Chinese Journal of Traumatology 21 (2018) 11–15

Contents lists available at ScienceDirect

Chinese Journal of Traumatology

journal homepage: http://www.elsevier.com/locate/CJTEE

Review Article

Normal saline for intravenous fluid therapy in critically ill patients

Fei-Hu Zhou [a], Chao Liu [a], Zhi Mao [a], Peng-Lin Ma [b, *]

[a] Department of Critical Care Medicine, Chinese People's Liberation Army General Hospital, Beijing 100853, China
[b] Department of Critical Care Medicine, 309th Hospital of Chinese People's Liberation Army, Beijing 100091, China

ARTICLE INFO

Article history:
Received 10 September 2016
Received in revised form
5 July 2017
Accepted 13 October 2017
Available online 31 January 2018

Keywords:
Normal saline
Critical care
Fluid resuscitation

ABSTRACT

The efficacy and safety of normal saline (NS) for fluid therapy in critically ill patients remain controversy. In this review, we summarized the evidence of randomized controlled trials (RCTs) which compared NS with other solutions in critically ill patients. The results showed that when compared with 6% hydroxyethyl starch (HES), NS may reduce the onset of acute kidney injury (AKI). However, there is no significant different in mortality and incidence of AKI when compared with 10% HES, albumin and buffered crystalloid solution. Therefore, it is important to prescribe intravenous fluid for patients according to their individual condition.

Introduction

Fluid resuscitation is a fundamental component of the management of acutely ill patients. The optimal dose and types of intravenous (IV) fluid for resuscitation remain undetermined.[1,2] 0.9% sodium chloride, or the so-called "normal saline" (NS), is one of the most commonly used IV fluid for seriously ill or injured patients. Since NS has a totally different level of chloridion from the plasma, its administration would be inevitably causes hyperchloremic metabolic acidosis.[3,4] And the chloride has an important role in tubuloglomerular feedback mechanisms.[5] As the chloride concentration in the distal tubule fluid rises, feedback occurs via the macula densa, the afferent arteriole constricts, and the glomerular filtration rate drops.[6,7] However, whether this adverse event will affect mortality and the incidence of acute kidney injury (AKI) remains unknown. Meanwhile, whether the NS is the solution for crystalloid resuscitation[6] or not the first choice for crystalloid resuscitation[8] remains controversy.

Therefore, we summarized the evidence of randomized controlled trials (RCTs) which compared NS with other solutions in critically ill patients. The results were expected to lead to a better use of NS in critically ill patients, and may influence clinical outcomes positively.

NS for fluid resuscitation in critically ill patients

We selected RCTs comparing NS with other solutions in adult critically ill patients who required IV fluid therapy. The search strategy and inclusion criteria are listed in Table 1. The statistical analysis was performed using RevMan software (version 5.2; Cochrane Collaboration, Copenhagen, Denmark) for outcome measurements. The results of the risk ratio (*RR*) for dichotomous outcomes or the mean difference (MD) for continuous data were expressed as means and 95% confidence intervals (*CI*). A random-effects model was used regardless of heterogeneity. A p value less than 0.05 was considered to indicate a statistically significant difference. The outcomes reported across studies included mortality at 28 and 90 days, renal outcomes, and length of stay in intensive care units (ICU).

NS vs 6% hydroxyethyl starch (HES)

Seven RCTs investigated the efficacy and safety of 6% HES vs NS during the IV fluid therapy in critically ill patients. The results (Table 2) showed that more patients in the 6% HES group met the RIFLE (risk, injury, failure, loss, end-stage kidney disease) criteria for risk and injury ($p < 0.05$). Therefore, compared to NS, 6% HES may increase the risk of AKI when prescribed for critically ill patients. However, no significant differences were found between 6% HES and NS in all-cause mortality (at 28 days or at 90 days), renal replacement therapy, RBC transfusion and length of stay in ICU when used for fluid resuscitation in critically ill patients. No

* Corresponding author.
E-mail address: mapenglin1@163.com (P.-L. Ma).

Peer review under responsibility of Daping Hospital and the Research Institute of Surgery of the Third Military Medical University.

https://doi.org/10.1016/j.cjtee.2017.04.012

Table 1
Search strategy and inclusion criteria.

Review eligibility structure	
Population	Critically ill patients requiring acute volume replacement (e.g. resuscitation, but not maintenance fluid)
Intervention	Normal saline
Control	HES solutions, albumin, dextran, gelatin or buffered crystalloid solution
Outcomes	Primary outcome: incidence of mortality. Secondary outcomes: renal function, use of renal replacement therapy, lengths of stay in ICU, incidence of patients requiring of red cell transfusion.
Study design	Prospective randomized controlled trials
Review eligibility criteria	
Inclusion criteria	1. Randomized controlled trial; 2. Participants' age ≥18 years; 3. Indication for acute volume resuscitation (e.g. hypovolemia, hypotension, inadequate indicators of pre-load or filling pressures); 4. Allocation to resuscitation with normal saline compared with HES, albumin, or buffered crystalloid solution.
Exclusion criteria	1. Fluids used as maintenance rather than resuscitation; 2. What control group used is whole blood, or blood products; 3. Use of normal saline for elective pre-operative volume loading; 4. Elective surgical procedures (e.g. cardiac surgery); 5. Observational study designs, quasi-randomized, cross-over, or cluster randomized trials.

RCTs analysed the cost-effectiveness of the two fluid therapies. One cohort study did a pre-specified cost-effectiveness analysis from New South Wales enrolled in the Crystalloid vs HES trial (CHEST, NCT00935168),[9] and found that the total hospital costs (including ICU costs) at 24 months were similar between the HES and saline groups ($62,196 vs $62,617; $p = 0.83$). This suggested that there may be no difference in hospital costs when these two fluids were prescribed for fluid resuscitation in critically ill patients.

From the acquired evidence, when 6% HES was prescribed for critically ill patients, we must take more attention on the change of renal function and give supportive treatment immediately. More studies are needed and should focus on long-term outcomes, clinical relative adverse events and the impact on coagulation.

NS vs 10% HES

Only two RCTs[18,19] with 86 patients were enrolled in the comparison of NS vs 10% HES (Table 3). The results show that there were no differences in all-cause mortality (at 28 days), renal failure and length of stay in ICU between the two groups. For the limited patient data, the conclusion has high risk of inconsistency and thus cannot be applied to guide the clinical practice. It is necessary to use 10% HES according to patients' individual status.

NS vs. albumin

Five RCTs[10,11,15,18,20] evaluated the efficacy and safety of albumin vs NS during the IV fluid therapy in critically ill patients (Table 4). There were no differences in all-cause mortality (at 28 days or at 90 days), renal function, renal replacement therapy and length of stay in ICU between albumin and NS groups. Furthermore, two recent meta-analysis[21,22] evaluated albumin vs other fluids for resuscitation in patients with sepsis and suggested that the present evidence did not demonstrate significant advantage of using human albumin solutions at reducing all-cause mortality. Meanwhile, Jiang et al[21] reported that 4%–5% albumin may be relative safer than 20%–25% albumin for fluid resuscitation. However, the high cost of albumin may limit its wide applicability.[23,24] Therefore, according to the current state of knowledge, we should carefully consider the hospital costs and the concentration when albumin was prescribed for critically ill patients.

Table 2
Comparison of 6% HES and NS on fluid resuscitation.

Parameters	No. of patients		*RR* (95% *CI*)	Heterogeneity I^2 (*p* value)	Test for effect (*p* value)
	HES	NS			
All-cause mortality (90 days)[10–15]	828/4089	958/4497	0.97 (0.81, 1.16)	51% (0.07)	0.73
All-cause mortality (28 days)[13–16]	647/4073	746/4476	0.99 (0.86, 1.13)	27% (0.25)	0.85
All-cause mortality 28 days)–trauma[17]	12/56	6/53	1.89 (0.77–4.68)	Not applicable	0.17
All-cause mortality (28 days)–sepsis[13,15]	136/475	181/652	1.03 (0.85, 1.25)	0% (0.41)	0.75
AKI- RIFLE- risk[13,14,17]	1809/3465	1935/3483	0.94 (0.90, 0.98)	0% (0.56)	0.006
AKI-RIFLE- risk–trauma[17]	8/56	12/53	0.63 (0.28, 1.42)	Not applicable	0.27
AKI-RIFLE- risk–sepsis[13]	13/100	11/95	1.12 (0.53, 2.38)	Not applicable	0.76
AKI-RIFLE- injury[13,14,17]	1138/3421	1266/3488	0.91 (0.85, 0.97)	0% (0.51)	0.004
AKI-RIFLE-injury–trauma[17]	4/56	8/53	0.47 (0.15, 1.48)	Not applicable	0.20
AKI-RIFLE-injury–sepsis[13]	4/100	5/95	0.76 (0.21, 2.75)	Not applicable	0.68
AKI- RIFLE- failure[13,14]	341/3343	308/3470	1.15 (0.99, 1.33)	0% (0.35)	0.06
AKI-RIFLE- failure–sepsis[13]	5/100	7/95	0.68 (0.22, 2.06)	Not applicable	0.49
Renal replacement therapy[14,17]	237/3408	199/3428	1.20 (1.00, 1.44)	0% (0.47)	0.05
Use of renal replacement therapy–trauma[17]	2/56	3/53	0.63 (0.11, 3.63)	Not applicable	0.61
RBC transfusion[13]	29/100	20/96	1.38 (0.84, 2.26)	Not applicable	0.21
	Length of stay		MD (95% *CI*)	Heterogeneity I^2 (*p* value)	Test for effect (*p* value)
	HES	NS			
Guidet et al[13]	15.4 ± 11.1	20.2 ± 22.2	−1.58 (−6.53, 3.37)	76% (0.04)	0.53
Myburgh et al[14]	7.3 ± 0.2	6.9 ± 0.2			

AKI: acute kidney injury; *CI*: confidence interval; HES: hydroxyethyl starch; MD: mean difference; NS: normal saline; RIFLE: risk, injury, failure, loss, end-stage kidney disease; *RR*: relative risk.

Table 3
Comparison of 10% hydroxyethyl starch (HES) and NS on fluid resuscitation.

Parameters	No. of patients		*RR* (95% *CI*)	Heterogeneity I^2 (*p* value)	Test for effect (*p* value)
	HES	NS			
All-cause mortality (28 days)[18,19]	27/51	11/35	1.63 (0.92, 2.88)	Not applicable	0.47
All-cause mortality (28 days)—sepsis[19]	9/21	6/19	1.36 (0.59, 3.10)	0% (0.41)	0.75
AKI- RIFLE- failure —sepsis[19]	3/21	1/19	2.71 (0.31, 23.93)	Not applicable	0.37
	Length of stay		MD (95% *CI*)	Heterogeneity I^2 (*p* value)	Test for effect (*p* value)
	HES	NS			
McIntyre et al[19]	7.5 (3–13)	5 (1–13)	1.50 (−4.01, 7.01)	Not applicable	0.59

AKI: acute kidney injury; *CI*: confidence interval; HES: hydroxyethyl starch; MD: mean difference; NS: normal saline; RIFLE: risk, injury, failure, loss, end-stage kidney disease; *RR*: relative risk.

Table 4
Comparison of albumin and NS on fluid resuscitation.

	No. of patients		*RR* (95% *CI*)	Heterogeneity I^2 (*p* value)	Test for effect (*p* value)
	albumin	NS			
All-cause mortality (90 days)[10,11,15]	36/101	355/3055	1.39 (0.48, 4.01)	87% (0.0006)	0.54
All-cause mortality (28 days)[15,18,20]	759/3568	1009/4511	1.06 (0.87, 1.29)	29% (0.25)	0.58
All-cause mortality 28 days)—trauma[20]	81/596	59/590	1.36 (0.99, 1.86)	Not applicable	0.06
All-cause mortality (28 days)—sepsis[15,20]	204/662	374/1172	0.94 (0.74, 1.19)	37% (0.21)	0.60
renal replacement therapy[15,20]	45/3473	41/3460	1.09 (0.72, 1.67)	Not applicable	0.68
	Length of stay		MD (95% *CI*)	Heterogeneity I^2 (*p* value)	Test for effect (*p* value)
	albumin	NS			
Finfer S[21]	6.5 ± 6.6	6.2 ± 6.2	0.30 (−0.00, 0.60)	Not applicable	0.05

AKI: acute kidney injury; *CI*: confidence interval; HES: hydroxyethyl starch; MD: mean difference; NS: normal saline; RIFLE: risk, injury, failure, loss, end-stage kidney disease; *RR*: relative risk.

NS vs buffered crystalloid solution

Buffered crystalloid solution with electrolyte composition closely mimics human plasma in its content of electrolytes, osmolality, and pH.[25,26] And it has been considered as a good alternative to NS for critically ill patients with AKI.[27,28] However, from two RCTs[29,30] results (Table 5), we concluded that when compared with NS, the buffered crystalloid solution cannot reduce mortality or the risk of AKI. One cluster randomized trials[31] indicated that there was no significant different between NS and Ringer's lactate solution. Another cost-minimization analysis[32] results suggested that the use of Plasma-Lyte A was associated with a relatively higher fluid acquisition cost but a reduced need for magnesium replacement in critically injured trauma patients. Therefore, further large scale RCTs are needed to assess the efficacy in higher-risk populations and significant adverse events.

In this review, we compared NS vs other fluids for IV fluid therapy in critically ill patients. There is little doubt that excess exogenous chloride administration has been shown to induce renal artery vasoconstriction, AKI, hyperchloremic metabolic acidosis, gastrointestinal dysfunction, and the secretion of inflammatory cytokines.[4,33] Although some observational studies have reported an increased mortality risk associated with the use of NS,[34,35] our results and some recent meta-analysis[22,36,37] results showed that patients mortality and the risk of AKI were not changed with the excess exogenous chloride administration.

Unfortunately, inappropriate NS infusion management in hospitals may lead to clinical relative adverse events, prolong length of stay in ICU or increase the mortality. Many of the errors in NS infusion management are due to inadequate knowledge and training. Several survey research[38–41] also suggested that lack of adequate clinician preparation, poor fluid balance monitoring and

Table 5
Comparison of buffered crystalloid and NS on fluid resuscitation.

	No. of patients		*RR* (95% *CI*)	Heterogeneity I^2 (*p* value)	Test for effect (*p* value)
	Buffered crystalloid	NS			
All-cause mortality (90 days)[30]	87/1152	95/1110	1.05 (0.78, 1.40)	Not applicable	0.75
All-cause mortality (28 days)[29]	3/22	4/24	1.50 (0.40, 5.65)	Not applicable	0.55
AKI- RIFLE- risk[30]	123/1067	107/1025	1.10 (0.86, 1.41)	Not applicable	0.43
AKI- RIFLE- injury[30]	46/1067	57/1025	0.78 (0.53, 1.13)	Not applicable	0.19
AKI- RIFLE- failure[30]	54/1067	36/1025	1.44 (0.95, 2.18)	Not applicable	0.08
renal replacement therapy[30]	38/1152	38/1110	0.96 (0.62, 1.50)	Not applicable	0.87
	No. of patients		MD (95% *CI*)	Heterogeneity I^2 (*p* value)	Test for effect (*p* value)
	Buffered crystalloid	NS			
Received pRBC transfusion[29]	22	24	−5.00 (−38.99, 28.99)	Not applicable	0.77

AKI: acute kidney injury; *CI*: confidence interval; MD: mean difference; NS: normal saline; pRBC: packed red blood cells; RIFLE: risk, injury, failure, loss, end-stage kidney disease; *RR*: relative risk.

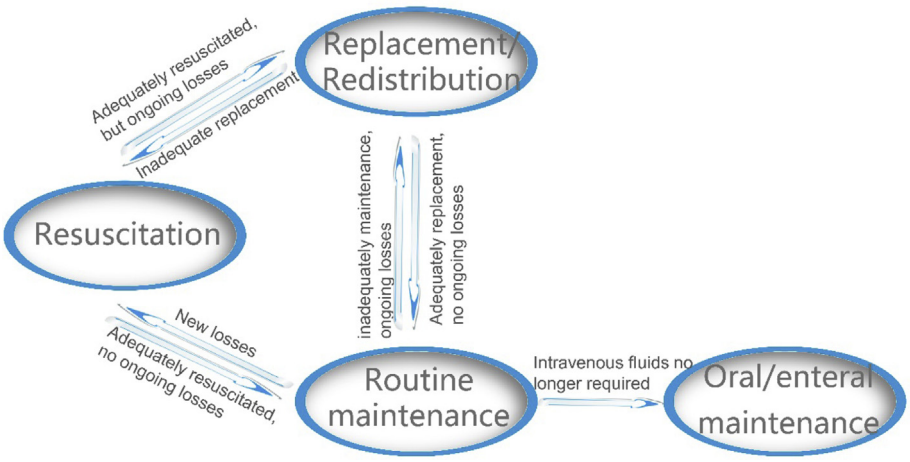

Fig. 1. The 4 Rs-resuscitation, routine maintenance, replacement and redistribution.[43]

inadequate knowledge are associated with increased clinical risk and harm. Meanwhile, improved knowledge led to improved confidence in NS infusion management.[42] Therefore, it is necessary to use the present evidence to manage NS infusion, and we summarized some principles as follows.

1. Assess the fluid and electrolyte status of critically ill patients. Provide NS for patients whose demand cannot be met through oral or enteral routes, and stop as soon as possible.
2. A NS infusion management plan should be made, in which NS prescription over the next 24 h and monitoring program were indispensable.
3. The rate and volume of NS should be carefully considered; and the 4 Rs[43] (resuscitation, routine maintenance, redistribution and reassessment) should be also remembered (Fig. 1).
4. Other sources of fluid and electrolyte intake should be taken into account, including any oral or enteral intake, and intake from drugs, IV nutrition, blood and blood products.
5. If possible, provide written information for patients and their family members.

In conclusion, NS as the most commonly used IV fluid for critically ill patients occupies a very important position in fluid resuscitation. A good understanding of its advantage and disadvantage when compared with other fluid prescribed for critically ill patients is conducive to make good clinical decision.

References

1. Myburgh JA, Mythen MG. Resuscitation fluids. *N Engl J Med*. 2013;369:1243–1251. https://doi.org/10.1056/NEJMra1208627.
2. Scales K, NICE CG. 174: intravenous fluid therapy in adults in hospital. *Br J Nurs*. 2014;23:S6–S8. https://doi.org/10.12968/bjon.2014.23.Sup8.S6.
3. Ke L, Calzavacca P, Bailey M, et al. Systemic and renal haemodynamic effects of fluid bolus therapy: sodium chloride versus sodium octanoate-balanced solution. *Crit Care Resusc*. 2014;16:29–33.
4. Chowdhury AH, Cox EF, Francis ST, et al. A randomized, controlled, double-blind crossover study on the effects of 2-L infusions of 0.9% saline and plasma-lyte(R) 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. *Ann Surg*. 2012;256:18–24. https://doi.org/10.1097/SLA.0b013e318256be72.
5. Yunos NM, Bellomo R, Story D, et al. Bench-to-bedside review: chloride in critical illness. *Crit Care*. 2010;14:226. https://doi.org/10.1186/cc9052.
6. Young P. Saline is the solution for crystalloid resuscitation. *Crit Care Med*. 2016;44:1538–1540. https://doi.org/10.1097/CCM.0000000000001844.
7. Morsing P, Velazquez H, Ellison D, et al. Resetting of tubuloglomerular feedback by interrupting early distal flow. *Acta Physiol Scand*. 1993;148:63–68. https://doi.org/10.1111/j.1748-1716.1993.tb09532.x.
8. Semler MW, Rice TW. Saline is not the first choice for crystalloid resuscitation fluids. *Crit Care Med*. 2016;44:1541–1544. https://doi.org/10.1097/CCM.0000000000001941.
9. Taylor C, Thompson K, Finfer S, et al. Hydroxyethyl starch versus saline for resuscitation of patients in intensive care: long-term outcomes and cost-effectiveness analysis of a cohort from CHEST. *Lancet Respir Med*. 2016;4:818–825. https://doi.org/10.1016/S2213-2600(16)30120-5.
10. Rackow EC, Falk JL, Fein IA, et al. Fluid resuscitation in circulatory shock: a comparison of the cardiorespiratory effects of albumin, hetastarch, and saline solutions in patients with hypovolemic and septic shock. *Crit Care Med*. 1983;11:839–850.
11. van der Heijden M, Verheij J, van Nieuw Amerongen GP, et al. Crystalloid or colloid fluid loading and pulmonary permeability, edema, and injury in septic and nonseptic critically ill patients with hypovolemia. *Crit Care Med*. 2009;37:1275–1281. https://doi.org/10.1097/CCM.0b013e31819cedfd.
12. Dubin A, Pozo MO, Casabella CA, et al. Comparison of 6% hydroxyethyl starch 130/0.4 and saline solution for resuscitation of the microcirculation during the early goal-directed therapy of septic patients. *J Crit Care*. 2010;25:659.e1–e8. https://doi.org/10.1016/j.jcrc.2010.04.007.
13. Guidet B, Martinet O, Boulain T, et al. Assessment of hemodynamic efficacy and safety of 6% hydroxyethylstarch 130/0.4 vs. 0.9% NaCl fluid replacement in patients with severe sepsis: the CRYSTMAS study. *Crit Care*. 2012;16:R94. https://doi.org/10.1186/cc11358.
14. Myburgh JA, Finfer S, Bellomo R, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med*. 2012;367:1901–1911. https://doi.org/10.1056/NEJMoa1209759.
15. Annane D, Siami S, Jaber S, et al. Effects of fluid resuscitation with colloids vs crystalloids on mortality in critically ill patients presenting with hypovolemic shock: the CRISTAL randomized trial. *JAMA*. 2013;310:1809–1817. https://doi.org/10.1001/jama.2013.280502.
16. Li F, Sun H, Han XD. [The effect of different fluids on early fluid resuscitation in septic shock]. *Zhongguo Wei Zhong Bing Ji Jiu Yi Xue*. 2008;20:472–475.
17. James MF, Michell WL, Joubert IA, et al. Resuscitation with hydroxyethyl starch improves renal function and lactate clearance in penetrating trauma in a randomized controlled study: the FIRST trial (Fluids in Resuscitation of Severe Trauma). *Br J Anaesth*. 2011;107:693–702. https://doi.org/10.1093/bja/aer229.
18. Veneman TF, Oude Nijhuis J, Woittiez AJ. Human albumin and starch administration in critically ill patients: a prospective randomized clinical trial. *Wien Klin Wochenschr*. 2004;116:305–309.
19. McIntyre LA, Fergusson D, Cook DJ, et al. Fluid resuscitation in the management of early septic shock (FINESS): a randomized controlled feasibility trial. *Can J Anaesth*. 2008;55:819–826. https://doi.org/10.1007/BF03034053.
20. Finfer S, Bellomo R, Boyce N, et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med*. 2004;350:2247–2256. https://doi.org/10.1056/NEJMoa040232.
21. Jiang L, Jiang S, Zhang M, et al. Albumin versus other fluids for fluid resuscitation in patients with sepsis: a meta-analysis. *PLoS One*. 2014;9, e114666. https://doi.org/10.1371/journal.pone.0114666.
22. Patel A, Laffan MA, Waheed U, et al. Randomised trials of human albumin for adults with sepsis: systematic review and meta-analysis with trial sequential analysis of all-cause mortality. *BMJ*. 2014;349:g4561. https://doi.org/10.1136/bmj.g4561.
23. Latour-Perez J. New recommendations for the use of serum albumin in patients with severe sepsis and septic shock. *Crit Care Med*. 2013;41:e289. https://doi.org/10.1097/CCM.0b013e31828ced28.
24. Lyu PF, Murphy DJ. Economics of fluid therapy in critically ill patients. *Curr Opin Crit Care*. 2014;20:402–407. https://doi.org/10.1097/MCC.0000000000000117.

25. Yunos NM, Bellomo R, Glassford N, et al. Chloride-liberal vs. chloride-restrictive intravenous fluid administration and acute kidney injury: an extended analysis. *Intensive Care Med*. 2015;41:257–264. https://doi.org/10.1007/s00134-014-3593-0.
26. Pfortmueller CA, Fleischmann E. Acetate-buffered crystalloid fluids: current knowledge, a systematic review. *J Crit Care*. 2016;35:96–104. https://doi.org/10.1016/j.jcrc.2016.05.006.
27. Yunos NM, Bellomo R, Hegarty C, et al. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. *JAMA*. 2012;308:1566–1572. https://doi.org/10.1001/jama.2012.13356.
28. Krajewski ML, Raghunathan K, Paluszkiewicz SM, et al. Meta-analysis of high- versus low-chloride content in perioperative and critical care fluid resuscitation. *Br J Surg*. 2015;102:24–36. https://doi.org/10.1002/bjs.9651.
29. Young JB, Utter GH, Schermer CR, et al. Saline versus Plasma-Lyte A in initial resuscitation of trauma patients: a randomized trial. *Ann Surg*. 2014;259:255–262. https://doi.org/10.1097/SLA.0b013e318295feba.
30. Young P, Bailey M, Beasley R, et al. Effect of a buffered crystalloid solution vs saline on acute kidney injury among patients in the intensive care unit: the split randomized clinical trial. *JAMA*. 2015;314:1701–1710. https://doi.org/10.1001/jama.2015.12334.
31. Semler MW, Wanderer JP, Ehrenfeld JM, et al. Balanced crystalloids versus saline in the intensive care unit: the SALT randomized trial. *Am J Respir Crit Care Med*. 2017;195:1362–1372. https://doi.org/10.1164/rccm.201607-1345OC.
32. Smith CA, Duby JJ, Utter GH, et al. Cost-minimization analysis of two fluid products for resuscitation of critically injured trauma patients. *Am J Health Syst Pharm*. 2014;71:470–475. https://doi.org/10.2146/ajhp130295.
33. Frazee E, Kashani K. Fluid management for critically ill patients: a review of the current state of fluid therapy in the intensive care unit. *Kidney Dis (Basel)*. 2016;2:64–71. https://doi.org/10.1159/000446265.
34. Raghunathan K, Shaw A, Nathanson B, et al. Association between the choice of IV crystalloid and in-hospital mortality among critically ill adults with sepsis*. *Crit Care Med*. 2014;42:1585–1591. https://doi.org/10.1097/CCM.0000000000000305.
35. Raghunathan K, Bonavia A, Nathanson BH, et al. Association between initial fluid choice and subsequent in-hospital mortality during the resuscitation of adults with septic shock. *Anesthesiology*. 2015;123:1385–1393. https://doi.org/10.1097/ALN.0000000000000861.
36. Rochwerg B, Alhazzani W, Sindi A, et al. Fluid resuscitation in sepsis: a systematic review and network meta-analysis. *Ann Intern Med*. 2014;161:347–355. https://doi.org/10.7326/M14-0178.
37. Qureshi SH, Rizvi SI, Patel NN, et al. Meta-analysis of colloids versus crystalloids in critically ill, trauma and surgical patients. *Br J Surg*. 2016;103:14–26. https://doi.org/10.1002/bjs.9943.
38. Chung LH, Chong S, French P. The efficiency of fluid balance charting: an evidence-based management project. *J Nurs Manag*. 2002;10:103–113.
39. Coombes ID, Mitchell CA, Stowasser DA. Safe medication practice: attitudes of medical students about to begin their intern year. *Med Educ*. 2008;42:427–431. https://doi.org/10.1111/j.1365-2923.2008.03029.x.
40. Kelly C, Noonan CL, Monagle JP. Preparedness for internship: a survey of new interns in a large Victorian health service. *Aust Health Rev*. 2011;35:146–1451. https://doi.org/10.1071/AH10885.
41. Weisgerber M, Flores G, Pomeranz A, et al. Student competence in fluid and electrolyte management: the impact of various teaching methods. *Ambul Pediatr*. 2007;7:220–225. https://doi.org/10.1016/j.ambp.2007.01.005.
42. Olson AF. Outpatient management of electrolyte imbalances associated with anorexia nervosa and bulimia nervosa. *J Infusion Nurs*. 2005;28:118–122.
43. National Clinical guideline Centre (UK). *Intravenous Fluid Therapy: Intravenous Fluid Therapy in Adults in Hospital*. London: Royal College of Physucuans (UK); 2013. https://www.ncbi.nlm.nih.gov/pubmed/25340240.