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ERAS4OLT.org Working Group; Morkane, Clare M.; Sapisochin, Gonzalo; Mukhtar, Ahmed M.; Reyntjens, Koen M.E.M.; Wagener, Gebhard; Spiro, Michael; Raptis, Dimitri A.; Klinck, John R.

Published in:
Clinical Transplantation

DOI:
10.1111/ctr.14651

Received: 12 January 2022 | Revised: 28 February 2022 | Accepted: 28 February 2022

DOI: 10.1111/ctr.14651

Clinical TRANSPLANTATION
The Journal of Clinical and Translational Research
WILEY

ORIGINAL ARTICLE

Perioperative fluid management and outcomes in adult deceased donor liver transplantation – A systematic review of the literature and expert panel recommendations

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This work was conducted in preparation for the ILTS – ERAS4OLT.org Consensus Conference on Enhanced Recovery for Liver Transplantation, January 2022, Valencia, Spain.

Abstract

Background: Fluid management practices during and after liver transplantation vary widely among centers despite better understanding of the pathophysiology of end-stage liver disease and of the effects of commonly used fluids. This reflects a lack of high quality trials in this setting, but also provides a rationale for both systematic review of all relevant studies in liver recipients and evaluation of new evidence from closely related domains, including hepatology, non-transplant abdominal surgery, and critical care.

Objectives: To develop evidence-based recommendations for perioperative fluid management to optimize immediate and short-term outcomes following liver transplantation.

Data sources: Ovid MEDLINE, Embase, Scopus, Google Scholar, and Cochrane Central.

Methods: Systematic review following PRISMA guidelines and recommendations using the GRADE approach derived from an international expert panel. Studies included those evaluating the following postoperative outcomes: acute kidney injury, respiratory complications, operative blood loss/red cell units required, and intensive care length of stay.

PROSPERO protocol ID: CRD42021241392

Results: Following expert panel review, 18 of 1624 screened studies met eligibility criteria for inclusion in the final quantitative synthesis. These included six single center RCTs, 11 single center observational studies, and one observational study comparing centers with different fluid management techniques. Definitions of interventions and outcomes varied between studies. Recommendations are therefore based substantially on expert opinion and evidence from other clinical settings.

Conclusions: A moderately restrictive or "replacement only" fluid regime is recommended, especially during the dissection phase of the transplant procedure. Sustained

hypervolemia, based on absence of fluid responsiveness, elevated filling pressures and/or echocardiographic findings, should be avoided (*Quality of Evidence*: Moderate | *Grade of Recommendation*: Weak for restrictive fluid regime. Strong for avoidance of hypervolemia). Mean Arterial Pressure (MAP) should be maintained at >60–65 mmHg in all cases (*Quality of Evidence*: Low | *Grade of Recommendation*: Strong). There is insufficient evidence in this population to support preferential use of any specific colloid or crystalloid for routine volume replacement. However, we recommend against the use of 130/.4 HES given the high incidence of AKI in this population.

KEYWORDS
albumin, cardiac output, central venous pressure, colloid, crystalloid, fluid, goal-directed fluid, inotropes, intraoperative, liver transplant, perioperative, vasopressors

1 | INTRODUCTION

The aim of perioperative fluid management in most surgical settings is to optimize intravascular volume and regional microvascular perfusion, reducing the risk of complications and supporting rapid recovery. This has been an important element of the Enchased Recovery after Surgery (ERAS) approach since its inception, and the complexity of liver transplantation suggests that liver recipients could have much to gain. However, wide variation in clinical practice remains, reflecting not only the small number of randomized trials in this population, but longstanding controversies in perioperative medicine.

In other populations, including patients undergoing major abdominal surgery, cardiac surgery, trauma and critical care, studies of fluid restriction, goal-directed fluid therapy, crystalloids, synthetic colloids and albumin have yielded conflicting or inconclusive results. However, many provide insights that may be helpful in the transplant context, while non-surgical trials of fluid management in patients with decompensated cirrhosis may be even more informative. This review attempts to combine formal evaluation of the narrowly defined literature with a consensus perspective on a much wider range of recently published data.

The following questions were developed collaboratively with the ERAS4OLT Scientific Committee to address the main sources of variation in perioperative fluid management and related clinical outcomes.

- **Question A**: What intraoperative fluid balance (or estimated state of intravascular filling) is associated with optimal immediate and short-term outcomes in adult deceased donor liver transplantation?
- **Question B**: What is an appropriate minimum mean arterial pressure (MAP), using vasopressor infusion(s) if necessary, for optimal immediate and short-term outcomes in adult deceased donor liver transplantation?
- **Question C**: What fluids (crystalloid vs. colloid, synthetic colloid vs. albumin, .9% NaCl vs balanced electrolyte solutions) should be used intraoperatively for optimal immediate and short-term outcomes in adult deceased donor liver transplantation?

2 | METHODS

2.1 | Protocol and registration

PROSPERO protocol ID CRD42021241392.

2.2 | Eligibility criteria

Table 1 lists the inclusion and exclusion criteria for the systematic review.

2.3 | Information sources

Databases searched included: Ovid Medline (1946-present), Embase (1974-present), Scopus (1970-present), Google Scholar (2004-present), Clinicaltrials.gov (2008-present), and the Cochrane Central Register of Controlled Trials (1996-present). The search date was March 2, 2021. No study authors were contacted for details of additional studies.

2.4 | Search

The following search strategy was used and adapted to individual databases (by expanding MeSH terms for example) by professional medical librarians from the University of Zurich (intraoperative OR perioperative OR intra-operative OR peri-operative) AND ("fluid management" OR "fluid replacement" OR "fluid balance" OR fluid* OR crystalloids OR colloids OR saline OR "ringer's lactate" OR Hartmann's OR "balanced salt" OR albumin OR gelofusine OR albumin OR "hydroxyethyl starch" OR inotropes OR noradrenaline OR dobutamine OR vasopressin OR argipressin OR phenylephrine OR metaraminol OR epinephrine OR Norepinephrine OR levophed OR "goal-directed fluid" OR "cardiac output" OR "cardiac volume" OR "volume optimization" OR "cardiac index" OR "central venous pressure OR CVP) AND ((liver OR hepatic) AND (transplant OR transplantation))".

TABLE 1 Systematic review eligibility criteria

	Included	Excluded
Population	Adults with ESLD who underwent deceased orthotopic liver transplantation	Children Living donor recipients Combined liver-kidney transplantation
Interventions	Perioperative fluid replacement (crystalloid vs. colloids, albumin vs. synthetic colloids, saline vs. balanced salt solutions) Perioperative fluid balance targets (restrictive vs. liberal, low vs. high CVP, goal directed vs. clinician preference) Targeted intraoperative blood pressure parameters and interaction of fluids and vasopressors	Studies without perioperative outcomes Exploratory, physiology-based studies including comparison of techniques to assess cardiac output/device evaluation and validation Studies assessing surgical techniques Use of fluids for other goals, for example, hypertonic saline for neuroprotection
Controls	Patients receiving standard care	
Observations	Operative blood loss/red cell units required Postoperative complications: 1. Acute kidney injury 2. Respiratory complications ICU length of stay	Any other observations

Studies were not restricted by language or date of publication. Case reports, conference abstracts, unpublished studies and studies with fewer than 10 participants were excluded.

2.5 | Study selection

Studies were screened in abstract for eligibility using Endnote v.10, then downloaded for full text review and inclusion by two reviewers independently (MV and MM). Disagreements about inclusion were arbitrated by a third reviewer (DAR). Total 3336 records were initially found, with 18 studies left for inclusion after duplicate removal and screening (see PRISMA flow diagram). Of these 18 studies, two reported data from the same retrospective cohort of patients. Additional studies considered relevant by the expert review panel but outside criteria for inclusion, were cited in the discussion.

2.6 | Quality of studies and recommendations grading

The "Grading of Recommendations Assessment, Development and Evaluation" (GRADE) approach was used for grading quality of evidence and strength of recommendations.[1] The GRADE system was designed to provide a comprehensive and structured approach to rating the quality of evidence (QOE) for systematic reviews, and to grade the strength of recommendations for development of guidelines in health care. We applied the modified GRADE approach for QOE assessment derived from systematic reviews using estimates summarized narratively.[2] The QOE was rated separately for each outcome. The direction and strength of recommendation was assessed individually by all authors and disagreements resolved by consensus.[3,4]

3 | RESULTS

3.1 | Study selection

Out of the 1624 studies screened, 1297 were excluded at the abstract stage for reasons such as abstract only publication or not meeting primary inclusion criteria, leaving 327 full-text articles to be assessed for eligibility. Following further exclusions for reasons including conference abstracts, case reports, and reviews (Figure 1), 61 full-text articles remained for review by the expert panel. Of these 61 studies, a further 43 were excluded by the panel as not meeting defined inclusion criteria (or clear exclusions present including live donor recipients), leaving 18 studies for inclusion in the quantitative synthesis (study characteristics and outcomes are reported in Tables 2 and 3). Of these 18 studies, two report data from the same retrospective cohort of patients.

3.2 | Study characteristics

Table 2 summarized the main outcomes of the relevant studies included in the systematic review.

3.3 | Results of individual studies

Table 3 reported the results of the individual studies.

3.4 | Quality of evidence

The panel decided that "optimal fluid balance" in Question A implies a strong association with perioperative blood loss, renal injury, respiratory complications, and requirement for intensive care. Other outcomes are either,

1. surrogates of limited interest to the patient,
2. too uncommon to allow statistical inference of causation (e.g., perioperative death), or

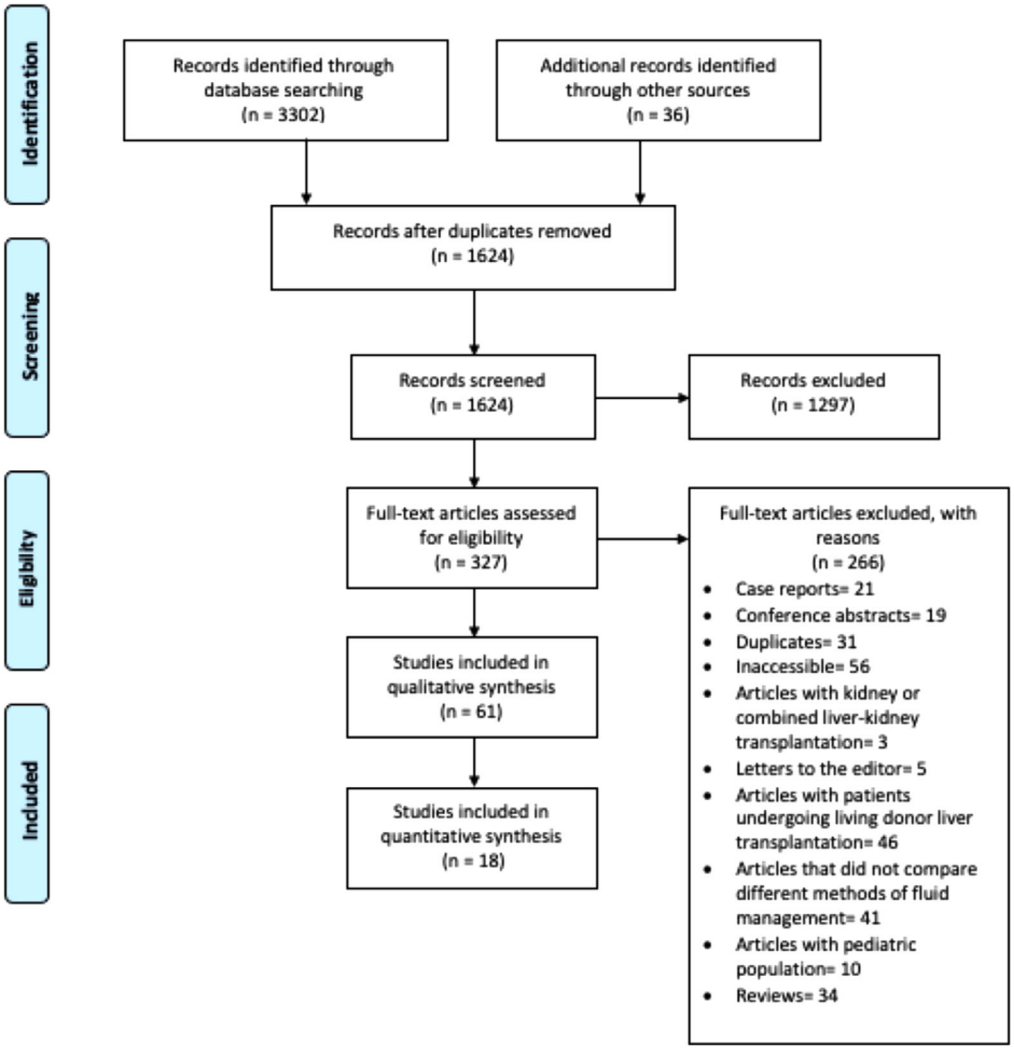

FIGURE 1 Prisma flow diagram

3. not reported in any high quality study and/or very likely to be accounted for by one of the above variables

The summary of findings for the main outcomes, including the QOE assessment according to the GRADE approach are summarized in Tables 4–7.

3.5 | Recommendations

Question A: What intraoperative fluid balance (or estimated state of intravascular filling) is associated with optimal immediate and short-term outcomes in adult deceased donor liver transplantation?

Recommendation: A moderately restrictive or "replacement only" fluid regime is recommended, especially during the dissection phase in the presence of portal hypertension, since blood loss is likely to be reduced. This involves replacement of combined losses, usually incorporating low-to-moderate dose vasopressor to maintain MAP at or above 60–65 mmHg. Sustained hypervolemia, based on absence of fluid responsiveness, elevated filling pressures, and/or echocardiographic findings, should be avoided. QOE: Moderate. Strength of Recommendation: Weak for restrictive fluid regime. Strong for avoidance of hypervolemia.

Question B: What is an appropriate minimum MAP, using vasopressor infusion(s) if necessary, for optimal immediate and short-term outcomes in adult deceased donor liver transplantation?

Recommendation: MAP (MAP) should be maintained at >60–65 mmHg in all cases. QOE: Low. Strength of Recommendation: Strong.

Question C: What fluids (crystalloid vs. colloid, synthetic colloid vs. albumin, .9% NaCl vs. balanced electrolyte solutions) should be used intraoperatively for optimal immediate and short-term outcomes in adult deceased donor liver transplantation?

Recommendation: There is insufficient evidence in this population to support preferential use any specific colloid or crystalloid for routine volume replacement. However, low quality evidence suggests it may be safer to avoid 6% 130/.4 HES because of the high risk of AKI in these patients. QOE: Low. Strength of Recommendation: Strong.

TABLE 2 Study characteristics

	Study type	No. of patients	Main outcomes assessed
Broad, 2016	Double blind, randomized controlled pilot trial	30 received 8.4% sodium bicarbonate, 30 received 0.9% sodium chloride infusions	Primary outcome: AKI within the first 48 postoperative hours
Carrier, 2019 Carrier, 2020	Retrospective cohort study assessing impact of fluid balance on AKI Retrospective study of same cohort assessing impact of vasopressors on AKI	Total of 532 patients	Primary outcome: 48 h AKI Secondary outcomes: 7 day AKI, need for postoperative renal replacement therapy, time to extubation in the ICU, time to ICU discharge, survival up to 1 year
Hand, 2015	Retrospective comparative cohort study	174 patients, 50 received 5% albumin, 25 received both 5% albumin and HES and 99 received HES only	Evaluation of the association between type of intraoperative colloid administered and AKI
Cywinski, 2010	Retrospective cohort study	Total of 144 patients	Association between postoperative CVP management and: Postoperative allograft function Graft and patient survival ICU and hospital LOS Infections
Jiang, 2012	Retrospective comparative cohort study	32 patients receiving < = 100 ml/kg vs. 70 patients receiving > 100 ml/kg intraoperative fluid	Extubation time Time to first passage of flatus ICU length of stay Postoperative blood gases
Jipa, 2017	Retrospective comparative cohort study	23 patients who did, and 17 who did not, experience postoperative pulmonary complications	Pulmonary complications PACU length of stay
Lekerika, 2014	Retrospective comparative cohort study	44 patients receiving a liberal fluid strategy vs. 45 patients receiving a restrictive fluid strategy	Transfusion of RBCs, FFP, colloids, and crystalloids Postoperative renal function Hospital length of stay
Martin, 2019	Randomized controlled trial (feasibility)	60 patients were randomized to either 12 h of GDFT using non-invasive cardiac output monitoring ($n = 30$) or standard care ($n = 30$)	Primary outcome: feasibility Secondary outcomes included survival, postoperative complications, quality of life, and resource use
Massicotte 2012	Retrospective comparative cohort study	500 consecutive OLTs. The transfusion rate of the first 61 OLTs was compared with the last 439 following a change in practice (maintenance of low CVP).	Main predictors of intraoperative blood transfusion
Ponnudural, 2005	Randomized controlled trial	65 patients were randomized to receive either a vasopressor with controlled fluid administration (n = 33) or to fluid administration only (placebo) ($n = 32$)	Postoperative ventilatory support and endotracheal reintubation
Reydellet, 2014	Retrospective comparative cohort study	50 patients undergoing OLT were included during two successive 6-month periods before and after the implementation of a protocol including GDFT (control group $n =$ 25 and protocol group $n = 25$)	Impact of the introduction of a GDFT protocol on fluid balance and postoperative outcomes
Sahmeddini, 2014	Randomized controlled trial	67 patients Restricted fluid group (0.9% sodium chloride 5 ml/kg/h), $n = 34$. Non-restricted fluid group (0.9% sodium chloride 10 ml/kg/h), $n = 33$	Early post-operative respiratory and renal insufficiency

(Continues)

TABLE 2 (Continued)

	Study type	No. of patients	Main outcomes assessed
Schroeder, 2004	Retrospective comparative cohort study, comparing two transplant centres	151 patients across two transplant centers. 73 patients in transplant center 1 (low CVP) and 78 patients in transplant center 2 (normal CVP)	Peak post-op creatinine, RRT ICU and hospital length of stay, mortality
Wang, 2013	Randomized trial	65 patients randomly allocated to a low CVP group ($n = 33$) or a control group ($n = 32$)	Postoperative pulmonary complications Volume of intraoperative blood loss and transfusion
Zhang, 2005	Randomized trial	30 patients were randomly assigned to receive dopamine ($n = 15$) or dopamine plus norepinephrine infusions ($n = 15$)	Renal function, ICU length of stay Transfusion
Zhang, 2020	Retrospective comparative cohort study	Data from132 patients were analyzed. Patients were divided into those with post-OLT AKI ($n = 66$) and those without AKI ($n = 66$)	Association between cumulative fluid balance and post-OLT AKI
Zhou, 2015	Retrospective comparative cohort study	A total of 394 patients were divided into RI (renal impairment) ($n = 139$) and non-RI ($n = 255$) groups (on the basis of renal function within the first postoperative week.	Influence of HES (6% HES 200/.5 and 6% HES 130/.4) on renal function post OLT

Abbreviations: AKI, acute kidney injury; CVP, central venous pressure; FFP, fresh frozen plasma; GDFT, goal directed fluid therapy; HES, hydroxyethyl starch; ICU, intensive care unit; OLT, orthotopic liver transplant; RBC, red blood cells; RI, renal impairment

Table 8 (Questions A–C) report the evidence to recommendation framework according to the GRADE approach.

4 | DISCUSSION

The evidence considered was limited to investigations performed in adult deceased donor liver transplant recipients, which included six single center RCTs, 11 single center observational studies, and one observational study comparing centers with different fluid management techniques. Definitions of interventions and outcomes varied between studies, further reducing evidence quality. Recommendations are therefore based substantially on expert opinion and evidence from other clinical settings, including living donor liver transplant, non-transplant major abdominal surgery, critical care, and small explanatory/physiology studies in liver transplant and other populations.

5 | SUMMARY

The best available evidence (Table 4) suggests that a euvolemic (replacement-only) approach to intravascular fluid losses, avoiding high-normal or high central venous pressures and using low-to-moderate dose vasopressor infusions, can be associated with reduced red cell transfusion requirement and fewer postoperative respiratory complications without increasing the risk of acute kidney injury.

The risks and benefits of specific vasopressors and of any target minimum MAP have not been reliably determined in this population. However, AKI and other outcomes are strongly associated with the absolute and relative hypotension defined as "reperfusion syndrome" and with the severity and duration of intraoperative MAP<65.[5,6] Researchers consistently described protocolized vasopressor use to maintain MAP >60–65 mmHg (Table 5).

There is also very limited evidence on both intraoperative and postoperative goal-directed fluid therapy, a technique showing a variable effect on fluid balance depending on protocol details.[7,8] Likewise, population-specific data to inform recommendations on type of crystalloid or colloid-containing fluid used as an adjunct to red cell and plasma replacement are not yet available, except that, based on low-quality evidence, administration of 130/.4 HES may be inadvisable given the high risk of AKI in this setting (Table 6). Expert opinion also suggests that the sodium content of resuscitation fluids should be considered in recipients with moderate-to-severe hyponatremia, in whom rapid increases in plasma sodium may cause neurological injury.

It is important to note a recurring theme in the literature on fluid management, which accounts for strong and opposing views on many of the interventions described: the vulnerability of observational studies and low quality RCTs to confounding by co-morbidities and surgical acuity. Treatment of sicker patients may involve fluid management strategies that are inferred to be causally linked to poor outcomes, despite the use of statistical techniques intended to remove bias. Over a span of more than two decades, for example, several authorities have advocated a ban on colloids, in particular albumin solutions, in all critically ill and surgical patients outside experimental settings,[9–11] yet this would be unacceptable to many clinicians experienced in liver transplantation. The importance of well-designed, multicenter RCTs cannot be overstated.

TABLE 3 Study outcomes

	Acute kidney injury	Postoperative respiratory complications	Operative blood loss/red cell units required	ICU length of stay
Broad, 2016	AKI at 48hrs postoperatively, *n* (%) Sodium bicarbonate group 11 (37) Sodium chloride 10 (33). p = 1.0	Postoperative pneumonia, *n* (%) Sodium bicarbonate group 5 (17) Sodium chloride 11 (37). *p* = .14	Packed RBCs received, (units),' mean (SD): Sodium bicarbonate group: 3.13 (4.25) Sodium chloride 3.50 (3.37). *p* = .44	ICU stay (hours), median (IQR) Sodium bicarbonate 35 (30:42) Sodium chloride 38 (30:50) *p* = .46
Carrier, 2020	For the primary outcome of AKI at 48 h, neither the presence nor the dose of vasopressor was associated with 48 h AKI (of any grade)	Not reported	Intraoperative RBC transfusions. Number of observed cases (proportion in %) No vasopressors 45 (16%) Vasopressors 94 (39%)	Time to ICU discharge (days), median (95% CI) No vasopressors 2.8 (2.6,3.3) Vasopressors 3.2 (2.9,3.6)
Hand, 2015	Significant difference in the incidence of AKI between patients receiving albumin compared to HES (*p* = .044) on propensity-matched analysis	Not reported	Percentage of patients receiving RBCs: albumin only (90%), albumin and HES (92%), HES only (87%)	Mean (SD) days on ICU albumin only 2.3 (2.0) albumin and HES 2.7 (2.3) HES only 2.5 (5.3)
Cywinski, 2010	No difference between high and low CVP group in maximum serum creatinine in first 7 postoperative days.	Not reported	No significant difference between groups in blood products administered. High CVP group: 27% received adrenaline vs. 13% in low CVP group, *p* = .04.	Median (IQR) days on ICU: High CVP: 3 (2-4) Low CVP: 3 (2-4), P = NS
Jiang, 2012	Not reported	Fewer patients with intraoperative fluid < = 100 ml/kg than >100 ml/kg experienced postoperative pulmonary complications	Compared to patients without pulmonary complications, those with pulmonary complications were more likely to receive > .05 U/kg RBCs (91.49% vs. 76.36%, *p* = .041) and > 25 ml/kg plasma (63.83 vs. 43.64%, *p* = .042) intraoperatively	Median (range) hours on ICU: High intraoperative transfusion: 62 (14–600) Low intraoperative transfusion: 36.5 (8–144), *p* < .001
Jipa, 2017	Not reported	Patients with pulmonary complications were more likely to receive intraoperative fluid administration > 100 ml/kg (*p* = .02), a greater volume of crystalloid solutions (*p* = .04) and a positive fluid balance >45 ml/kg (*p* = .01)	Blood loss: patients with pulmonary complications 4526 ± 3451 ml vs. without pulmonary complications 3505 ± 3534 ml, *p* = .18. RBC units: patients with pulmonary complications 6.6 ± 5.4 U vs. without pulmonary complications 4.2 ± 4.4 U, *p* =.07)	PACU LOS: Patients with pulmonary complications 6.3 ± 2.1 days vs without pulmonary complications 4.3 ± 1 days, *p* = .01
Lekerika, 2014	No significant difference in postoperative acute kidney failure, need for diuretics, or hemofiltration.	No significant difference in postoperative TRALI, ARDS, APE, need for non-invasive or invasive ventilation, or invasive ventilation duration.	RBCs transfused: liberal group 7 units vs. restrictive group 3 *p* = < .001	Liberal group 6.9 ± 9.4 days Restrictive group 4.8 ± 2.5 days, P = NS

(Continues)

TABLE 3 (Continued)

	Acute kidney injury	Postoperative respiratory complications	Operative blood loss/red cell units required	ICU length of stay
Martin, 2019	AKI requiring renal replacement therapy at hospital discharge, freq (%) GDFT group 9 (30) Standard care 8 (26.7) $p = .774$	Not reported	Mean (SD) packed red cells administered (ml) GDFT group 177 (456) Standard care group 150 (316)	ICU length of stay, mean (SD) (days) GDFT group 6.8 (10.4) Standard care 6.8 (8.7)
Massicotte, 2012	Not reported	Not reported	RBC units transfused per patient, mean (SD) First 61 patients .3 (.7) Last 439 patients .5 (1.3) p = NS Blood loss, mean (SD), ml First 61 patients 1050 (614) Last 439 1072 (990)	Not reported
Ponnudural, 2005	Not reported	Number of patients with pulmonary interstitial oedema, mean (SD) Vasopressor group 6, Placebo group 7	RBCs transfused (ml/kg). mean (SD) Vasopressor group 13.66 (10.33) Placebo group 14.17 (13.58)	Duration of ICU stay (days), mean (SD) Vasopressor group 3.67 (3.40) Placebo 3.80 (2.84)
Reydellet, 2014	D2 serum creatinine (umol/L), median (IQR) Control group 75 (63–126) Protocol group 83 (61–125)	Not reported	RBCs transfused (ml), median (IQR) Control group 0 (0–1500) Protocol group 900 (0–1500) $p = .30$	Duration of ICU stay (days), median (IQR) Control group 7 (4–13) Protocol group 5 (3–9) $p = .10$
Sahmeddini, 2014	No difference in postoperative urine output, serum creatinine or requirement for postoperative RRT between groups	Number of patients with pulmonary oedema, number (%) Restricted fluid group 0 (0%) Non-restricted fluid group 5 (15%), p =.01	Not reported	Duration of ICU stay (days), mean ± SD Restricted crystalloid group 1.9 ± .5 Non-restricted crystalloid group 2.7 ± 0.4 (p = .003)
Schroeder, 2004	Peak postoperative creatinine (mg/dl), mean (SD) Low CVP 3.2 ± .3 Normal CVP 1.8 ± .2, p = <.01 More frequent need for postoperative RRT in low CVP group (p = <0.01)	Not reported	Packed red blood cells received (units), mean (SD) Low CVP 3.8 ± .7 Normal CVP 11.6 ± 2.0 p = <.01	ICU length of stay (days), mean (SD) Low CVP 3.0 ± .7 Normal CVP 2.1 ± 1.1 p = NS
Wang, 2013	Not reported	Total rate of postoperative pulmonary complications, number (%) Low CVP 14 (42.8) Control group 23 (71.4) $p = .02$	RBC transfusion (ml) Low CVP 2681 ± 1508 Control group 5006 ± 2658 $p = .0312$ Blood loss (ml) Low CVP 3891 ± 2724 Control group 5648 ± 3442 p = 0.022	Not reported

(Continues)

TABLE 3 (Continued)

	Acute kidney injury	Postoperative respiratory complications	Operative blood loss/red cell units required	ICU length of stay
Zhang, 2005	No significant difference in creatinine over the course of surgery between groups.	Not reported	Total blood loss (ml) mean ± SD Dopamine group 4666 ± 2033 NA + dopamine group 5096 ± 3922 $p = .767$	Time to ICU discharge (hours) Mean ± SD Dopamine group 43.2 ± 16.9 NA+dopamine group 40.6 ± 9.3
Zhang, 2020	On multivariate logistic regression analysis, cumulative fluid balance >25ml/kg in the first 72 h was associated with AKI (p =.021)	Pulmonary infection (number, %) AKI group 6 (9.1) No AKI 4 (6.1) $p = .744$	RBC (units), median (IQR) AKI group 10 (6–14) No AKI group 8 (6–12) $p = .406$ Blood loss (ml), median (IQR) AKI group 1500 (875–3000) No AKI 1050 (800–1600) $p = .018$	ICU length of stay (days), mean ± SD AKI group 5.0 (3.0–7.0) No AKI 5.0 (4.0–7.0) $p = .551$
Zhou, 2015	No significant difference was found in the proportion of patients administered HES transfusions between RI and non-RI groups.	Not reported	RBC units administered, mean ± SD RI group 16 (22) Non-RI group 12 (14) p = 0.001	ICU length of stay (hours), mean ± SD RI group 30 (116) Non-RI group 24 (51) p = 0.002

Abbreviations: AKI, acute kidney injury; APE: acute pulmonary oedema; ARDS, acute respiratory distress syndrome; HES, hydroxyethyl starch; ICU, intensive care unit; NA, noradrenaline; NS, non-significant; RBC, red blood cells; RI, renal impairment; RRT, renal replacement therapy; TRALI, transfusion related acute lung injury.

6 | FLUID BALANCE

Intravenous fluids distribute disproportionately to splanchnic vascular beds in advanced liver disease, increasing splanchnic blood volume and blunting increases in central blood volume and cardiac output associated with fluid administration.[12,13] During the transplant procedure, this "splanchnic steal" probably reduces the effectiveness of fluids given to correct hypotension. Moreover, fluid loading may aggravate portal hypertension and bleeding, especially during hepatectomy. Use of vasopressors, which counteract the direct and sympatholytic effects of anesthetic agents on vascular tone, enables a restrictive approach to fluid balance by reducing splanchnic inflow and portal pressure, moderating these effects.[14–17] Alpha-1-mediated venoconstriction may also reduce pooling in splanchnic capacitance vessels, transferring blood to an underfilled systemic circulation.[18] Randomized trials of restrictive transfusion practice in cirrhotic patients with acute variceal bleeding, and of beta-blockade in prevention, support the hypothesis that lower portal pressure reduces bleeding in this population.[19,20]

However, assessment of fluid balance from the disparate studies screened for this review proved challenging. Fluid balance per se (net volume of administered fluids less measured losses) was infrequently reported, and often needed to be calculated from multiple reported input and loss categories, or inferred from described techniques and reported hemodynamic parameters. Measures to minimize positive fluid balance included fluid restriction ± phlebotomy to achieve a reduction of CVP from baseline (e.g., 40%) or an absolute value of <5 mmHg, usually involving titration of vasopressors to maintain arterial blood pressure. One study achieved relative fluid restriction by giving bolus fluids according to a prescribed hemodynamic algorithm taking no account of CVP[7] (Reydellet 2014). Fluid balance in these studies was never "zero," but was reported as less positive than controls. Despite this heterogeneity, an association between volume restriction during dissection and lower blood loss was clear in two RCTs and one large observational cohort, with none of these reporting significant increases AKI, postoperative RRT or other adverse outcomes (Table 4).[21–23]

An important consideration in the clinical application of moderate restriction is the degree of IVC occlusion associated with hepatectomy. Both full cross-clamping of the IVC (caval replacement technique) and side-clamping with partial caval occlusion (caval preservation or "piggyback" technique) require temporary volume expansion shortly before IVC clamping, with or without vasopressors and/or venovenous bypass. This is proportionate to the degree of caval occlusion, and filling pressures rapidly fall once clamping is performed. Although this may be followed by significant loss of intravascular volume through transudation into the lower body during the anhepatic phase[24] (Paulsen 1989), fluid replacement during the period of caval clamping should be cautious to avoid overfilling once caval clamps are removed. Again, reliance on temporary supplementation of vasopressor may be appropriate.

TABLE 4 Summary of findings

Intervention: minimizing perioperative fluid balance by replacing losses and restricting infusion to volume required to sustain safe organ perfusion									
Summary of findings									
Number of studies									
RCT	Observational comparative	Observational non-comparative	Effect from comparative studies:	Limitations	Inconsistency	Indirectness	Imprecision	Publication Bias	Quality of Evidence (GRADE)
Outcome 1: Acute Kidney Injury (AKI)									
2	7	0	RCTs: NO EFFECT; OTHERS INCONSISTENT	Serious	Serious	Serious	Not serious	Not likely	LOW
Outcome 2: Postoperative respiratory complications									
3	2	0	2/3 RCTs SHOW EFFECT; 1/3 UNDERPOWERED; 2/2 OBS STUDIES SUGGEST EFFECT	Serious	Not serious	Not serious	Serious	Not likely	LOW
Outcome 3: Operative blood loss / red cell units required									
1	2		LOWER IN INTERVENTION GROUP IN ALL STUDIES	Not serious in RCT; serious in observational	Not serious	Not serious	Not serious	Not likely	MODERATE
Outcome 4: ICU LOS									
1	7	0	LOWER IN INTERVENTION GROUP IN 4 STUDIES, NS IN 4, = TREND TO SHORTER ICU LOS	Not serious	Not serious	Not serious	Not serious	Not likely	LOW

Note: "fluid balance" refers primarily to total fluids administered versus estimated losses during the intraoperative period. When not reported specifically as "intraoperative fluid balance" this was assumed to be significantly lower in the intervention group when the reported technique was clearly restrictive AND administered volumes were significantly lower. One study outside this definition (e.g., reporting only combined intraoperative and up to 24 h postoperative fluid balance) was included. Note that two cohort studies of later, cumulative post-op FB (72 h and 96 h) showed a strong association with AKI/RRT but were excluded since outside definition and highly likely to be confounded by treatment of incipient renal failure.

Regarding other potential benefits and risks related to fluid balance, two RCTs and two non-randomized studies reported reduced postoperative pulmonary complications and shorter ICU length of stay associated with moderate restriction.[22,25–27] One observational study, which involved two centers with different intraoperative techniques (so high risk of bias), reported increased rates of renal injury and reduced 30-day survival with a "low CVP" technique.[28] However, this was not observed in higher quality studies, and a similar GRADE-compliant systematic review in both deceased and living donor liver transplantation found no association between restrictive practices and AKI. Effects on blood loss, pulmonary complications and ICU LOS were also similar.[29] Nonetheless, a cautious approach to volume restriction is supported by a large randomized study in high-risk patients undergoing major abdominal surgery (liver transplants excluded), which reported no net benefit from fluid restriction and a higher incidence of AKI in the restricted arm.[30]

7 | GOAL-DIRECTED FLUID THERAPY (GDFT)

In this review, a single retrospective study of intra- and early postoperative GDFT in liver recipients, using an algorithm that delivered moderate fluid restriction compared to controls, showed no effect on blood loss or AKI but reduced duration of mechanical ventilation ($p < .05$) and ICU LOS ($p < .10$).[7] A small RCT investigating early postoperative GDFT in this setting was associated with increased fluid administration compared to controls, but did not show reduced AKI or other benefit; a higher rate of biliary complications was a significant finding, plausibly Type 1 error given the small size of the trial.[8]

In large RCTs in major non-transplant surgery, benefits from GDFT over a moderately restrictive (replacement-based) regime appeared to be marginal.[31–33] However, other studies in these settings have been more positive, and a suitably powered OPTIMIZE II trial is underway. GDFT combining HES with balanced electrolyte solutions has

TABLE 5 Summary of findings

INTERVENTION: USE OF VASOPRESSOR/TARGET MAP									
Number of studies									
RCT	Observational comparative	Observational non-comparative	Effect from comparative studies	Limitations	Inconsistency	Indirectness	Imprecision	Publication Bias	Quality of Evidence (GRADE)
Outcome 1: Acute Kidney Injury (AKI)									
1	3	0	NO EFFECT	Serious	Not serious	Not serious	Serious	Not likely	LOW
Outcome 2: Postoperative respiratory complications									
1	0	0	INDETERMINATE (INAPPROPRIATE STAT TESTING)	Serious	Not applicable (single study)	Not serious	Serious	Not likely	LOW
Outcome 3: Operative blood loss / red cell units required									
0	1	0	NO EFFECT	Serious	Not applicable (single study)	Not serious	Serious	Not likely	LOW
Outcome 4: ICU LOS									
0	3	0	NO EFFECT	Not serious	Not serious	Not serious	Not serious	Not likely	LOW

In screened studies, use of vasopressors was generally defined as required to maintain MAP >60 mmHg; no prospective studies investigated MAP target values in relation to outcomes.

demonstrated better clinical outcomes and no difference in AKI in major abdominal surgery,[34] while subcutaneous P_aO_2 values appear to be unaffected by the type of fluid given in a GDFT regime.[35] An emerging trend is use of closed loop automated GDFT to deliver this combination, adhering to maximum colloid dose recommendations (30 ml/kg) and improving compliance with this demanding technique.[34,36]

8 | VASOPRESSORS/TARGET MAP

While investigators have described effects of several vasopressors on the splanchnic and systemic circulations in this population, an optimal target minimum for MAP has not been reliably determined. However, AKI and other outcomes are strongly associated with the absolute and relative hypotension defined as "reperfusion syndrome," and with the severity and duration of intraoperative MAP <65 mmHg (Table 5).[6,5,37,38] Researchers cited in this review consistently described protocolized vasopressor use to maintain MAP >60–65 mmHg. The arguments against sole use of aggressive intravascular filling to correct hypotension have been presented above, but the comparative risks and benefits of different vasopressors as adjuncts to fluid have not been investigated.

A large observational study in non-cardiac surgery suggests a threshold effect for renal and myocardial injury at MAP less than 55 mm Hg.[39] A more recent RCT supports adjustment of a minimum blood pressure target based on resting preoperative values, not on a standard target of systolic >80 mmHg.[40] Other studies are ongoing, but it is reassuring to note that NA-supported MAP in the range of 60–90 mm Hg did not impair gut microperfusion in post-cardiac surgery vasoplegia, and that mucosal microperfusion was preserved on both NA and PE infusions despite reduced splanchnic blood flow.[41,42]

An important consideration in vasopressor use relates to the accuracy of invasive blood pressure measurements. Radial arterial pressures may underestimate true MAP during vasopressor infusion, although this error can be avoided by use of long radial catheters (e.g., 20 g × 20 cm) or direct brachial or femoral cannulation.[43] Therefore, we suggest that vasopressor treatment, especially at moderate or higher doses, should be guided by MAP values from one of these alternate techniques or from a non-invasive brachial blood pressure monitor of appropriate cuff size.[44]

9 | FLUID TYPE: COLLOIDS VERSUS CRYSTALLOIDS, ROLE OF BALANCED ELECTROLYTE SOLUTIONS

Only two studies screened for this review addressed of the types of crystalloid and colloid fluid used perioperatively in our defined population. One small RCT comparing 8.4% bicarbonate infusion with .9% sodium chloride as prophylaxis for AKI, did not demonstrate any effect (Table 7).[45] A single retrospective study in deceased donor liver transplantation investigated HES 130/.4 and 4.5% human albumin solution used to maintain intravascular volume and appeared to link HES 130/.4 to increased AKI (Table 6).[46] This is supported by systematic reviews of fluid therapy in other settings, including renal transplantation.[47–49] However, dose may be relevant. A small RCT in living donor liver recipients with a ceiling dose of 50 ml/kg found no effect on renal outcomes,[50] and a randomized trial of 1002 patients undergoing major

TABLE 6 Summary of findings

INTERVENTION: FLUID TYPE 130/.4 HES vs. ALBUMIN									
Number of studies									
RCT	Observational comparative	Observational non-comparative	Effect from comparative studies	Limitations	Inconsistency	Indirectness	Imprecision	Publication Bias	Quality of Evidence (GRADE)
Outcome 1: Acute Kidney Injury (AKI)									
0	1	0	Clearly higher in intervention group in only study	Serious	Not applicable (single study)	Not serious	Not serious	Not likely	LOW
Outcome 2: Postoperative respiratory complications NO DATA									
Outcome 3: Operative blood loss / red cell units required NO DATA									
Outcome 4: ICU LOS NO DATA									

TABLE 7 Summary of findings

INTERVENTION: SODIUM BICARBONATE vs. 0.9% NaCl INFUSIONS									
Number of studies									
RCT	Observational comparative	Observational non-comparative	Effect from comparative studies	Limitations	Inconsistency	Indirectness	Imprecision	Publication Bias	Quality of Evidence (GRADE)
Outcome 1: Acute Kidney Injury (AKI)									
1	0	0	NO EFFECT	Not serious	Not applicable (single study)	Not serious	Not serious	Not likely	MODERATE
Outcome 2: Postoperative respiratory complications NO DATA									
Outcome 3: Operative blood loss / red cell units required NO DATA									
Outcome 4: ICU LOS NO DATA									

abdominal surgery given up to 1500 ml HES 130/.4 versus Lactated Ringer's alone found no differences in AKI by RIFLE criteria.[51] However, this panel's view is that alternatives to hetastarch are probably safer.

Studies of modified fluid (succinylated) gelatin, widely used in Europe, have shown volume expansion and duration of effect similar to HES 130/.4 in other settings despite its much lower molecular weight,[52,53] but no trials in liver transplantation have been reported. Human albumin solution is used worldwide though constrained in many countries by high cost. It appears to be safe though not consistently beneficial in advanced cirrhosis and other settings.[54–56] An RCT in living donor recipients demonstrated significantly higher net perioperative fluid balance with 5% albumin versus 6% HES 130/.4 controls, but no difference in renal or other outcomes.[50] More significantly, a large recent RCT of 20% HAS infusion to correct serum albumin in hospitalized patients with decompensated cirrhosis failed to show improved outcomes over standard care (median dose 200 g vs. 20 g over 15 days), and pulmonary edema and pneumonia were more common in the treatment group.[54] A pharmacokinetic investigation in liver transplant recipients given albumin infusion at 100 mg per kg per hour during and after surgery demonstrated cumulative extravascular loss of more than 68% of the net administered dose, much higher than seen in non-transplant abdominal surgery and associated with higher postoperative weight gain. It also showed that recovery of liver synthetic capacity was typically rapid and vigorous.[57] Taken together, these studies suggest that the administration of large doses of HAS to correct peri-transplant hypoalbuminemia may not be beneficial.

A total of .9% sodium chloride and colloids with high chloride content have been associated with hyperchloremic acidosis, renal vasoconstriction, and adverse surgical and critical care outcomes, potentially avoided through use of balanced electrolyte solutions.[58–62] Although evidence of an effect on important outcomes is weak, many centers now favor balanced electrolyte solutions and reduced-sodium colloids to avoid excessive sodium and chloride administration. This

TABLE 8 Evidence to recommendation framework according to the GRADE approach

Question A: What intraoperative fluid balance (or estimated state of intravascular filling) is associated with optimal immediate and short term outcomes in adult deceased donor liver transplantation?

	Judgement		
Decision domain	Yes	No	**Reason for Judgement**
Balance between desirable and undesirable outcomes (estimated effects), with consideration of values and preferences (estimated typical) *Given the best estimate of typical values and preferences, are you confident that the benefits outweigh the harms and burden or vice versa?*	YES		Undesirable effects are reported with both high and low (negative) fluid balance intraoperatively; avoidance of these is assumed to be consistent with values and preferences
Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes) *Is there high, moderate or low-quality evidence?*	YES		Evidence is low to moderate quality; reporting of risks of AKI is conflicting, with higher quality evidence supporting minimal adverse effect if any.
Confidence in Values and Preference, and their Variability *Are you confident about the typical values and preferences and are they similar across the target population?*	YES		As above (first domain in this table)
Resource implications *Are the resources worth the expected net benefit from following the recommendation?*		NO	Too little evidence to judge
Overall quality of evidence: Moderate			
Strength of recommendations: Weak for maintenance of euvolemia ("replacement only"), including use of vasopressors to maintain MAP >60–65 mmHg, which may reduce blood loss and post-op respiratory complications without increasing AKI; Strong for avoidance of hypervolemia (avoid high positive intraoperative/early postoperative fluid balance) for similar reasons. GDFT, which may lead to higher positive fluid balance if not used in tightly defined circumstances, needs further evaluation.			
Question B: What is an appropriate minimum mean arterial pressure, using vasopressor infusion(s) if necessary, for optimal immediate and short-term outcomes in adult deceased donor liver transplantation?			
Balance between desirable and undesirable outcomes (estimated effects), with consideration of values and preferences (estimated typical) *Given the best estimate of typical values and preferences, are you confident that the benefits outweigh the harms and burden or vice versa?*	YES		Stated target values are well established in prevention of serious complications in other settings; vasopressors are widely used in ESLD and LT.
Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes) *Is there high, moderate or low-quality evidence?*	YES		As above
Confidence in values and preference, and their variability *Are you confident about the typical values and preferences and are they similar across the target population?*	YES		As above
Resource implications *Are the resources worth the expected net benefit from following the recommendation?*		NO	As above

(Continues)

TABLE 8 (Continued)

Overall quality of evidence: VERY LOW (NOT DIRECTLY EVALUATED)			
Strength of recommendation: Strong for maintenance of MAP ≥60--65 mmHg.			
Question C: What fluids (crystalloid vs. colloid, synthetic colloid vs. albumin, .9% NaCl vs balanced electrolyte solutions) should be used intraoperatively for optimal immediate and short term outcomes in adult deceased donor liver transplantation? Note only the following can be assessed from the selected papers: a) 130/.4 HES b) 8.4% $NaHCO_3$ infusion			
	Judgement		
Decision domain	Yes	No	**Reason for Judgement**
Balance between desirable and undesirable outcomes (estimated effects), with consideration of values and preferences (estimated typical) *Given the best estimate of typical values and preferences, are you confident that the benefits outweigh the harms and burden or vice versa?*	YES		a. HES: Good quality evidence in other settings suggests 130/.4 HES use is associated with increased risk of AKI. Since baseline AKI risk is known to be high in ESLD and LT, expert consensus is that it is safer to avoid this colloid: i.e., likely that harms > benefits b. NaHCO3: too little evidence to judge
Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes) *Is there high, moderate or low-quality evidence?*	YES		a. HES: confident b. NaHCO3: too little evidence to judge
Confidence in Values and Preference, and their Variability *Are you confident about the typical values and preferences and are they similar across the target population?*	YES		
Resource implications *Are the resources worth the expected net benefit from following the recommendation?*	YES		
Overall Quality of Evidence: LOW			
Recommendation: Strong against use of 130/.4 HES since the incidence of AKI in this population is high.			

trend may be reinforced by the need to avoid rapid increases in plasma sodium, which have been associated with disequilibrium myelinolysis and severe neurological disability, especially in liver recipients with marked hyponatremia.[63]. However, a recent high quality multi-center randomised trial of resuscitation with saline versus balanced electrolyte solution (Plasma-Lyte 148) in critical care, which included more than 2000 post-surgical patients, has demonstrated no difference in 90-day survival or renal injury despite expected increases in serum chloride in the saline arm. This has contradicted other studies with weaker designs, but the authors do not exclude important differences in unspecified sub-groups, including liver recipients, not included in the trial.[64]

Thus, it is clear that liver transplant clinicians' perceptions of risks and benefits of colloid versus crystalloid and balanced crystalloid versus .9% sodium chloride, are based almost entirely on local experience and data from non-transplant settings, including abdominal surgery, cardiac surgery and critical care. Practice has also been influenced by advances in the understanding of the effects of administered fluids on intravascular volume and tissue perfusion, and of fluid translocation at microcirculatory level. For example, the translocation of administered crystalloid to the interstitium, and therefore its effect in sustaining intravascular volume, is now known to depend on intravascular filling and the state of the vascular endothelial glycocalyx.[65] This "context sensitivity," with less translocation at lower venous pressures, may explain recent evidence that the volume of crystalloid required for intravascular replacement can be as low as 1.5 times that of colloid.[36,66] This suggests that use of crystalloids instead of synthetic colloids or HAS to supplement blood products during surgical hemorrhage is more appropriate and practical than many previously believed. Conversely, hypervolemia appears to facilitate ANP-mediated glycocalyx disruption and fluid translocation, aggravating tissue edema and renal injury.[67] Taken with evidence of the maldistribution of administered fluids in end-stage liver disease, this should discourage the previously common practice of aggressive volume loading in liver recipients for hemodynamic stability.

Moreover, our recommendations cannot take into account local conditions, including recipient case-mix, donor quality, surgical techniques, unit experience, and costs, all of which can influence local practice and may be of considerable importance without being acknowledged or represented in the literature. Choice of crystalloid and colloid, for example, may be determined by local regulatory approval and availability, relative costs, perceived risks of potassium, sodium and

chloride excess, compatibility with blood products, and ease of use with rapid infusion equipment. Differential effects on coagulation, by dilution and by direct effects on coagulation pathways, may also influence this choice, as may the potential of exogenous lactate in some balanced electrolyte solutions to alter plasma lactate concentrations used to monitor graft function.[68] Defining optimal fluid management in individual centers will always need to take these factors into account. Efficacy in published research, especially if marginal, may not translate into effectiveness in all centers.

10 | LIMITATIONS

The fundamental limitation of this review is the low quality of evidence available in the unique setting of liver transplantation, both in the absence of randomized studies addressing many key questions and in the low numbers enrolled in those that have been attempted. This results from the small number of transplants performed compared to most surgical specialties, and the related difficulty in obtaining agency funding for multicenter prospective trials. Wide variability in many important outcomes and limited consensus on outcome definitions also appear to be relevant. Recommendations are therefore based on data from retrospective studies and non-transplant settings, making their applicability to these patients a matter of subjective judgment.

11 | CONCLUSION

The expert panel recommends a euvolemic or moderately restrictive approach to fluid balance in adult deceased donor liver transplant, both to reduce transfusion requirement and to enable early extubation by minimizing postoperative respiratory complications (Quality of Evidence, Moderate; Strength of Recommendation, Weak). It recommends maintenance of MAP >60–65 mmHg (Quality of Evidence, Low; Strength of Recommendation, Strong). This review has outlined recent advances in the understanding of fluid management in this and other surgical settings. The panel's view is that ERAS-focused research in this area can only progress through coordinated tracking of interventions and outcomes in individual units, who share this data in multi-center observational and interventional studies. Collaborating units should jointly define key outcomes, pursue regular observational analysis, and generate adequately powered randomized trials.

Topics for future research in perioperative fluid management may include the following:

1. International agreement on a standard minimum dataset for intraoperative reporting, including precise definitions of interventions and outcomes.
2. Multicenter RCTs comparing AKI and post-operative respiratory outcomes in:
   a. Balanced crystalloid alone versus balanced synthetic colloid versus balanced crystalloid plus HAS
   b. Effectiveness of standardized intraoperative euvolemic management versus GDFT modified to avoid excessive fluid balance (as per Reydellet[7])
3. Explanatory studies to assess:
   a. Relative accuracy of MAP determinations from standard radial, long radial, brachial, femoral, and brachial NIBP during vasopressor infusion.
   b. Effects of post-reperfusion vasopressors on hepatic blood flow ± renal function (norepinephrine, phenylephrine, vasopressin/terlipressin).
   c. Optimal dose and timing of perioperative albumin support.

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ACKNOWLEDGMENTS

This manuscript was prepared for the ERAS4OLT.org consensus conference 2022, which is partially funded by the International Liver Transplantation Society (ILTS).

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

John R. Klinck: Critical revision of study design, data analysis and interpretation, drafting article, critical revision of article. Clare M. Morkane: Data analysis and interpretation, drafting article, critical revision of article. Gonzalo Sapisochin: Data analysis and interpretation, critical revision of article. Ahmed M. Mukhtar: Data analysis and interpretation, critical revision of article. Koen M. E. M. Reyntjens: Data analysis and interpretation, critical revision of article. Gebhard Wagener: Data analysis and nterpretation, critical revision of article. Michael Spiro: Concept and design of study, critical revision of article, approval of article. Dimitri A. Raptis: Concept and design of study, critical revision of article, approval of article.

DATA AVAILABILITY STATEMENT

No additional supporting data.

REFERENCES

1. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol*. 2011;64(4):383–394. https://doi.org/10.1016/j.jclinepi.2010.04.026

2. Murad MH, Mustafa RA, Schünemann HJ, Sultan S, Santesso N. Rating the certainty in evidence in the absence of a single estimate of effect. *Evid Based Med*. 2017;22(3):85–87. https://doi.org/10.1136/ebmed-2017-110668
3. Andrews J, Guyatt G, Oxman AD, et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. *J Clin Epidemiol*. 2013;66(7):719–725. https://doi.org/10.1016/j.jclinepi.2012.03.013
4. Andrews JC, Schünemann HJ, Oxman AD, et al. GRADE guidelines: 15. Going from evidence to recommendation–determinants of a recommendation's direction and strength. *J Clin Epidemiol*. 2013;66(7):726–735. https://doi.org/10.1016/j.jclinepi.2013.02.003
5. Joosten A, Lucidi V, Ickx B, et al. Intraoperative hypotension during liver transplant surgery is associated with postoperative acute kidney injury: a historical cohort study. *BMC Anesthesiol*. 2021;21(1):12. https://doi.org/10.1186/s12871-020-01228-y
6. Jun I-G, Kwon H-M, Jung K-W, et al. The impact of postreperfusion syndrome on acute kidney injury in living donor liver transplantation: a propensity score analysis. *Anesth Analg*.. 2018;127(2):369–378. https://doi.org/10.1213/ANE.0000000000003370
7. Reydellet L, Blasco V, Mercier MF, et al. Impact of a goal-directed therapy protocol on postoperative fluid balance in patients undergoing liver transplantation: a retrospective study. *Ann Fr Anesth Reanim*. 2014;33(4):e47–e54. https://doi.org/10.1016/j.annfar.2013.12.016
8. Martin D, Koti R, Gurusamy K, et al. The cardiac output optimisation following liver transplant (COLT) trial: a feasibility randomised controlled trial. *Hpb*. 2020;22(8):1112–1120. https://doi.org/10.1016/j.hpb.2019.11.011
9. Reviewers CIGA, Reviewers CIGA. Human albumin administration in critically ill patients: systematic review of randomised controlled trials Why albumin may not work. *BMJ*. 1998;317(7153):235–240. https://doi.org/10.1136/bmj.317.7153.235
10. Roberts I, Blackhall K, Alderson P, Bunn F, Schierhout G. Human albumin solution for resuscitation and volume expansion in critically ill patients. *Cochrane Database Syst Rev*. 2011. https://doi.org/10.1002/14651858.CD001208.pub4
11. Haase N, Perner A. Colloid solutions in the perioperative setting. *BMJ*. 2015;350(mar27 6):h1656-h1656. https://doi.org/10.1136/bmj.h1656
12. Hadengue A, Moreau R, Gaudin C, Bacq Y, Champigneulle B, Lebrec D. Total effective vascular compliance in patients with cirrhosis: a study of the response to acute blood volume expansion. *Hepatology*. 1992;15(5):809–815. https://doi.org/10.1002/hep.1840150511
13. Møller S, Bendtsen F, Henriksen JH. Effect of volume expansion on systemic hemodynamics and central and arterial blood volume in cirrhosis. *Gastroenterology*. 1995;109(6):1917–1925. https://doi.org/10.1016/0016-5085(95)90759-9
14. Massicotte L, Perrault M-A, Denault AY, et al. Effects of phlebotomy and phenylephrine infusion on portal venous pressure and systemic hemodynamics during liver transplantation. *Transplantation*. 2010;89(8):920–927. https://doi.org/10.1097/TP.0b013e3181d7c40c
15. Wagener G, Gubitosa G, Renz J, et al. Vasopressin decreases portal vein pressure and flow in the native liver during liver transplantation. *Liver Transpl*. 2008;14(11):1664–1670. https://doi.org/10.1002/lt.21602
16. Narahara Y, Kanazawa H, Taki Y, et al. Effects of terlipressin on systemic, hepatic and renal hemodynamics in patients with cirrhosis. *J Gastroenterol Hepatol*. 2009;24(11):1791–1797. https://doi.org/10.1111/j.1440-1746.2009.05873.x
17. Mukhtar A, Salah M, Aboulfetouh F, et al. The use of terlipressin during living donor liver transplantation: effects on systemic and splanchnic hemodynamics and renal function*: *Crit Care Med*. 2011;39(6):1329–1334. https://doi.org/10.1097/CCM.0b013e3182120842
18. Martin GS, Kaufman DA, Marik PE, et al. Perioperative Quality Initiative (POQI) consensus statement on fundamental concepts in perioperative fluid management: fluid responsiveness and venous capacitance. *Perioper Med*. 2020;9(1):12. https://doi.org/10.1186/s13741-020-00142-8
19. Villanueva C, Colomo A, Bosch A, et al. Transfusion strategies for acute upper gastrointestinal bleeding. *N Engl J Med*. 2013;368(1):11–21. https://doi.org/10.1056/NEJMoa1211801
20. Odutayo A, Desborough MJR, Trivella M, et al. Restrictive versus liberal blood transfusion for gastrointestinal bleeding: a systematic review and meta-analysis of randomised controlled trials. *Lancet Gastroenterol Hepatol*. 2017;2(5):354–360. https://doi.org/10.1016/S2468-1253(17)30054-7
21. Hong SH, Park CS, Jung HS, et al. A comparison of intra-operative blood loss and acid-base balance between vasopressor and inotrope strategy during living donor liver transplantation: a randomised, controlled study: vasopressor vs inotrope strategy for liver transplantation. *Anaesthesia*. 2012;67(10):1091–1100. https://doi.org/10.1111/j.1365-2044.2012.07198.x
22. Wang B, He HK, Cheng B, Wei K, Min S. Effect of low central venous pressure on postoperative pulmonary complications in patients undergoing liver transplantation. *Surg*. 2013;43(7):777–781. https://doi.org/10.1007/s00595-012-0419-y
23. Massicotte L, Denault AY, Beaulieu D, et al. Transfusion rate for 500 consecutive liver transplantations: experience of one liver transplantation center. *Transplantation*. 2012;93(12):1276–1281. https://doi.org/10.1097/TP.0b013e318250fc25
24. Paulsen AW, Whitten CW, Ramsay MA, Klintmalm GB. Considerations for anesthetic management during veno-venous bypass in adult hepatic transplantation. *Anesth Analg*. 1989;68(4):489–496.
25. Sahmeddini MA, Janatmakan F, Khosravi MB, et al. Restricted crystalloid fluid therapy during orthotopic liver transplant surgery and its effect on respiratory and renal insufficiency in the early post-operative period: a randomized clinical trial. *Int*. 2014;5(3):113–119.
26. Jiang GQ, Peng MH, Yang DH. Effect of perioperative fluid therapy on early phase prognosis after liver transplantation. *Hepatobiliary Pancreat Dis Int*. 2008;7(4):367–372.
27. Jipa LN, Droc G, Diculescu M. The influence of intraoperative fluid management on postoperative pulmonary complications in liver-transplant patients. *Archives of the Balkan Medical Union*. 2017;52(3):278–284.
28. Schroeder RA, Collins BH, Tuttle-Newhall E, et al. Intraoperative fluid management during orthotopic liver transplantation. *J Cardiothorac Vasc Anesth*. 2004;18(4):438–441.
29. Carrier FM, Sylvestre MP, Massicotte L, Bilodeau M, Chasse M. Effects of intraoperative hemodynamic management on postoperative acute kidney injury in liver transplantation: an observational cohort study. *PLoS One*. 2020;15(8):e0237503. https://doi.org/10.1371/journal.pone.0237503
30. Myles PS, Bellomo R, Corcoran T, et al. Restrictive versus liberal fluid therapy for major abdominal surgery. *N Engl J Med*. 2018;378(24):2263–2274. https://doi.org/10.1056/NEJMoa1801601
31. Pearse RM, Harrison DA, MacDonald N, et al. Effect of a perioperative, cardiac output–guided hemodynamic therapy algorithm on outcomes following major gastrointestinal surgery: a randomized clinical trial and systematic review. *JAMA*. 2014;311(21):2181. https://doi.org/10.1001/jama.2014.5305
32. Wrzosek A, Jakowicka-Wordliczek J, Zajaczkowska R, et al. Perioperative restrictive versus goal-directed fluid therapy for adults undergoing major non-cardiac surgery. *Cochrane Database Syst Rev*. 2019. https://doi.org/10.1002/14651858.CD012767.pub2

33. Diaper J, Schiffer E, Barcelos GK, et al. Goal-directed hemodynamic therapy versus restrictive normovolemic therapy in major open abdominal surgery: A randomized controlled trial. *Surgery*. 2021;169(5):1164–1174. https://doi.org/10.1016/j.surg.2020.09.035
34. Joosten A, Delaporte A, Ickx B, et al. Crystalloid *versus* colloid for intraoperative goal-directed fluid therapy using a closed-loop system. *Anesthesiology*. 2018;128(1):55–66. https://doi.org/10.1097/ALN.0000000000001936
35. Reiterer C, Kabon B, Zotti O, Obradovic M, Kurz A, Fleischmann E. Effect of goal-directed crystalloid- versus colloid-based fluid strategy on tissue oxygen tension: a randomised controlled trial. *Br J Anaesth*. 2019;123(6):768–776. https://doi.org/10.1016/j.bja.2019.08.027
36. Joosten A, Coeckelenbergh S, Alexander B, et al. Hydroxyethyl starch for perioperative goal-directed fluid therapy in 2020: a narrative review. *BMC Anesthesiol*. 2020;20(1):209. https://doi.org/10.1186/s12871-020-01128-1
37. Umbro I, Tinti F, Scalera I, et al. Acute kidney injury and post-reperfusion syndrome in liver transplantation. *WJG*. 2016;22(42):9314. https://doi.org/10.3748/wjg.v22.i42.9314
38. Mizota T, Hamada M, Matsukawa S, Seo H, Tanaka T, Segawa H. Relationship between intraoperative hypotension and acute kidney injury after living donor liver transplantation: a retrospective analysis. *J Cardiothorac Vasc Anesth*. 2017;31(2):582–589. https://doi.org/10.1053/j.jvca.2016.12.002
39. Walsh M, Devereaux PJ, Garg AX, et al. Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery. *Anesthesiology*. 2013;119(3):507–515. https://doi.org/10.1097/ALN.0b013e3182a10e26
40. Futier E, Lefrant J-Y, Guinot P-G, et al. Effect of individualized vs standard blood pressure management strategies on postoperative organ dysfunction among high-risk patients undergoing major surgery: a randomized clinical trial. *JAMA*. 2017;318(14):1346. https://doi.org/10.1001/jama.2017.14172
41. Nygren A, Thorén A, Ricksten S-E. Norepinephrine and intestinal mucosal perfusion in vasodilatory shock after cardiac surgery. *Shock*. 2007;28(5):536–543. https://doi.org/10.1097/shk.0b013e318063e71f
42. Nygren A, Thorén A, Ricksten S-E. Vasopressors and intestinal mucosal perfusion after cardiac surgery: Norepinephrine vs. phenylephrine: *Crit Care Med*. 2006;34(3):722–729. https://doi.org/10.1097/01.CCM.0000201879.20281.C6
43. Fuda G, Denault A, Deschamps A, et al. Risk factors involved in central-to-radial arterial pressure gradient during cardiac surgery. *Anesth Analg*. 2016;122(3):624–632. https://doi.org/10.1213/ANE.0000000000001096
44. Lakhal K, Macq C, Ehrmann S, Boulain T, Capdevila X. Noninvasive monitoring of blood pressure in the critically ill: Reliability according to the cuff site (arm, thigh, or ankle). *Crit Care Med*. 2012;40(4):1207–1213. https://doi.org/10.1097/CCM.0b013e31823dae42
45. Weinberg L, Broad J, Pillai P, et al. Sodium bicarbonate infusion in patients undergoing orthotopic liver transplantation: a single center randomized controlled pilot trial. *Clin Transplant*. 2016;30(5):556–565. https://doi.org/10.1111/ctr.12721
46. Hand WR, Whiteley JR, Epperson TI, et al. Hydroxyethyl starch and acute kidney injury in orthotopic liver transplantation: a single-center retrospective review. *Anesth Analg*. 2015;120(3):619–626. https://doi.org/10.1213/ANE.0000000000000374
47. Zarychanski R, Abou-Setta AM, Turgeon AF, et al. Association of hydroxyethyl starch administration with mortality and acute kidney injury in critically Ill patients requiring volume resuscitation: a systematic review and meta-analysis. *JAMA*. 2013;309(7):678. https://doi.org/10.1001/jama.2013.430
48. Mutter TC, Ruth CA, Dart AB. Hydroxyethyl starch (HES) versus other fluid therapies: effects on kidney function. *Cochrane Database Syst Rev*. 2013. https://doi.org/10.1002/14651858.CD007594.pub3
49. Wagener G, Bezinover D, Wang C, et al. Fluid management during kidney transplantation: a consensus statement of the committee on transplant anesthesia of the American Society of anesthesiologists. *Transplantation*. 2021;105(8):1677–1684. https://doi.org/10.1097/TP.0000000000003581
50. Mukhtar A, Aboulfetouh F, Obayah G, et al. The safety of modern hydroxyethyl starch in living donor liver transplantation: a comparison with human albumin. *Anesthesia & Analgesia*. 2009;109(3):924–930. https://doi.org/10.1213/ane.0b013e3181aed54f
51. Kabon B, Sessler DI, Kurz A, the Crystalloid–Colloid Study Team. Effect of Intraoperative goal-directed balanced crystalloid *versus* colloid administration on major postoperative morbidity. *Anesthesiology*. 2019;130(5):728–744. https://doi.org/10.1097/ALN.0000000000002601
52. Lobo DN, Stanga Z, Aloysius MM, et al. Effect of volume loading with 1 liter intravenous infusions of 0.9% saline, 4% succinylated gelatine (Gelofusine) and 6% hydroxyethyl starch (Voluven) on blood volume and endocrine responses: a randomized, three-way crossover study in healthy volunteers. *Crit Care Med*. 2010;38(2):464–470. https://doi.org/10.1097/CCM.0b013e3181bc80f1
53. Awad S, Dharmavaram S, Wearn CS, Dube MG, Lobo DN. Effects of an intraoperative infusion of 4% succinylated gelatine (Gelofusine ®) and 6% hydroxyethyl starch (Voluven ®) on blood volume †. *Br J Anaesth*. 2012;109(2):168–176. https://doi.org/10.1093/bja/aes098
54. China L, Freemantle N, Forrest E, et al. A randomized trial of albumin infusions in hospitalized patients with cirrhosis. *N Engl J Med*. 2021;384(9):808–817. https://doi.org/10.1056/NEJMoa2022166
55. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med*. 2004;350(22):2247–2256. https://doi.org/10.1056/NEJMoa040232
56. Patel A, Laffan MA, Waheed U, Brett SJ. 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(jul22 10):g4561-g4561. https://doi.org/10.1136/bmj.g4561
57. Amouzandeh M, Nowak G, Januszkiewicz A, Wernerman J, Rooyackers O, Norberg Å. Albumin mass balance and kinetics in liver transplantation. *Crit Care*. 2018;22(1):152. https://doi.org/10.1186/s13054-018-2053-6
58. Chowdhury AH, Cox EF, Francis ST, Lobo DN. A randomized, controlled, double-blind crossover study on the effects of 2-L infusions of 0.9% saline and Plasma-Lyte® 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. *Ann Surg*. 2012;256(1):18–24. https://doi.org/10.1097/SLA.0b013e318256be72
59. Yunos NM, Bellomo R, Glassford N, Sutcliffe H, Lam Q, Bailey M. Chloride-liberal vs. chloride-restrictive intravenous fluid administration and acute kidney injury: an extended analysis. *Intensive Care Med*. 2015;41(2):257–264. https://doi.org/10.1007/s00134-014-3593-0
60. Nadeem A, Salahuddin N, El Hazmi A, et al. Chloride-liberal fluids are associated with acute kidney injury after liver transplantation. *Crit Care*. 2014;18(6):625. https://doi.org/10.1186/s13054-014-0625-7
61. Sen A, Keener CM, Sileanu FE, et al. Chloride content of fluids used for large-volume resuscitation is associated with reduced survival. *Crit Care Med*. 2017;45(2):e146–e153. https://doi.org/10.1097/CCM.0000000000002063
62. Masevicius FD, Rubatto Birri PN, Risso Vazquez A, et al. Relationship of at admission lactate, unmeasured anions, and chloride to the outcome of critically Ill patients. *Crit Care Med*. 2017;45(12):e1233–e1239. https://doi.org/10.1097/CCM.0000000000002730
63. Morard I, Gasche Y, Kneteman M, et al. Identifying risk factors for central pontine and extrapontine myelinolysis after liver

transplantation: a case–control study. *Neurocrit Care*. 2014;20(2):287–295. https://doi.org/10.1007/s12028-013-9928-9

64. Finfer S, Micallef BN, Hammond S, et al. Balanced Multielectrolyte Solution versus Saline in Critically Ill Adults. *N Engl J Med* 2022;386:815–826. https://doi.org/10.1056/NEJMoa2114464. Epub 2022 Jan 18.
65. Nishimura A, Tabuchi Y, Kikuchi M, Masuda R, Goto K, Iijima T. The amount of fluid given during surgery that leaks into the interstitium correlates with infused fluid volume and varies widely between patients: *Anesth Analg*. 2016;123(4):925–932. https://doi.org/10.1213/ANE.0000000000001505
66. Chappell D, Jacob M, Hofmann-Kiefer K, Conzen P, Rehm M. A rational approach to perioperative fluid management. *Anesthesiology*. 2008;109(4):723–740. https://doi.org/10.1097/ALN.0b013e3181863117
67. Chappell D, Bruegger D, Potzel J, et al. Hypervolemia increases release of atrial natriuretic peptide and shedding of the endothelial glycocalyx. *Crit Care*. 2014;18(5):538. https://doi.org/10.1186/s13054-014-0538-5
68. Zitek T, Skaggs ZD, Rahbar A, Patel J, Khan M. Does intravenous lactated Ringer's solution raise serum lactate? *J Emerg Med*. 2018;55(3):313–318. https://doi.org/10.1016/j.jemermed.2018.05.031

How to cite this article: Morkane CM, Sapisochin G, Mukhtar AM, et al., Perioperative fluid management and outcomes in adult deceased donor liver transplantation – A systematic review of the literature and expert panel recommendations. *Clin Transplant* 2022;36:e14651. https://doi.org/10.1111/ctr.14651