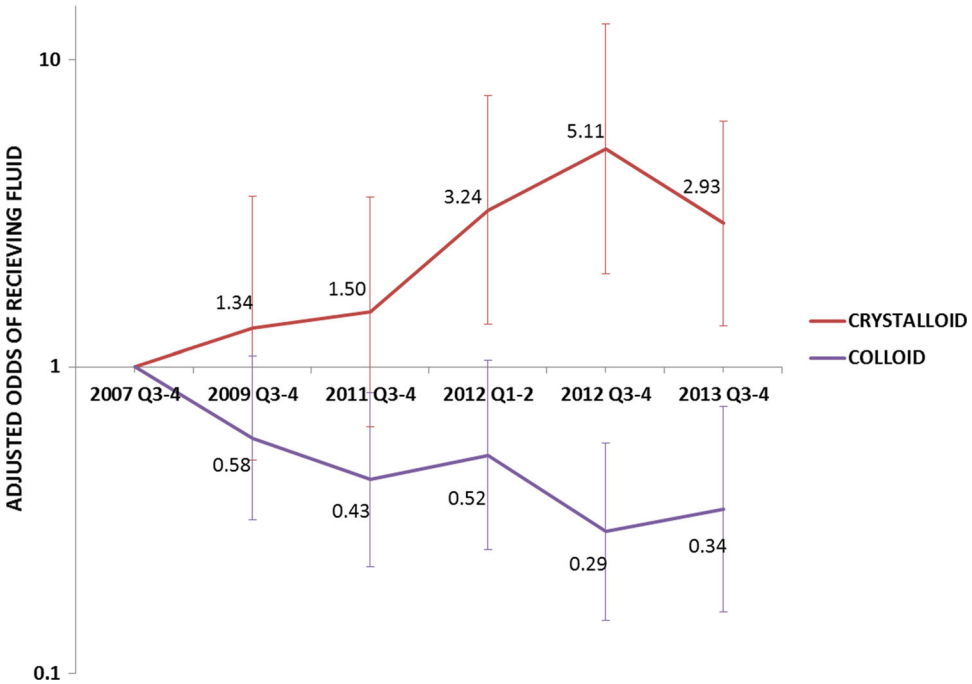

Fig. 2 Adjusted odds of patients receiving a crystalloid or colloid for fluid resuscitation

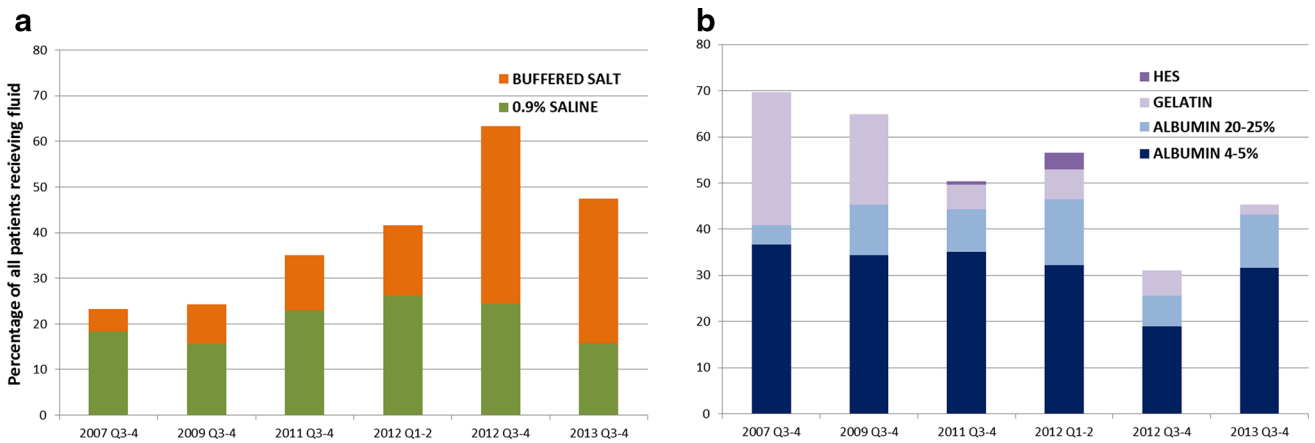

Fig. 3 Proportion of all patients receiving selected types of crystalloid (**a**) and colloid (**b**) solutions between 2007 and 2013. Only selected fluids are reported and percentages do not match Fig. 1 as patients can have more than one type of fluid administered

significant difference in haemodynamic resuscitation endpoints between colloids and crystalloids; rather, colloids are associated with an increase in blood transfusion requirements and increased costs [2, 4, 5]. We observed that the use of albumin remained consistent over the inception period. This may indicate a preference for albumin due to Australian practices where albumin is provided free-of-charge to public hospitals, but also to the impact of the results of the SAFE study [2] and in the subgroup of those with sepsis [7] where the use of albumin was associated with a decrease in the adjusted risk of death.

In addition, we observed a reduction in the proportion of patients receiving resuscitation fluids over this time series. The drivers for this change is likely to be multifactorial, as they are for selecting the type of fluid. These may include adoption of a selective or restrictive fluid resuscitation strategy to mitigate the recognised associations of high-volume crystalloid resuscitation and the development of interstitial oedema and adverse outcomes [34, 35].

Strengths and limitations

Our study provides a unique longitudinal snapshot of clinical practice in Australian and New Zealand ICUs over a 6-year time period. The methods used were consistent across each of the study time points.

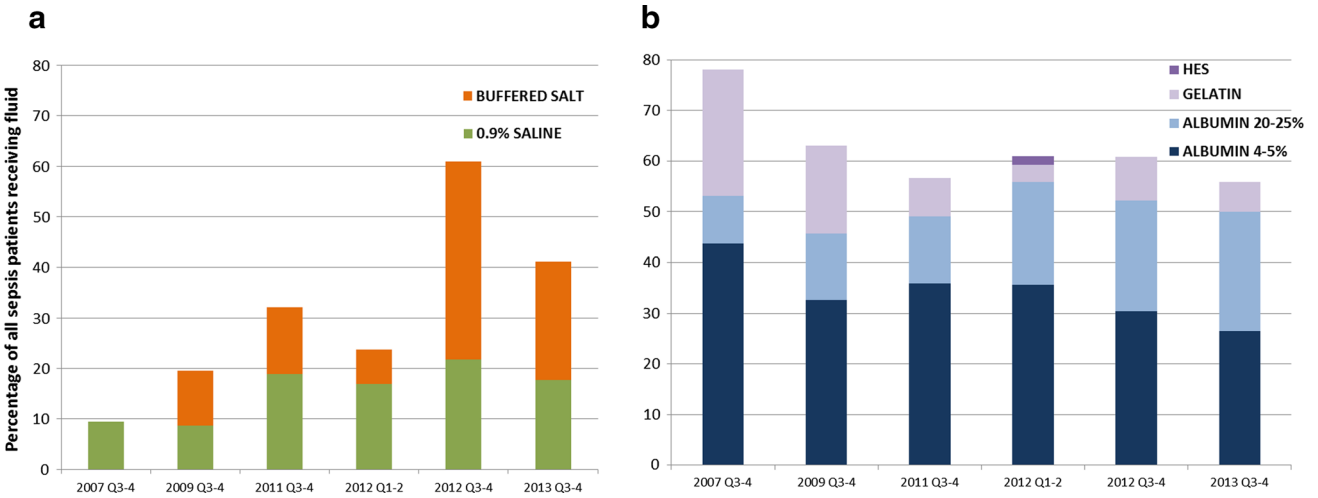

Fig. 4 Proportion of sepsis patients receiving selected types of crystalloid (**a**) and colloid (**b**) solutions between 2007 and 2013. Only selected fluids are reported and percentages do not match Fig. 1 as patients can have more than one type of fluid administered

To account for potential site selection bias, a sensitivity analysis was undertaken including sites participating in at least five or more of the data collection time points and demonstrated consistent trends in comparison to the main analysis. We also sought to minimise confounding bias by adjusting our analysis to account for characteristics that influenced type of resuscitation fluid used.

As our study is observational, we did not report differences in patient-centred outcomes or interval mortality rates and therefore no inferences on these parameters can be made from our study. We note that the study results may not be generalizable to other countries, as it was conducted in Australia and New Zealand only. Similarly, we recognise that drivers of clinician inferences are complex and variable and may not necessarily reflect direct translation of research into clinical practice.

Future studies

Based on our findings and the limited evidence behind the safety and efficacy of buffered salt solutions, there is now an imperative to conduct further randomised-controlled trials, in particular a trial comparing the efficacy and safety of resuscitation with 0.9 % saline to a buffered salt solution.

Conclusion

Fluid resuscitation practices changed in Australian and New Zealand ICUs from 2007 to 2013. While use of 0.9 % saline has remained unchanged over the 6-year period, there has been an increased use of buffered salt solutions and a decreased use of semi-synthetic colloids.

Conflicts of interest The George Institute for Global Health, the institution of NH, CT, MS, SF, PG, LW, and JM, has received unrestricted grants (administered through the University of Sydney) and travel expenses (SF, JM) in relation to the design and conduct of the Crystalloid versus Hydroxyethyl Starch Trial from Fresenius Kabi, and an unrestricted grant (SF) and advisory board fees and travel expenses (JM) from Baxter HealthCare in relation to fluid resuscitation research (2014). NH received a National Health and Medical Research Council of Australia post-graduate scholarship (2012–2014) that has supported part of this work. CT undertakes consulting work for pharmaceutical companies. CT has not personally undertaken work for CSL, Fresenius Kabi or Baxter. BL owns shares in BioCSL. IS has no conflicts of interest. JM is supported by a Practitioner Fellowship from the National Health and Medical Research Council of Australia.

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