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HANDBOOK

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Foreword

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Human albumin is widely used in critically ill patients, including for the correction of hypoproteinaemia and fluid resuscitation of septic shock.

In patients with hypovolaemic shock, human albumin has a higher fluid resuscitation efficiency than crystalloids, based on the assumption that crystalloid resuscitation will not be as effective because of its shorter intravascular half-life.

This latest handbook from *Hospital Pharmacy International* includes joint contributions and insight from Chinese and European thought leaders. It is intended to give a comparative picture of the judicious use of albumin across these territories and across several therapy areas, including discussions around its pharmacoeconomics.

Contributors to the handbook examine indications of albumin use. In the ICU, for example, they discuss issues around timing and course of treatment for critically ill patients, and how albumin may have a role beyond volume replacement, particularly in conditions such as acute respiratory distress syndrome and severe burns, where fluid management is crucial. Evidence for early use of albumin in addition to crystalloid is also reviewed.

The value of long-term albumin therapy is considered in relation to cirrhosis: and the concept of how effective albumin is a good indicator of the severity of liver cirrhosis or complications and improves the evaluation of patient prognosis or the treatment effects is introduced. Serum effective albumin concentration as a better indicator for short- and long-term human albumin treatment than total serum albumin level is further discussed.

There are differences in guidance for albumin prescribing between China and the EU, some of which are explored in the handbook. For example, a Chinese expert consensus supports the use of albumin in cardiac surgery for volume replacement, pump priming and correction of hypoalbuminaemia.

These recommendations, however, differ from some recent guidelines. The 2024 Transfusion Medicine Guidelines, for example, adopt a more restrictive approach, cautioning against the inappropriate use of albumin based on a lack of clear, evidence-based criteria, as well as concerns about cost and ethics.

Differences also exist in guidelines developed by generalist groups and specialist groups in hepatology. Generalist guidelines, which tend to be more conservative, focus on standardised protocols to ensure broad and consistent application. Meanwhile, specialist guidelines emphasise the importance of clinical judgment and individualised treatment plans, advocating for using albumin in a broader spectrum of conditions where it may provide therapeutic benefits.

These differences highlight the ongoing debate about whether to take an application and cost strategies or a more nuanced, individualised strategy.

The importance of individualised therapy is a key issue discussed in the section on the use of albumin to manage hypoalbuminaemia during the peri-operative period in gastrointestinal surgeries. Albumin therapy can benefit these high-risk patients, especially when initiated early and tailored to an individual's needs.

It must be acknowledged that no guidelines are entirely devoid of bias, be it in terms of cost-effectiveness, ethical considerations or clinical outcomes. In practice, there are many occasions where clinical situations demand intervention even though clear evidence to support that intervention may be lacking: consensus recommendations can provide valuable guidance to support clinicians in navigating these grey areas.

It is essential to recognise the rationale behind varying recommendations and how best to integrate these to optimise patient care

Therefore, while clinical judgment could guide the use of albumin to avoid over-reliance and potential adverse effects, consensus guidelines remain an important supplement in informing and refining clinical practice.

Understanding these issues and differences is crucial to enabling the effective translation of European guidelines for clinical practice in China. It is essential to recognise the rationale behind the varying recommendations and consider how best to integrate these perspectives to optimise patient care.

This handbook aims to present a balanced view that can serve as a comprehensive resource to support informed decision-making in the use of albumin across therapy areas. We hope you enjoy reading it and find it educational, informative and enlightening.

Thank you for reading.

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ICU: use of albumin in fluid replacement

This article explores the ongoing debate regarding the utility of serum albumin levels as a marker to guide albumin therapy, examining both the evidence and the uncertainties surrounding this practice. It provides a comprehensive analysis of albumin's use in fluid resuscitation and its benefits and limitations, and underscores the importance of devising tailored strategies for fluid management in the intensive care unit

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Fluid management is a crucial aspect of therapeutic intervention in the critical care setting, particularly for patients experiencing haemodynamic instability and various forms of shock. Among the different types of shock, septic shock is one of the most challenging to manage due to its complex pathophysiology, which involves profound vasodilation, capillary leak, and significant fluid loss from the intravascular space.[1] These changes result in a critical need for volume replacement to restore adequate tissue perfusion and prevent organ failure.

Traditionally, crystalloids have been the first line of therapy for fluid resuscitation in critically ill patients. However, crystalloids alone may not always be sufficient to achieve the desired haemodynamic stability, particularly in cases of severe sepsis or septic shock where vascular permeability is increased and the risk of fluid overload is significant.[2] In this context, albumin, a natural colloid derived from human plasma, has been increasingly recognised for its potential advantages in fluid resuscitation.

The appeal of albumin lies in its colloid osmotic properties (albumin maintains 70%–80% of the effective colloid osmotic pressure in plasma and helps to preserve the integrity of the vascular endothelium), which enable it to exert a more sustained volume-expanding effect than crystalloids. By retaining fluid within the intravascular compartment, albumin can help maintain adequate blood pressure and reduce the overall fluid volume needed, which may be particularly beneficial in preventing the harmful effects of fluid overload, such as oedema and impaired organ function.[3] Moreover, albumin has additional physiological roles, including acting as a carrier for various endogenous and exogenous substances, exerting anti-inflammatory effects, and scavenging free radicals, all of which may contribute to its therapeutic potential in critically ill patients.

Resuscitation refers to the initial phase of fluid therapy aimed at rapidly restoring haemodynamic stability, whereas the optimisation phase is based on the fine-tuning of fluid management under strict haemodynamic monitoring to maintain stability while minimising the risks of both under-resuscitation and fluid overload.[4]

How have the recommendations been informed?

Current clinical guidelines and recommendations for fluid management in the Intensive Care Unit (ICU), which have been informed by systematic reviews and meta-analyses conducted by organisations such as the Cochrane Collaboration, will be evaluated. However, it is crucial to acknowledge that these guidelines, while useful, may not always fully account for the intricate nature of individual patient circumstances in critical care. Thus, here we stress the significance of tailored fluid management strategies, which combine evidence-based practices and clinical monitoring, to improve patient outcomes in the ICU.

Early initiation of albumin in addition to crystalloid therapy

Rationale for early albumin use

The utilisation of albumin in conjunction with crystalloids at the onset of septic shock resuscitation has been reinforced by studies demonstrating advantages in terms of haemodynamic and fluid balance.[5] The superior colloid osmotic effect of albumin allows for more efficient plasma expansion as each gram of albumin can retain 18 mL of circulating water, and the infusion of 10 g albumin can expand the volume by nearly 200 mL. Human serum albumin can also protect the function of the vascular endothelium by maintaining the integrity of the glycocalyx layer on the endothelial cells,[6] which is particularly beneficial in conditions such as septic shock where vascular permeability is often impaired.

Evidence from clinical trials

The ALBIOS trial is a significant study that sheds light on the advantages of incorporating albumin into crystalloids during resuscitation.[7] In this study, patients with severe sepsis or septic shock were given albumin with the aim of maintaining a serum albumin level of 30 g/L or more. The results demonstrated that while albumin administration was correlated with improved haemodynamic parameters, such as a higher mean arterial pressure and a more favourable fluid balance, it did not show a substantial reduction in 28-day or 90-day mortality in the overall population of the study. However, subgroup analysis of patients with septic shock found a decrease in mortality rate in the human serum albumin group (relative risk 0.87, 95% CI 0.77–0.99).[7]

A systematic review comparing the roles of human serum albumin solution and crystalloid solution in sepsis fluid resuscitation, including the EARSS study (Early Albumin Resuscitation during Septic Shock)[8] and the RASP study (Lactated Ringer Versus Albumin in Early Sepsis Therapy study)[9] was conducted based on the ALBIOS study and two other randomised controlled trials (RCTs). The results showed

that in sepsis patients, human serum albumin solution resuscitation was not superior to crystalloid solution resuscitation, but in severe sepsis and septic shock patients, human serum albumin solution resuscitation reduced patient mortality compared to crystalloid solution resuscitation. An observational study involving 6,188 adult patients who underwent extracorporeal circulation cardiac surgery for valvular and/or coronary artery disease, recorded in the Cerner HealthFacts® database, showed that the use of albumin solutions on the day of or the day after cardiac surgery significantly reduced in-hospital mortality and the 30-day all-cause readmission rate compared to the use of crystalloid solutions alone.[10]

These findings highlight the possible utility of albumin in specific subsets of critically ill patients, particularly those with septic shock who do not adequately respond to crystalloids alone. In such cases, albumin may help decrease the need for vasopressors and improve overall fluid management, which could lead to better outcomes.[5]

Clinical implications and individualisation of therapy

The central message from the ALBIOS trial and other studies is the importance of individualised resuscitation strategies. While early albumin use may offer benefits in septic shock, the evidence does not support its broader application across all critically ill patients. Clinicians should carefully consider the individual patient's condition, including factors such as baseline serum albumin levels, fluid responsiveness and liquid tolerance, and the risk of fluid overload when deciding to use albumin.[11]

Moreover, small-volume resuscitation becomes increasingly relevant in ICU settings where cumulative positive fluid balance is a concern.[12] Albumin's ability to achieve desired haemodynamic effects with less overall fluid volume may be particularly beneficial in patients who require ongoing fluid administration for non-resuscitation purposes, such as medication delivery or maintenance fluids.[13]

Clarifying serum albumin level as a non-indicator of haemodynamic stability

Misconceptions in clinical practice

A misconception in clinical practice is that serum albumin levels directly correlate with haemodynamic stability. This assumption has led some clinicians to discontinue albumin therapy once serum albumin levels exceed 30 g/L, under the belief that the patient's haemodynamic status has been adequately restored. However, this approach is not supported by current evidence or expert consensus.

Insights from Chinese guidelines

The Chinese guidelines on using albumin in critically ill patients provide a nuanced view of this issue. They recommend that albumin infusion may be discontinued when serum albumin levels reach 30 g/L, but only if the patient's haemodynamics are stable.[14] This recommendation is classified as a weak recommendation, reflecting the uncertainty and need for individualised clinical judgment. The guidelines emphasise that while serum albumin levels are an important parameter, they should not be the sole determinant in decision-making. Instead, clinicians should consider a broader range of clinical indicators that reflect the stability of haemodynamics, including blood pressure, urine output, and lactate levels, when assessing haemodynamic stability and deciding whether to continue or discontinue albumin therapy.

The use of serum albumin levels as a surrogate for haemodynamic stability is an oversimplification of a complex clinical situation. While serum albumin levels provide useful information and are correlated with haemodynamic stability, they should be considered as part of a broader clinical picture.[15] The ALBIOS trial demonstrated that targeting a specific serum albumin level could improve haemodynamics and fluid balance, but it did not establish a clear threshold at which albumin therapy should be discontinued.[7] This suggests that serum albumin levels should be used as one of several factors in guiding fluid management, rather than as a definitive indicator of when to stop albumin therapy.

Clinical decisions should instead be based on a comprehensive assessment of the patient's condition, including haemodynamic parameters like blood pressure, urine output and lactate levels. Serum albumin may play a role in individualised albumin administration, particularly in guiding adjustments to therapy rather than determining its cessation. The Chinese guidelines highlight the importance of individualised patient care and caution against relying solely on serum albumin levels for making critical therapeutic decisions.[14]

Clinical recommendations

Given the current evidence, clinicians should avoid using serum albumin levels as the sole criterion for initiating or discontinuing albumin therapy. Instead, a holistic approach should be taken, considering the patient's overall clinical →

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status and ongoing haemodynamic needs. The role of albumin in the ICU should be individualised, with serum albumin levels providing supplementary information rather than serving as a primary decision-making tool.

Albumin in the spectrum of fluid management

Evidence and current guidelines

The use of albumin across the entire spectrum of fluid management, including resuscitation, optimisation, stabilisation and deresuscitation, is not universally supported by high-quality evidence. The Cochrane systematic reviews and recent meta-analyses have generally found no significant survival benefit of albumin over crystalloids in most critically ill patients. Consequently, guideline recommendations, such as those from the International Collaboration for Transfusion Medicine Guidelines[16] and the European Society of Intensive Care Medicine,[17] advise against using albumin as a first-line resuscitation fluid.

These guidelines reflect the limitations of current evidence, which often does not capture the complexities of real-world ICU practice. They are primarily based on RCTs, which may not adequately address the diverse and individualised needs of critically ill patients.[18] Despite the lack of strong evidence, albumin remains a valuable tool in certain clinical scenarios, particularly where its volume-expanding properties can offer advantages over crystalloids.

The role of expert opinion and individualised care

Guideline recommendations, while important, are not without bias.[19] In medical fields characterised by complex and rapidly changing scenarios, such as critical care, the reliance on evidence-based medicine alone may be insufficient. Expert opinions from scientifically informed intensivists play a crucial role in guiding the individualisation of fluid management. These experts often advocate for using albumin in specific cases where they believe the benefits outweigh the potential risks, despite the absence of robust RCT evidence.[14]

For example, in patients with septic shock who remain hypotensive despite adequate crystalloid administration, the addition of albumin may be justified based on clinical experience and the observed haemodynamic benefits in trials. Given that human serum albumin can also bind to the glycoprotein complexes on the surface of the vascular endothelium, protecting the function of the vascular endothelium, it is also an appropriate time to actively use albumin for resuscitation in cases of septic shock with significant manifestations of capillary leakage.[5,7,20] This personalised approach, informed by evidence and expert judgment, is essential in managing the complex fluid needs of ICU patients.[21]

Balancing benefits and risks

The decision to use albumin should be carefully weighed, considering the potential benefits and risks. In the resuscitation phase, albumin may be particularly useful in achieving rapid intravascular volume expansion with less total fluid, potentially reducing the risk of fluid overload. During the stabilisation and deresuscitation phases, however, the focus should shift to maintaining a delicate balance, avoiding excessive fluid administration while ensuring adequate tissue perfusion.[22] The use of albumin in these later phases should be guided by ongoing reassessment of the patient's fluid status and haemodynamic response, with the understanding that serum albumin levels alone should not dictate therapy adjustments.

Conclusion

The issue of using albumin for volume replacement in critically ill patients in the ICU is a complex one that requires careful evaluation of both the available evidence and the individual patient's needs. While early administration of albumin in septic shock may provide benefits in terms of haemodynamics, its use across all phases of fluid management should be guided by carefully considering the potential benefits and risks. Serum albumin levels, while useful, should not be the sole factor in deciding whether to use albumin therapy.

Current evidence-based medicine often discourages the general use of albumin due to a lack of consistent evidence across diverse patient populations. However, these guidelines also emphasise the need for more focused clinical trials to understand better the role of albumin administration in specific clinical contexts. Ultimately, an individualised care approach, informed by clinical expertise and supported by the evidence, remains essential for optimising outcomes in fluid management in the ICU.

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ICU: use of albumin besides volume replacement

This article explores the evolving role of albumin in the ICU, focusing on its use in conditions where its benefits may be derived from mechanisms other than volume replacement

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Albumin, a multifaceted protein with a range of physiological roles,[1] has been traditionally employed in critical care primarily for volume replacement in patients experiencing hypovolaemia. However, the therapeutic applications of albumin extend beyond mere volume expansion.[2]

Albumin in the management of hypoalbuminaemia

Pathophysiological significance

Hypoalbuminaemia, defined as serum albumin levels < 35 g/L, is a frequent finding in critically ill patients, often associated with poor outcomes, including increased morbidity and mortality.[3] Albumin is crucial in maintaining oncotic pressure, modulating inflammation, and providing antioxidant protection.[1] In the intensive care unit (ICU), hypoalbuminaemia is often exacerbated by conditions such as sepsis, surgery and acute respiratory distress syndrome (ARDS), where capillary leak and fluid shifts lead to a further decline in albumin levels.[4]

Therapeutic use of albumin

The Chinese guidelines emphasise the importance of maintaining serum albumin levels above 30 g/L during major surgery, particularly in patients with preexisting hypoalbuminaemia.[5] They note that correcting hypoalbuminaemia is crucial for preventing severe drops in albumin levels, which can fall < 25 g/L in nearly 10% of ICU patients.[6] Such severe hypoalbuminaemia is associated with an increased risk of complications, including acute kidney injury (AKI),[7] necessitating proactive albumin supplementation to improve patient outcomes. Thus, in critically ill patients, particularly those undergoing major surgery or experiencing severe inflammatory states, the correction of hypoalbuminaemia with albumin administration is recommended to mitigate associated risks.

In cardiac surgery, a randomised controlled trial (RCT) demonstrated that preoperative correction of hypoalbuminaemia with albumin significantly reduced the incidence of AKI and improved postoperative renal function.[8] This underscores the importance of addressing hypoalbuminaemia in surgical patients to reduce the risk of postoperative complications, particularly in those with cardiac conditions.

Similarly, in patients with sepsis, where the risk of AKI is heightened due to systemic inflammation and capillary leak, the correction of hypoalbuminaemia is recommended to stabilise intravascular volume and support renal function.[9] Maintaining normal serum albumin levels can decrease the incidence of AKI and enhance outcomes in septic patients, according to consensus guidelines.

Albumin administration improves oxygenation parameters in acute respiratory distress syndrome (ARDS) patients with hypoproteinaemia, underscoring its role in enhancing pulmonary function and reducing pulmonary oedema.[10] This benefit is particularly important in ARDS, where fluid management is critical to avoid exacerbating respiratory failure.

The role of hypoalbuminaemia in individualised therapeutic decisions

The narrative surrounding hypoalbuminaemia has evolved, particularly in light of discussions highlighted in the article by Joannidis et al,[11] which argues that albumin substitution to correct hypoalbuminaemia from all causes does not reduce mortality. In the ICU, where acute illness and significant capillary leak coexist, hypoalbuminaemia is crucial in personalising treatment. Although RCTs show mixed results on the universal benefit of albumin administration, severe hypoalbuminaemia in critically ill patients necessitates thoughtful consideration of albumin therapy.[3]

The Chinese guidelines reflect this approach, recommending the correction of severe hypoalbuminaemia to prevent complications such as AKI in high-risk patients.[5] Clinical evidence supports albumin's role in stabilising patients with severe hypoalbuminaemia, especially when combined with acute illness or major surgery stress.

Use of albumin in AKI

The use of albumin in AKI is controversial. Firstly, albumin should be used with caution in AKI, but hypoalbuminaemia is detrimental to the prevention and treatment of AKI.

Hypoalbuminaemia as a risk factor

Hypoalbuminaemia has been identified as a significant risk factor for the development of AKI,[7,12] particularly in septic patients.[13] The pathophysiological mechanisms include loss of oncotic pressure, exacerbating fluid shifts and causing renal hypoperfusion, and decreased binding capacity for substances, potentially increasing nephrotoxicity.[14]

The consensus document on sepsis-associated AKI highlights the importance of managing hypoalbuminaemia as part of →

the therapeutic strategy to prevent and treat AKI.[9] Albumin's ability to maintain intravascular volume and modulate inflammatory responses is beneficial in preserving renal function during critical illness.

Prevention and management of AKI

In RCTs, the use of albumin (including hyperoncotic solutions) has not been shown to be harmful to kidney or other outcomes.[15] However, clear evidence of benefit is also lacking, and any benefits might be limited to specific patient populations.

Administering albumin in AKI, especially in septic or hypoalbuminaemic patients, offers protective benefits. By maintaining oncotic pressure and enhancing renal perfusion, albumin reduces the risk of additional kidney damage. The consensus document recommends albumin as a component of a comprehensive fluid management strategy to prevent AKI onset and aid renal recovery in affected patients.[9]

In individuals experiencing acute-on-chronic liver failure and AKI, initiating volume expansion with albumin at the initial stage of AKI is recommended to prevent progression and enhance outcomes, especially in those at risk of developing shock.[16] Albumin concentrations of 4%–5% are recommended for fluid resuscitation in shock cases, while 20%–25% concentrations are preferred for stable patients without shock. Individualised dosing based on dynamic monitoring, cardiopulmonary assessment and fluid responsiveness is crucial to prevent complications such as fluid overload.[16]

Clinical trials and observational studies suggest that albumin supplementation, particularly in hypoalbuminaemic patients, may lower AKI incidence and enhance renal outcomes. Consensus documents recommend considering albumin in AKI management, tailored to each patient's condition, including fluid balance, haemodynamic stability and comorbidities.[17]

Albumin and kidney replacement therapy

The recent guidelines from the Transfusion Medicine Collaboration group caution against the routine use of hyperoncotic albumin for intradialytic hypotension (IDH) during kidney replacement therapy (KRT), primarily due to its high cost and its preferential effect on haemodynamic endpoints without showing significant additional benefits in long-term outcomes.[18] This recommendation primarily pertains to chronic kidney disease patients receiving thrice-weekly dialysis, where albumin's cost-effectiveness is crucial. Nonetheless, this reasoning may not be entirely applicable to ICU patients in critical condition, where the immediate clinical benefits of stabilising haemodynamics during KRT might surpass concerns about cost and the relatively weak evidence base.

In studies assessing hyperoncotic albumin, consistent haemodynamic improvements were observed. For instance, in a randomised crossover trial involving 65 inpatients undergoing haemodialysis for AKI or maintenance, pretreatment with 25% albumin resulted in significantly fewer episodes of IDH compared to normal saline.[19] Similarly, another study in septic patients with anuric AKI showed that priming the haemodialysis circuit with 17.5% albumin not only limited IDH but also facilitated greater ultrafiltration.[20] Furthermore, the SAFER-SLED study, a double-blind, placebo-controlled randomised trial, reported that ICU patients with AKI who received hyperoncotic albumin experienced less haemodynamic instability during sustained low-efficiency dialysis (SLED) than those who received saline, although the study highlighted the need for more research to confirm these findings.[21]

The guideline's cautious approach balances cost concerns and the limited evidence for routine hyperoncotic albumin use in the broader dialysis population. Nonetheless, in the ICU's critical care setting, where unique challenges and potential immediate benefits exist, a more liberal, patient-specific application of hyperoncotic albumin may be justified.[11]

Use of albumin in ARDS

ARDS presents significant challenges in fluid management due to increased pulmonary permeability and the risk of pulmonary oedema.[22] This condition requires careful fluid balance, as positive fluid balance has been linked to prolonged mechanical ventilation, extended ICU stays, and higher mortality rates.[23]

Hypoalbuminaemia, a common feature in critically ill patients, further exacerbates these issues by reducing oncotic pressure, promoting fluid shifts into the interstitial and alveolar spaces.[24] Intravenous albumin, particularly in combination with diuretics like furosemide, has been explored to address these challenges. Notably studies, including those by Martin et al,[25,26] demonstrate that this combination can enhance oxygenation, improve net negative fluid balance, and maintain haemodynamic stability in hypoalbuminaemic patients with ARDS. These benefits are achieved by restoring oncotic pressure, thereby reducing pulmonary oedema and facilitating fluid mobilisation. However, these interventions have not consistently demonstrated a survival benefit, limiting their routine application.[27]

Optimal fluid management in ARDS is highly dependent on the phase of the disease and patient-specific characteristics.[28] Early in ARDS, fluid resuscitation may be necessary to maintain organ perfusion, especially in the presence of septic shock.[29] As the patient stabilises, a restrictive fluid strategy, including deresuscitation measures like diuretics and albumin, may be employed to mitigate fluid overload. This strategy has been shown to increase ventilator-free days and reduce ICU stays without significantly impacting mortality.[29,30]

The heterogeneity of ARDS phenotypes underscores the need for individualised treatment approaches. For instance, hyperinflammatory and hypoinflammatory phenotypes respond differently to fluid management strategies.[31] Emerging evidence suggests that targeted therapies, guided by biomarkers and clinical profiles, may optimise outcomes. Albumin's anti-inflammatory actions, such as its ability to scavenge free radicals and modulate immune responses, may influence relevant pathomechanisms in hypoalbuminaemia; however, its role in this context remains unexplored.[32]

While the role of albumin in ARDS remains adjunctive,[33] its use should be considered in patients with significant hypoalbuminemia or fluid overload unresponsive to standard management. Careful monitoring of fluid responsiveness and pulmonary status is essential to balance the risks and benefits of albumin therapy.[30] Future research should focus on refining ARDS sub-phenotyping and exploring personalised fluid management strategies to enhance patient outcomes.

Albumin use in burns

Beyond volume expansion

Albumin is crucial in treating patients with burns exceeding 20% of the total body surface area (TBSA), beyond just volume expansion. The latest American Burn Association (ABA) Clinical Practice Guidelines highlight albumin's role in addressing burn shock, characterised by severe intravascular volume loss, increased microvascular permeability and tissue oedema.[34] These guidelines advocate for albumin use, especially in extensive burns, not only to boost intravascular volume but

also to lower overall resuscitation fluid needs and enhance urine output during acute resuscitation. Mortality was excluded as an endpoint because the studies primarily aimed to assess immediate haemodynamic benefits and fluid management outcomes of albumin use rather than long-term survival, which necessitates larger and longer trials for accurate evaluation.

Clinical evidence and recommendations

The ABA guidelines underscore that albumin should be considered in burn resuscitation to lower the amount of crystalloids needed, which helps in preventing 'fluid creep' – a phenomenon where excessive fluid administration leads to complications such as pulmonary oedema and compartment syndrome. The guidelines suggest that albumin's introduction should be timely, preferably within the first 24 hours post-injury, to optimise its benefits.[34]

Infectious diseases

Modulating inflammation and infection

Albumin's functions include fluid regulation, inflammation modulation and infection control. Hypoalbuminaemia is frequently linked to increased inflammation, complicating infectious disease progression. By modulating inflammation and transporting various drugs, including antibiotics, albumin plays a role in managing infections in critically ill patients.[35]

Impact on antibiotic pharmacokinetics and pharmacodynamics

Antibiotics with high protein-binding properties exhibit increased free levels in the presence of hypoalbuminaemia, leading to enhanced target site penetration but also increased renal clearance, which can negatively impact the continuity of effective drug levels.[36] This disruption in drug continuity has been shown to impair clinical outcomes.[37] Through therapeutic drug monitoring and appropriate dose adjustments, antibiotic therapy can be optimised to maintain therapeutic levels.[38] In addition, correcting hypoalbuminaemia with albumin supplementation may improve antibiotic pharmacokinetics,[39] although there are no outcome studies that confirm the effectiveness of this approach conclusively.[35]

Therefore, the use of albumin to enhance antibiotic therapy remains an option within individualised patient management in the ICU, tailored to the specific needs and conditions of critically ill patients.

Conclusion

The utilisation of albumin in ICU settings transcends its traditional function of volume replacement, as it presents therapeutic advantages across a wide array of conditions. The diverse properties of albumin make it a valuable resource in managing the intricate requirements of critically ill patients. Nevertheless, its administration must be individualised, considering each patient's specific circumstances, by weighing the benefits against potential risks and cost considerations.

In conclusion, the prudent use of albumin, tailored to the distinct challenges of ICU patients, has the capacity to improve outcomes in this high-risk population.

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Serum effective albumin concentration in liver cirrhosis: relevance in clinical practice

Current knowledge suggests that effective albumin is a good indicator of the severity of liver cirrhosis or ongoing complications and improves the evaluation of patient prognosis or the monitoring of short- and long-term treatment effects

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From 4.0 to 5 g/dL of albumin circulates in the blood of healthy humans, making albumin the most abundant serum protein. Human albumin (HA) is a pleiotropic molecule possessing several functions.

Structure and functions

Its relatively elevated molecular weight accounts for the plasma oncotic pressure of 70%–75%. Its net negative charges contribute to this property as they activate the Gibbs-Donnan effect, attracting and binding cations and water that move from the interstitial to the intravascular compartment. As a result, HA is the principal regulator of body fluid distribution. If its prolonged circulating half-life is taken into account, it is unsurprising that HA is an effective plasma expander employed in many clinical contexts, including liver cirrhosis.[1,2]

The HA molecule contains 35 cysteine residues that ensure the stability of its spatial conformation through internal disulfide bonds, except for cysteine in position 34, which remains free. Its structure contains three homologous domains (sites I, II, and III), each comprising two separate sub-domains (A and B). These domains and the free cysteine in position 34 exert several non-oncotic functions, some well-defined while others are being unveiled by current research activity.[1,2]

Thanks to the free cysteine in position 34 and its sulphydryl group, albumin is the human body's most abundant circulating anti-oxidative system. Indeed, it counteracts oxidative stress in physiological and pathological conditions by efficiently scavenging reactive oxygen and nitrogen species. The resultant effects of this process consist of reversible and irreversible disulfide bonds with sulfhydryl compounds so that, in healthy individuals, the reduced form (mercaptalbumin) accounts for 70%–80% of circulating albumin, about 20% present reversible disulfide bonds (non-mercaptalbumin 1; HNA1), and the remaining amount is oxidated irreversibly to sulfinic or sulfonic acid (non-mercaptalbumin 2; HNA2).

In disease states, including decompensated cirrhosis and acute-on-chronic liver failure (ACLF), the amounts of HNA1 and HNA2 can increase substantially.[3]

Another relevant HA function is binding, transport, and solubilisation, which is achieved thanks to several binding sites with different affinities for many compounds.[1,2] As a result, albumin can bind and transport several exogenous and endogenous hydrophobic molecules, including many drugs, fatty acids, cholesterol, bilirubin, bile salts, thyroxine and other hormones, prostaglandins, nitric oxide (NO), lipopolysaccharide and other pathogen-associated molecular patterns (PAMPs), and damage-associated molecular patterns (DAMPs) deriving from the diseased liver. Binding and transport ultimately influence the metabolism of these substances and subtract molecules circulating as free components from inappropriate interactions.

Immunomodulation is another relevant non-oncotic property of HA exerted through the interaction of several mechanisms that are not entirely well-defined. Some consist of indirect actions, such as binding and transport, which subtract molecules capable of activating immune cells, such as PAMPs and DAMPs, from interaction with pattern recognition receptors. Others are more direct, such as albumin internalisation into leukocytes, where albumin can block cytokines synthesis by interaction with toll-like receptors.[4]

The evidence of the favourable impact of HA on the systemic activation of immune cells derives from a study showing that the normalisation of serum albumin concentration following the administration of 1.5 g HA to patients with decompensated cirrhosis for 12 weeks reduced circulating markers of inflammation, such as interleukin-6, interleukin-1 receptor antagonist, granulocyte colony-stimulating factor, and vascular endothelial growth factor.[5]

Other HA non-oncotic properties include: prevention or attenuation of the tissue damage induced by inflammation and oxidative stress; endothelial stabilisation; platelet aggregation inhibition; and influence on acid–base balance.[1,2] Finally, by tempering immune system activation, albumin could help rebalance the body's nutrient distribution to non-immune cells.[6]

Abnormalities of serum albumin in liver cirrhosis

Hypoalbuminaemia is a long-recognised feature in decompensated cirrhosis and is associated with a poor prognosis. The principal cause of this abnormality is the reduced synthesis by liver cells, while haemodilution due to renal retention of sodium and water and endothelial permeabilisation enhancing the albumin transcapillary escape also play a role.

Besides reduced concentration, serum albumin undergoes post-transcriptional molecular changes that impair one or more non-oncotic functions. As opposed to oncotic properties, which depend on highly conserved features such as high molecular weight and negative net charge, non-oncotic properties need the integrity of the molecular structure. Even

though the causes and mechanisms leading to serum albumin molecular damage are not fully clarified, the systemic inflammatory and pro-oxidant milieu of decompensated cirrhosis likely represents the prevalent injury.

Oxidation of the Cys 34 residue is the most frequently reported molecular abnormality.[7] The result is the increase of HNA1 and HNA2 along with the severity of cirrhosis culminating in ACLF.[3] The consequences of these abnormalities are relevant, as they impair albumin antioxidant and binding properties with endogenous and exogenous ligands. Furthermore, oxidised albumin fosters inflammation by activating leukocytes or peripheral blood mononuclear cells.[8]

The alteration of the N-terminal amino acid sequence of albumin (ischaemia-modified albumin; IMA) represents another abnormality described in many disease states, including cirrhosis. This molecular damage impairs the albumin binding capacity for highly reactive metal species. In alcoholic cirrhosis, the IMA to albumin ratio is increased and associated with patient mortality. Moreover, albumin transport and detoxification capacities are impaired.[9]

There are many other circulating altered isoforms of albumin. These can be assayed by matrix-assisted laser desorption/ionisation techniques with time of flight (MALDITOF) combined with HPLC.[10] These abnormalities include cysteinylation, C- and N-terminal truncation, glycosylation, sulfidation, sulfonylation, nitrosylation and dimerisation, alone or in combination.

The quantitative and qualitative abnormalities of albumin described have relevant clinical consequences in patients with cirrhosis, as they occur in a context of systemic inflammation and pro-oxidation that would require fully efficient function of albumin. Unfortunately, the laboratory methods routinely employed to assess serum albumin concentration in clinical practice do not provide any information on the albumin functional status. Instead, the knowledge of the amount of structurally and functionally intact albumin may provide invaluable information for patient management.

Relevance of albumin non-oncotic properties in clinical practice

The efficacy of HA as a plasma expander is undisputed. Whether, and how, HA administration acts via its non-oncotic functions remains undefined. However, evidence that these functions may play a relevant role has emerged over time. HA administration, but not hydroxyethyl starch, improved peripheral vascular resistance and stroke index in patients with cirrhosis and spontaneous bacterial peritonitis.[11]

The concomitant reduction of circulating factor VIII and Von Willebrand-related antigen suggest the attenuation of endothelial activation. HA administration, but not hydroxyethyl starch or saline, improved impaired cardiac contractility in rats with cirrhosis induced by carbon tetrachloride. This effect was associated with reductions in tumour necrosis factor-alpha and oxidative stress markers in the cardiac tissue.[12]

HA is widely employed as a toxin absorbent in extracorporeal liver assist devices such as MARS, Prometheus, SPAD, and DIALIVE. In patients with acute decompensation of cirrhosis, where increased circulating free prostaglandin E2 (PGE2) endangers macrophage function, albumin administration improves immune competence by binding PGE2.[13]

Long-term HA therapy in patients with cirrhosis and ascites reduces the incidence of complications and improves survival.[14] Because the amount of albumin administered was relatively low (40 g weekly), these effects may be ascribable, at least in part, to albumin's non-oncotic properties.

In most critically ill patients, albumin concentration should be at least 30 g/L. If possible, albumin concentration should be maintained above 35 g/L, the minimum physiological level. Studies show that a target albumin threshold of 40 g/L is beneficial for the long-term treatment of liver disease patients.[15]

For patients with decompensated cirrhosis, a high level of serum albumin during treatment may be an important indicator for predicting recompensation. In order to explore the target level of serum albumin associated with recompensation outcomes, a study enrolled patients with hepatitis B cirrhosis who first experienced ascites as a decompensation event and gave them 120 weeks of entecavir treatment.[16] Liver function and virological indicators were monitored every 12 weeks, and blood routine and renal function were checked every 24 weeks. Among the 320 patients included, 283 completed 120 weeks of entecavir treatment and follow-up, of which 56.2% achieved recompensation at week 120. Patients were divided into two groups according to whether recompensation was achieved →

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at week 120. Multivariate logistic regression analysis was used to determine the optimal prediction time, and a prediction model was established.

The result shows that patients with albumin levels reaching 34 g/L at 24 weeks have a significantly higher chance of recompensation after 120 weeks compared to those with albumin levels below 34 g/L.[16]

Restoring circulating intact albumin may, therefore, represent a target to be achieved in advanced cirrhosis.

Effective albumin as a novel target in the treatment of decompensated cirrhosis

Native, intact, and other terms have been used to describe HA without molecular abnormalities. Still, effective albumin, a definition underlying the molecule's functional integrity, has been almost universally used since 2013.[17]

Different methods, including MALDITOF combined with HPLC, determine the relative abundance of circulating effective albumin. Once this parameter is defined, the formula below defines effective albumin concentration:

Total serum albumin (g/dl or g/L) x relative abundance of effective (native albumin) (%) /100.

Few studies have assessed the amount of effective albumin in patients with liver cirrhosis. Baldassarre et al first provided information about the serum concentration of effective albumin in patients with cirrhosis at different stages of the disease, also assessing albumin binding and detoxification efficiency.[18]

In their study, the median serum effective albumin concentration in healthy subjects was 2.2 g/dL and decreaed to 2.0 g/dL in outpatients with compensated cirrhosis, 1.0 g/dL in patients hospitalised because of acute decompensation, and 0.8 g/dL in ACLF, ensuring a better patient stratification than total albumin concentration. Furthermore, serum effective albumin concentration was superior to total albumin in reflecting residual binding and detoxification activities of albumin and in predicting the 30-day development of ACLF and 90-day mortality in patients with acute decompensation.[18]

Administering 60 g 20% HA to patients with stable cirrhosis and ascites led to a modest but significant increase in effective albumin for up to a week. Still, the improvement in albumin binding and detoxification efficiency seen after HA infusion had waned by the end of the week.[18]

We should not disregard that effective albumin median levels (39%) were significantly lower than in healthy subjects (49%) and outpatients with decompensated cirrhosis (48%). This finding is consistent with several studies showing that commercial HA is far from being rich in effective albumin.[18] Indeed, there is evidence that commercial HA molecules present abnormalities, mostly cysteinylation at Cys 34 and N-terminal truncation.[19,20]

Having unveiled the potential clinical usefulness of determining the serum effective albumin concentration, an effort to improve the quality of commercial HA is therefore warranted.

Conclusion

Assessing the relative amount of albumin isoforms requires more complex techniques than the routine methods employed in clinical practice. However, high-throughput methods such as MALDITOF combined with HPLC provide results in a relatively short time at a contained cost. Thus, the assessment of serum effective concentration may enter clinical practice as a second-level evaluation in selected cases.

Based on current knowledge, the potential advantages of determining the effective status are numerous. Serum effective albumin concentration, alone or included in well-established prognostic tools, may better assess the severity of liver cirrhosis or ongoing complications and improve the evaluation of patient prognosis or the monitoring of treatment effects. Employing serum effective concentration to determine the degree of albumin dysfunction would be another relevant advancement, allowing efficient, personalised treatments.

Serum effective albumin concentration may become a far more meaningful target for HA short- and long-term treatments than serum albumin concentration. Indeed, the latter cannot provide any information about the molecule's functional state. For example, acute events such as bacterial infections may induce sudden drops in serum effective albumin concentration without significant changes in serum albumin concentration. HA administration may increase total serum albumin concentration in these conditions without correcting effective albumin levels.

Finally, because effective albumin is a good mirror for the status of albumin functions, effective albumin deficits may become a tool for adjusting the dosages of drugs whose pharmacokinetics and pharmacodynamics are affected by defects in albumin binding and detoxification activities.

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Value of long-term albumin therapy in decompensated liver cirrhosis

Long-term human albumin administration to patients with decompensated cirrhosis is a significant advancement in therapy. Even though many aspects of this treatment need refinement, there is convincing evidence that it can reduce the incidence of severe complications and improve patient survival

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Since its appearance on the battlefields of the Second World War, human albumin (HA) has been employed in several clinical contexts requiring blood volume expansion. HA has a high molecular weight, a negative net charge that attracts cations and water from the extravascular space, and a prolonged half-life. Furthermore, being the most abundant circulating protein, albumin plays a primary role in regulating body fluid distribution in the human body. All these aspects make HA an effective plasma expander.[1]

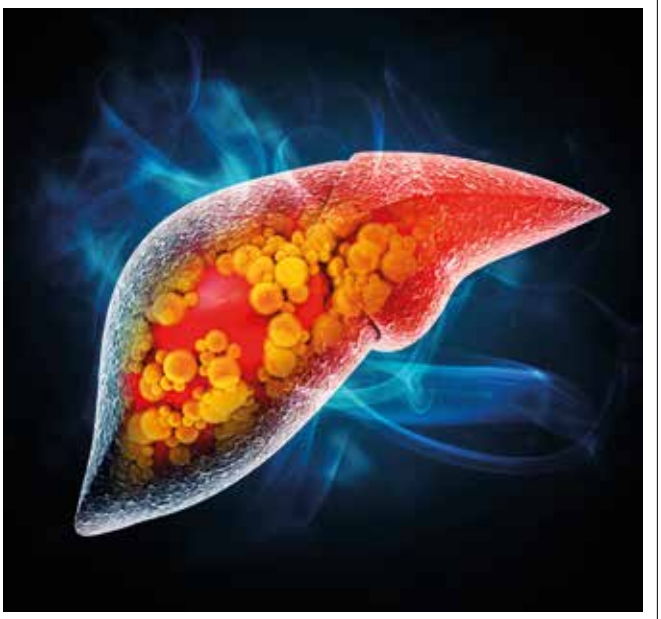
The use of HA in patients with cirrhosis dates back to the 1950s, mainly in an attempt to correct hypoalbuminaemia, but it received a substantial boost from the publication of the peripheral arterial vasodilation hypothesis.[2] (Figure 1). Since then, and for several decades, the pathophysiological background of decompensated cirrhosis was considered as the expression of peripheral arterial vasodilation mainly occurring in the splanchnic circulatory area and endangering effective volaemia. Thus, it is no wonder that many treatments to prevent or treat complications of cirrhosis, including HA infusion, aim at restoring effective hypovolaemia.

Indeed, the current, well-established indications for HA use in cirrhosis pertain to conditions characterised by an acute worsening of effective volaemia: prevention of paracentesis-induced circulatory dysfunction, prevention of renal dysfunction induced by spontaneous bacterial peritonitis (SBP), and diagnosis and treatment of hepatorenal syndrome combined with vasoconstrictors. These indications are supported by clinical practice guidelines worldwide[3–6] and confirmed by an international position statement[7] and a US expert review.[8]

Improved knowledge of the pathophysiology of decompensated cirrhosis

Over the last decade, the understanding of the pathophysiology of cirrhosis has improved.

The systemic spread of pathogen-associated molecular patterns (PAMPs) due to abnormal translocation from the gut and damage-associated molecular patterns (DAMPs) released by the diseased liver, after recognition by specific receptors, activates immune cells to produce pro-inflammatory cytokines and chemokines, along with reactive oxygen and nitrogen species. This cascade of events contributes to the development of splanchnic arterial vasodilation and circulatory dysfunction, and both favour multiorgan dysfunction and failure. (Figure 2).[9]



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Infections are highly prevalent among hospitalised patients with cirrhosis and with poor prognosis.

Among adults (aged >18 years) with cirrhosis who were non-electively admitted to 98 hospitals from 26 countries or regions across six continents, 31.9% had infection at the time of admission.[10] In addition, virus-related infections have gradually received attention.

Studies have found that 3.7% of patients with acute decompensated cirrhosis were infected with the B19 virus.[11] Metagenomic next-generation sequencing detected a high number of human cytomegalovirus infections in individuals with acute decompensation of cirrhosis, which may be correlated with adverse outcomes.[12]

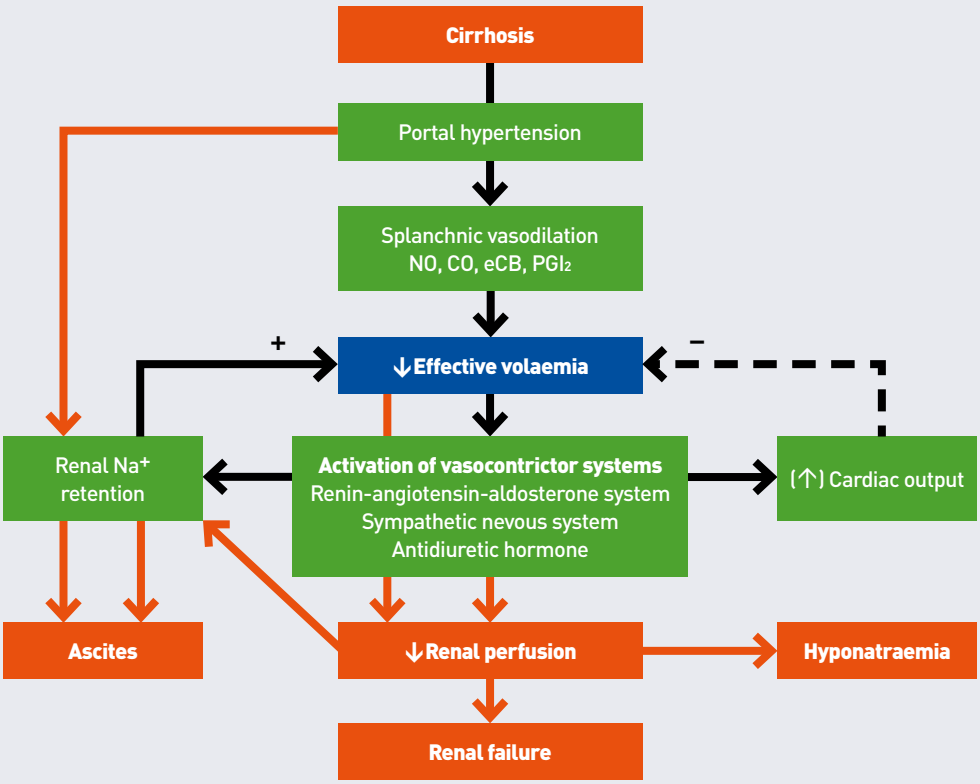
Properties of albumin

Besides its oncotic properties, albumin possesses functional domains with relevant properties, such as the free cysteine residue in position 34, which exerts potent antioxidant and scavenging activities, the amino-terminal, which binds and removes highly toxic reactive metal species, and other domains that bind and remove a variety of endogenous and exogenous substances, including PAMPs and DAMPs.

Moreover, albumin has immune-modulatory functions, →

FIGURE 1

Peripheral vasodilation hypothesis



NO: nitric oxide; **CO**: carbon monoxide; **eCB**: endogenous cannabinoids; **PGI_2**: prostaglandin I2.

Arterial vasodilation, mainly occurring in the splanchnic circulatory area, endangers effective volaemia. This evokes homeostatic compensatory responses promoting renal sodium retention and increased cardiac output. However, a price to be paid in the presence of portal hypertension is ascites formation. Moreover, despite these responses, effective hypovolaemia can persist. This is especially true in the advanced stages of cirrhosis, where cardiac dysfunction does not allow the cardiac output to increase sufficiently to cope with the needs of the systemic circulation. As a result, renal perfusion declines to renal failure. *Concepts from ref 2.*

protects capillary integrity, and influences acid–base balance and coagulation.[1] Considering this, besides promoting plasma volume expansion, HA could simultaneously act on several abnormalities by binding harmful molecules, modulating immune responses, exerting anti-oxidation, improving cardiac function, and restoring endothelial integrity. Therefore, albumin administration potentially represents an effective multi-target treatment.

Such an approach, which would require long-term HA administration, would represent a novel paradigm for treating decompensated cirrhosis, moving from measures addressing the prevention and therapy of specific complications of cirrhosis to a more comprehensive management profile. If successful, such an approach may exert a disease-modifying effect,[13] preventing organ failures and acute-on-chronic liver failure, reducing the need for hospitalisations and demands on the healthcare systems, and improving patient survival and quality of life.

Clinical studies of long-term HA administration

Few clinical trials have assessed the effect of long-term HA administration in patients with decompensated cirrhosis.

In the first study,[14] patients with cirrhosis and ascites needing diuretic administration received HA plus diuretics or diuretics alone. HA treatment, at a dose of 25 g weekly for one year and 25 g every two weeks for the following two years, improved the response rate to diuretics and prevented the recurrence of ascites.

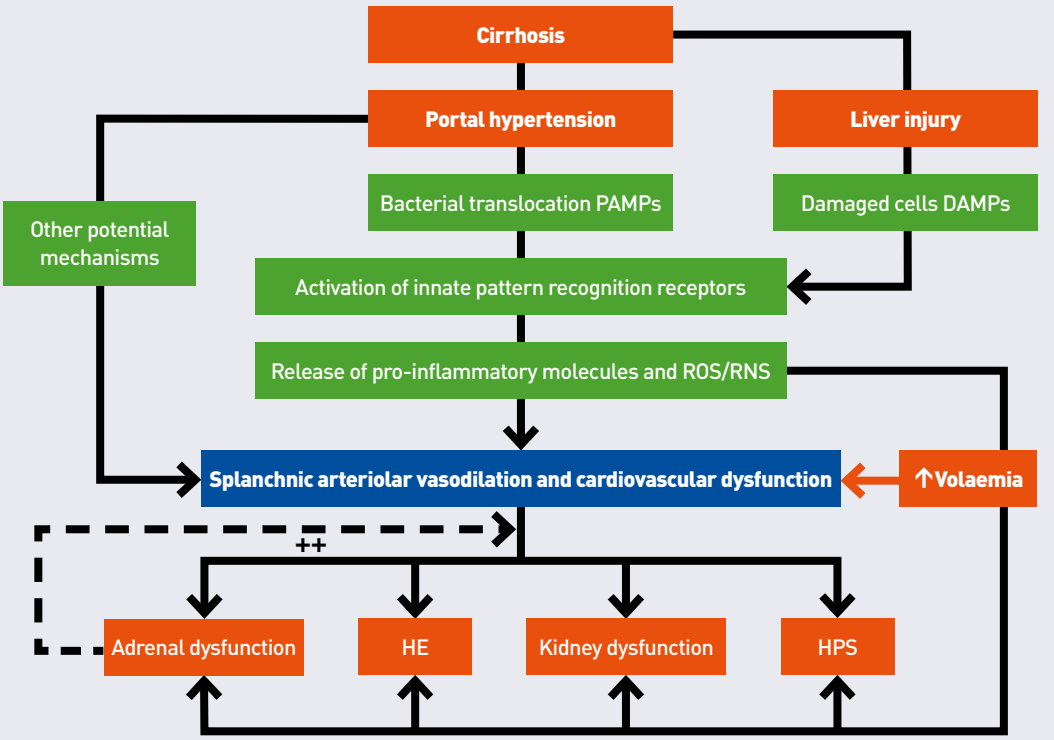
A subsequent follow-up extension to a median of 84 months improved the transplant-free survival of patients receiving HA.[14] Unfortunately, the small sample size in this study precluded a firm conclusion, and clinical practice guidelines did not support HA treatment in that context.

The ANSWER study, a large-scale, non-profit, multicentre, randomised, pragmatic clinical trial, evaluated the effects of long-term administration of HA to patients with cirrhosis and persistant non-complicated ascites requiring diuretic administration.[15]

A total of 431 patients were randomised 1:1 to either standard medical treatment (SMT), including human albumin administration for well-established indications, or SMT plus 40 g HA twice weekly for the initial two weeks, then 40 g once weekly for up to 18 months. The primary endpoint – overall survival – was reached, as the HA arm had significantly

FIGURE 2

Systemic inflammation hypothesis and potential targets of human albumin



ROS: reactive oxygen species; **RNS**: reactive nitrogen species; **HE**: hepatic encephalopathy; **HPS**: hepatopulmonary syndrome.

Pathogen-associated molecular patterns (PAMPs), due to abnormal translocation from the gut, and damage-associated molecular patterns (DAMPs) released by the liver, spread into the systemic circulation. After recognition by innate pattern recognition receptors, PAMPs and DAMPs activate immune cells. Consequently, immune cells enhance the production of pro-inflammatory cytokines and chemokines, along with reactive oxygen and nitrogen species. These events contribute to splanchnic arterial vasodilation and cardiocirculatory dysfunction favouring multiorgan dysfunction and failure. In this network, human albumin could find targets for its pleiotropic functions: besides promoting plasma volume expansion, albumin could bind harmful molecules, modulate immune responses, exert anti-oxidation, improve cardiac function and restore endothelial integrity. *Concepts from refs 1,9*.

better overall survival, with a 38% reduction of the hazard ratio for mortality.[15]

Besides reducing the need for large-volume paracentesis, HA led to other relevant results, such as the lower incidence of complications, such as refractory ascites, SBP and other bacterial infections, episodes of renal dysfunction, as defined by serum creatinine above 1.5 mg/dL, hepatorenal syndrome type 1, hepatic encephalopathy grade III or IV, hyponatraemia and hyperkalaemia. Gastro-oesophageal variceal and other portal hypertensive bleeds did not significantly differ between the two arms.[15]

The ANSWER study confirmed that long-term HA treatment can reduce the risk of SBP by 67% (relative risk (RR) 0.33; 95% CI 0.19~0.55; p<0.001) and reduce the risk of non-SBP bacterial infection by 30% (RR 0.70; 95% CI 0.54~0.90; p=0.05).[15]

Mainly owing to the reduced need for hospitalisations and a better quality of life, the incremental cost-effectiveness/quality-adjusted life years ratio of long-term HA was well below the threshold adopted by the National Institute for Health and Care Excellence (€21,265 vs €35,000) to consider a treatment cost-effective. Moreover, the bootstrap analysis showed that long-term HA was cost-effective in 92.5% of cases and cheaper than SMT in more than half of cases.[15]

Adverse events temporally related to HA administration were two mild and transient allergic reactions, an episode of dizziness with transient arterial hypotension, and two cases of sepsis likely due to venipuncture since the bacteriological analysis of HA batches did not reveal contamination.[15]

A prospective, non-randomised study enrolled 70 patients with refractory ascites who received either SMT or SMT plus 20 g of HA twice weekly confirmed the core results of the ANSWER trial: the patients who received HA had a lower mortality and a greater probability of being free from hospitalisation because of complications of cirrhosis.[16]

Long-term treatment of patients with decompensated liver cirrhosis: controversy and analysis

However, the MACHT study challenged these results.[17] This placebo-controlled clinical trial randomised patients listed for liver transplantation to receive either 40 g albumin every 15 days plus midodrine (from 15 to 30 mg/day according to their pressure response) or placebo.

Despite a mild improvement in effective volaemia, witnessed by decreased plasma renin activity and →

aldosterone concentration, the probability of developing complications, the primary endpoint, and survival did not differ between the two arms of the study.[17]

Similarly, the Albumin to Prevent Infection in Chronic Liver Failure (ATTIRE) study[18] showed that daily infusion of 20% HA in hospitalised patients with acute decompensation of cirrhosis resulted in serum albumin levels ≥30 g/ L. Still, there was no significant improvement in infection, renal dysfunction, or mortality.

These different results suggest that the improvement of clinical outcomes by human albumin may be related to factors such as patient characteristics, duration of albumin treatment, and dosing, which were different in these studies.

The primary composite endpoint of the ATTIRE study was new infection, kidney insufficiency, or death between days 3 and 15 after the initiation of treatment, so the treatment duration and follow-up time for endpoints were inadequate.[18]

The comparison of the characteristics of ANSWER and MACHT studies provides some relevant information. The studies differ in the sample size, design, and baseline severity of cirrhosis as assessed by the Model for End-Stage Liver Disease (MELD) score. More significantly, the median duration of HA exceeded one year in the ANSWER study, while it was about two months in the MACHT trial due to the high rate of liver transplantation. Furthermore, the amount of HA in the MACHT trial was about half the amount in the ANSWER study, which also used an initial loading dose.[15,17]

These aspects suggest that long-term HA administration should increase serum albumin concentration to yield beneficial effects. There is some evidence supporting this concept. In patients with decompensated cirrhosis and hypoalbuminaemia receiving 1.5 g/kg HA weekly, the increase of serum albumin concentration was far more relevant than in those who received 1 g/kg every two weeks.[19] Notably, beneficial effects on effective volaemia, pro-inflammatory cytokines and left ventricular function only occurred with the high dose of albumin.[19]

A post-hoc analysis of the ANSWER study database demonstrated a close relationship between on-treatment serum albumin at one month and survival.[20]

From this study, it also emerged that the survival benefit continues to progress even once the lower limit of the normal serum albumin concentration (3.5 g/dL) is reached. In this range of serum albumin concentration, 4 g/dL was the value best discriminating the patient sub-populations and, therefore, may represent the target to ensure optimal outcomes.[20]

Baseline serum albumin concentration and MELD score were the independent factors predicting the probability of reaching this target. This finding implies that patients with very low serum albumin and high MELD scores likely need higher amounts of HA to reach the optimal target of 4 g/dL at month one.[20] Therefore, the goal of long-term HA administration should be to fill the gap between the baseline serum albumin and a theoretical optimal on-treatment target.

As the extent of this gap is variable, mainly depending on the baseline albuminaemia and severity of cirrhosis, the need to go beyond a fixed dosage and schedule of albumin administration – as used in the ANSWER study – to a more individualised treatment is apparent.

Do different HA doses lead to different outcomes?

The Pilot-PRECIOSA study explored this question.[19,21]

Pilot-PRECIOSA[19,21] is a proof-of-concept, multicentre, non-randomised, prospective, open-label, phase IV clinical trial evaluating the effects of long-term human albumin (20%) therapy on cardiovascular circulation, renal function and

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systemic inflammation in patients with cirrhosis and ascites. Patients received low-dose (1 g/kg every two weeks, LAlbD group, n=15) or high-dose (1.5 g/kg per week, HAIbD group, n=16) 20% human albumin solution for 12 weeks treatment. The results showed that a higher proportion of patients in the HAlbD group (42.9%) were free of ascites at the end of the study compared with patients in the LAlbD group (0%). At baseline, 81.25% of patients in the HAlbD group and 86.7% of patients in the LAlbD group were free of hepatic encephalopathy, and at the end of the study, all patients were free of clinical hepatic encephalopathy.

The study suggests that a higher proportion of patients in the high-dose HA group were free of ascites compared with the low-dose group. Long-term infusion of human albumin appears to be an effective and safe treatment that can modify the course of the disease. Presumably, the therapeutic effect would be apparent when HA is administered in doses large and long enough to restore its physiological levels and functions.

In summary, the ANSWER study provided evidence that long-term albumin administration to patients with cirrhosis and ascites improves survival, reduces the occurrence of severe disease complications, is cost-effective by reducing the need for hospitalisations and improving patient quality of life, and is associated with elevated patient compliance (about 95%).[15]

In recent years, several meta-analyses have evaluated the effect of short- and long-term HA in patients with decompensated cirrhosis, providing differing results.

While almost all reported beneficial effects in the management of ascites and the occurrence of complications, the results of patient survival were conflicting, possibly due to the heterogeneity of the studies included in the meta-analyses.[22,23]

Future prospects and discussion

Hopefully, new studies will provide more solid information about many aspects of long-term HA treatment that still require clarification: the criteria for identifying those patients who would benefit most from this therapy, the definition of personalised albumin doses and schedules of administration as well as the target serum albumin concentration to be reached

to obtain the best results, the duration and the rules for stopping or resuming long-term HA treatment.

For example, the annual mortality rate of SBP is as high as 53.9%~78%.[24] Studies have shown that high-dose HA combined with antibiotics to treat SBP can reduce acute kidney injury and 90-day mortality.[25] However, prevention is better than cure; we look forward to evidence that long-term, high-dose HA infusion can prevent and reduce the occurrence of SBP and is more cost-effective.

In addition, a retrospective study of 11 tertiary hospitals in China showed that the incidence of acute kidney injury in SBP patients was 52.7%, with the average daily dose of human albumin infusion was only 0.2g/kg. It is speculated that the high incidence of acute kidney injury in SBP patients in China may be related to the low-dose of HA.[28] Therefore, conducting clinical studies on patients with end-stage liver disease due to HBV infection in China is necessary to explore whether long-term HA infusion can reduce the incidence of SBP, reduce the occurrence of acute kidney injury in SBP patients, and improve patient prognosis.

Patients with bacterial ascites and fungal peritonitis have a similar poor prognosis as SBP, but the international and Chinese guidelines do not mention the management of these conditions, especially regarding the use of HA. Therefore, China especially needs to explore the optimal dose and course of HA infusion for patients with HBV-related cirrhosis SBP to guide clinical practice.

The results of the two clinical studies on long-term treatment of decompensated liver cirrhosis with HA are eagerly awaited; one of which is the phase III PRECIOSA study (ClinicalTrials.gov ID NCT03451292).

This trial randomised patients recovering from acute cirrhosis decompensation to receive either SMT or SMT plus HA (1.5 g/kg body weight at enrolment; 1.5 g/kg body weight every 10 ± 2 days for up to 12 months), Enrolment and patient follow-up has now concluded and results are under scrutiny.[27]

The other is the ALB-TRIAL,[28] a precision medicine approach with biomarkers to predict HA long-term treatment response, which is about to start.

In the meantime, the debate between those who recommend and those who are against long-term HA administration to patients with decompensated cirrhosis will continue.

Two main points fostering perplexities about this treatment are the cost and availability of HA. The ANSWER study provides a unique evaluation of cost-effectiveness, clearly showing the cost-effectiveness of long-term HA, at least in Italy.[15] However, further studies in different countries are needed.

HA availability and its cost appear to be the main obstacles to wider long-term albumin administration, and studies devoted to identifying the clinical conditions that most benefit from it, and which carefully evaluate its cost-effectiveness in various contexts, are required. However, long-term HA administration should be used when possible and an international position statement devoted to HA use in patients with cirrhosis embraces these concepts.[7]

Conclusion

Long-term HA administration to patients with decompensated cirrhosis with ascites has provided a new perspective on the use of HA as a disease-modifying agent. This novel use implies a change of the treatment paradigm.

HA is given to patients with grade 2 and 3 uncomplicated ascites not only to treat the complication ascites *per se* but also because this clinical feature identifies a patient population for whom albumin, acting as a disease-modifying agent, improves survival, preserves the quality of life, reduces the occurrence of complications and the need for hospitalisations.

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Albumin in cardiac surgery: recommendations and guidance

A Chinese expert consensus supports the use of albumin in cardiac surgery for volume replacement, pump priming and correction of hypoalbuminaemia; however, this advice contrasts with recent international guidelines, which adopt a more restrictive approach. While clinical judgment should guide the use of albumin to avoid over-reliance and potential adverse effects, consensus guidelines remain crucial in informing and refining clinical practice

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Cardiac surgery is associated with significant physiological changes, including surgical trauma, excessive bleeding, haemodilution, renal failure and inflammation.[1] To manage these complications, fluid therapy with albumin during surgery plays an important role in preventing blood coagulation issues, preserving renal function, and reducing inflammation.[2–4] In contrast, alternative fluids such as hydroxyethyl starch may increase the risk of bleeding and acute kidney injury, while crystalloid can cause haemodilution, fluid overload, oedema, and altered platelet function.

Although albumin is commonly used for fluid resuscitation, pump priming, or correcting hypoalbuminaemia, clear guidelines on its use in these settings are lacking, which results in variations in albumin use across hospitals, unnecessary waste, and higher healthcare costs.[1,5]

Choice of fluid

The choice of fluid for volume resuscitation or cardiopulmonary bypass (CPB) priming is often based on physician preference or institutional protocols.[6] In the US, for example, crystalloid is preferred for volume expansion during CPB without bleeding, while 5% albumin is favoured for bleeding patients. For extracorporeal membrane oxygenation or ventricular assist devices, both crystalloid and 5% albumin are commonly used.

Although not cardiac surgery specific, German guidelines from the Association of the Scientific Intensive Care Societies recommend colloids, including albumin, for critically ill adults and perioperative use in paediatric patients when crystalloids are insufficient.[7] Furthermore, the Acute Disease Quality Initiative on Cardiac and Vascular Surgery-Associated Acute Kidney Injury suggests preoperative administration of albumin for patients undergoing off-pump coronary artery bypass, although the evidence supporting this practice is limited.[8]

Expert consensus in China: summary

In 2023, expert consensus on the use of human serum albumin in adult cardiac surgery was published in China to clarify the role of albumin infusion in perioperative care and improve patient outcomes.[1] This consensus was developed collaboratively by a multidisciplinary team of cardiac surgeons, anaesthesiologists, intensivists, perfusionists, and other healthcare professionals involved in the care of cardiac surgery patients.

Volume replacement

Volume replacement is crucial in perioperative cardiac surgery and is often needed to correct inadequate tissue perfusion or low intravascular volume, which can occur in cases of hypotension, oliguria, or hyperlactataemia.[1] The most commonly used fluids for maintaining or restoring circulating plasma volume during and after cardiac surgery are albumin, balanced crystalloids, and synthetic colloids.

The current Chinese guidelines recommend the use of albumin after crystalloid resuscitation in patients requiring further volume replacement during and after cardiac surgery to prevent excessive fluid retention (Table 1).[1] Fluid management in patients undergoing cardiac surgery is challenging due to factors such as blood loss, vasoplegia, and low cardiac output syndrome, and accurate assessment of intravascular volume is often difficult. As a result, over-resuscitation is relatively common and is associated with an increased risk of complications, including pulmonary oedema, acute kidney injury, heart failure, and mortality in patients undergoing cardiac surgery.[9,10]

Albumin provides more efficient and sustained intravascular volume expansion, with less fluid required for haemodynamic improvement than crystalloid.[1] Research indicates that albumin, especially in the first 24 hours after cardiac surgery, improves clinical outcomes, including reduced fluid retention, decreases norepinephrine use, and significantly lowers mortality.[11,12] These findings have increased interest in albumin to prevent over-resuscitation and excessive positive fluid balance in cardiac surgery patients.

The guidelines further suggest that albumin infusion may help maintain intravascular volume and arterial pressure during aggressive diuresis, which is used to relieve fluid overload and interstitial oedema after cardiac surgery (Table 1).[1] After the acute phase of fluid replacement, patients often experience fluid overload and present with excessive water and salt in the interstitial space, which is managed through diuresis. Because aggressive diuresis can cause intravascular volume deficiency and systemic hypotension, albumin can prevent diuresis-induced hypotension by expanding plasma volume.

Albumin can also help restore endothelial glycocalyx, which promotes the shift of interstitial fluid back to the bloodstream.[13] Notably, postoperative overload of interstitial salt and water is more common in high-risk patients and further studies are needed to investigate the benefit of albumin in this specific patient population.

TABLE 1

Recommendations for use of albumin in adult cardiac surgery

Recommendations (in bold)	COR (LOE)
Volume replacement	
A comprehensive multimodality approach by a multidisciplinary team is recommended to minimise haemodilution during cardiac surgery	I (C-EO)
Goal-directed fluid therapy is recommended to assess the volume status and optimise fluid resuscitation during and after cardiac surgery	I (B-NR)
It is reasonable to administer albumin following crystalloid resuscitation in patients who needs further volume replacement during and after cardiac surgery to avoid excessive positive fluid balance	IIb (B-NR)
Albumin infusion might be helpful to maintain intravascular volume and arterial pressure when aggressive diuresis is given to relieve fluid overload and interstitial oedema after cardiac surgery. Hypertonic (20% or 25%) albumin is preferred in this setting	IIb (C-LD)
Albumin is not routinely recommended as the first-line choice of fluid resuscitation during and after cardiac surgery	III (B-R)
Using albumin for fluid resuscitation in patients with haemorrhagic shock and uncontrolled bleeding is not recommended	III (C-EO)
Albumin infusion is reasonable to supplement prior volume and albumin loss in patients with bleeding-controlled haemorrhagic stroke	IIa (C-EO)
Pump priming	
Pump priming with albumin for optimising blood management might be reasonable	IIb (B-NR)
Pump priming with albumin might be considered in specific cardiac surgical populations, such as those undergoing heart transplantation, pulmonary thromboembolectomy, and deep hypothermia circulatory arrest	IIb (C-EO)
Correction of hypoalbuminaemia	
Albumin infusion is reasonable to correct preoperative hypoalbuminaemia in normovolaemic patients	IIb (B-NR)
Correcting postoperative hypoalbuminaemia by albumin infusion in normovolaemic patients might be beneficial	IIb (C-EO)

COR, class of recommendations; EO, expert opinion; LD, limited data; LOE, level of evidence; NR, non-randomised; R, randomised. Adapted from Xiang et al. 2023.[1]

According to the guidelines, albumin infusion is a reasonable approach to supplement volume and albumin loss in patients with bleeding-controlled haemorrhagic shock (Table 1).[1] Patients in haemorrhagic shock are typically resuscitated with crystalloid and blood transfusion during or after cardiac surgery. Once bleeding is controlled, additional volume replacement is often needed due to albumin loss from bleeding. Postoperative bleeding and blood transfusion can worsen systemic inflammation and damage the endothelial glycocalyx in cardiac surgical patients.[13] In this context, albumin infusion can help restore volume, reduce fluid overload, improve microvascular integrity, and decrease inflammation.

Pump priming

Albumin is currently used during CPB for pump priming, volume replacement and maintaining oncotic pressure.[1] Pump priming, which typically uses approximately 1.0–1.5 L of fluid, can lead to severe haemodilution, a decrease in colloid oncotic pressure and fluid overload.[14] Shear stress and pressure drops across the pump boot can trigger the release of inflammatory mediators, initiating a systemic inflammatory response and endothelial permeability breakdown.[1,15,16] In CPB surgery, albumin has been shown to reduce inflammation, prevent platelet adhesion, and coat CPB circuits, thereby reducing platelet adhesion and the consumption of other coagulation factors.[17]

According to two surveys, albumin is used for CPB priming by approximately 30% of healthcare responders in the US and approximately 8.7% in European countries.[6,18] Among those who used colloids, 28% used albumin in European centres.[18]

Based on currently available data, the Chinese guidelines suggest that pump priming with albumin for optimising blood management may be reasonable (Table 1). In addition, pump priming with albumin might be considered for specific cardiac surgeries, such as heart transplantation, pulmonary →

thromboembolectomy, and deep hypothermic circulatory arrest.

The use of albumin for pump priming in cardiac surgery was investigated in a meta-analysis of 21 controlled trials including 1,346 patients.[4] Compared with crystalloid, albumin priming was associated with lower postoperative platelet counts, a smaller decline in colloid osmotic pressure during bypass, and reduced fluid retention and weight gain.

Despite these benefits, the ALBICS trial did not demonstrate improved clinical outcomes with albumin in patients undergoing cardiac surgery with CPB.[19] In this large trial, treatment with 4% albumin solution for priming and perioperative intravenous volume replacement did not significantly reduce the risk of major adverse events over the following 90 days compared with Ringer acetate. This study, however, has several limitations, including its single-centre design and the inclusion of only low-risk patients (median EuroSCORE of 1.7), which may not represent the high-risk population that might benefit most from albumin. In addition, the albumin concentration used and the criteria for switching from crystalloids to albumin during resuscitation in this trial differed from routine practice, which might affect the results.

Regardless of these mixed findings, albumin is widely used in high-risk populations, including patients with low body weight, heart transplants, pulmonary thromboembolectomy, deep hypothermic circulatory arrest, advanced age, reoperations, thrombocytopenia, impaired heart function, and those requiring prolonged pump runs.[1]

Correction of hypoalbuminaemia

Cardiac surgery patients often present with preoperative hypoalbuminaemia, which can result from cardiac-related malnutrition, liver dysfunction, and chronic consumption.[1] Preoperative hypoalbuminaemia is associated with worse outcomes, including an increased risk of infection, acute kidney injury, and delirium. According to the recent Chinese guidelines, albumin infusion is considered reasonable for correcting preoperative hypoalbuminaemia, defined as serum albumin concentrations below 35 g/L, in patients with normal blood volume (Table 1).

While preoperative albumin levels are useful for assessing surgical risk, the benefits of albumin supplementation in cardiac surgery patients with hypoalbuminaemia remain debated due to limited evidence.[1]

A single-centre, randomised clinical trial demonstrated that albumin reduced the risk of postoperative acute kidney injury compared with saline in patients undergoing off-pump coronary artery bypass grafting with albumin concentrations below 4.0 g/L before surgery.[20] In detail, 13.7% of patients receiving albumin during surgery developed acute kidney injury, compared with 25.7% of patients receiving saline. However, there was no significant difference between the two treatment groups regarding mortality or other comorbidities. Notably, no patients experienced adverse events related to albumin infusion during surgery.

Cardiac surgery patients often develop postoperative hypoalbuminaemia, which can result from baseline albumin deficiency, operative losses, leakage to the extravascular space, and haemodilution.[1] Data showed that 61.5% of patients have serum albumin levels below 30 g/L after surgery.[21] Postoperative hypoalbuminaemia is associated with poor clinical outcomes, including reduced long-term survival and increased rates of postoperative respiratory failure, wound infection, and renal failure.[21,22] Albumin is frequently used after

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cardiac surgery to restore albumin levels to maintain oncotic pressure, relieve tissue oedema, and preserve microvascular integrity and metabolism.[1]

Based on the currently available evidence, the Chinese guidelines suggest that correcting postoperative hypoalbuminaemia with albumin infusion in normovolemic patients might be beneficial (Table 1).[1] However, future studies are needed to investigate whether albumin improves outcomes in patients with postoperative hypoalbuminaemia who do not require volume replacement.

The International Collaboration for Transfusion Medicine Guidelines

In contrast, the International Collaboration for Transfusion Medicine Guidelines do not recommend intravenous albumin for volume replacement or priming the cardiovascular bypass circuit in adult and paediatric patients undergoing cardiovascular or vascular surgery.[23]

This recommendation is based on the findings from a systematic review and meta-analysis of 43 randomised controlled trials involving 3,862 paediatric and adult patients undergoing cardiovascular surgery.[24] The pooled data from these trials showed that albumin infusion did not reduce rates of mortality compared with other solutions used for volume expansion, priming the CPB circuit, or both, such as gelatine, starches, or crystalloid solutions.

While albumin was associated with reduced fluid retention, there were no significant differences in rates of kidney failure, blood loss, lengths of ICU or hospital stays, blood component use, or cardiac index between patients receiving albumin and those receiving other fluids. However, the authors of this meta-analysis concluded that there is effectively insufficient evidence to either recommend for or against the use of albumin in the context of cardiovascular surgery.

Limitations of the current guidelines

The current guidelines for the use of albumin in patients undergoing cardiac surgery have several limitations.[1,23] These included uncertainty in the evidence from the literature for many different patient populations and a lack of comparative dosing strategies. More specifically, there is ambiguity regarding the choice between 4%–5% and 20%–25% albumin formulations, the optimal dose and dosing schedules for each indication, and the risk of fluid overload. The guidelines mainly focus on common uses of albumin and do not address all patient scenarios. Furthermore, many studies fail to report adverse reactions associated with intravenous albumin, which further complicates the risk assessment.

Future research is needed in several key areas, especially in assessing the role of albumin in patients undergoing cardiac surgery.[23] Further studies should explore therapeutic targets for albumin resuscitation, including haemodynamic effects and laboratory markers, as well as optimal formulations and dosing strategies. More research is also needed to evaluate the risks related to albumin, to better assess its risk-benefit profile, with a focus on patient-important outcomes.

Conclusions

The recently published expert consensus in China on the use of albumin in adult patients undergoing cardiac surgery highlights its potential clinical benefits in volume replacement, pump priming, and correcting hypoalbuminaemia.[1] According to these guidelines, it is reasonable to administer albumin after crystalloid resuscitation in cardiac surgery patients to prevent fluid overload and to supplement prior volume and albumin loss in patients with bleeding-controlled haemorrhagic stroke. Albumin can also maintain intravascular volume and arterial pressure during aggressive diuresis to relieve fluid and interstitial oedema.

In addition, pump priming with albumin may be reasonable for optimising blood management and might be considered for specific cardiac surgeries, such as heart transplantation, pulmonary thromboembolectomy, and deep hypothermic circulatory arrest. Finally, albumin infusion is recommended for correcting perioperative hypoalbuminaemia in normovolaemic patients.

Although clinical data show that albumin provides benefits over crystalloid and synthetic colloids in cardiac surgery patients, further research is needed to refine guidelines and assess the optimal use of albumin in cardiac surgery.

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GI surgery: perioperative hypoalbuminaemia and albumin therapy

Perioperative albumin level has emerged as a predictive factor of complications after gastrointestinal surgery. This article summarises studies that have evaluated the impact of hypoalbuminaemia on surgical outcomes, as well as the predictive value of changes in albumin levels regarding these parameters

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Hypoalbuminaemia, defined as serum albumin below 3.5 g/dL, is a well-established predictor of mortality, hospital length of stay, and postoperative complications in patients undergoing gastrointestinal (GI) surgery.[1–3]

Preoperative hypoalbuminaemia, in particular, is an independent risk factor for developing surgical site infections in GI surgery and is associated with deeper surgical site infections and prolonged inpatient stay.[4] Low albumin levels impair wound healing and suppress immune responses, which leads to worse outcomes in GI surgical patients.

Decreased albumin levels also change the binding and distribution of drugs, which result in altered pharmacokinetics, reduced efficacy of antibiotics and complicated infection management.[5] Hypoalbuminaemia is a strong predictor of antibiotic treatment failure, such as in cases of Staphylococcus aureus-related bacteremia.[6]

Risks and postoperative complications

The postoperative complications of GI surgery are relatively common, with literature indicating rates as high as nearly 50%.[7] Therefore, it is crucial to identify high-risk patients before surgery, such as those with comorbid cardiovascular diseases or malnutrition, in order to enhance clinical outcomes. While common biomarkers such as white blood cells, C-reactive protein (CRP), procalcitonin, and interleukin-6 are used to assess surgical risk, they have limitations such as low accuracy, slow response time, and economic burden.

Albumin, a negative acute phase protein, declines quickly in response to tissue inflammation or injury, primarily due to redistribution into the tissue spaces caused by increased vascular permeability.[8] Given albumin's immediate response to surgical stress, it can serve as a potential marker for assessing surgical stress and predicting postoperative complications.[3,9] The extent of albumin decrease, referred to as ΔAlb (delta albumin), is directly proportional to the severity of surgical trauma.[7]

Liver surgery

Despite considerable advances in liver surgery, the incidence of complications cannot be ignored.[10] Thus, accurate biomarkers are needed to predict postoperative complications undergoing liver surgery, including liver transplantation.

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A study involving 106 cases of liver surgeries evaluated the role of albumin as a surrogate biomarker for surgical stress. The results showed that surgical stress induces a rapid and significant reduction in albumin levels, followed by a slow increase from the first day after surgery. The postoperative albumin drop was significantly greater in patients with complications than those without complications (p=0.009).[10]

Similarly, a prospective study on 92 hepatectomy patients demonstrated that both preoperative and postoperative albumin levels correlated with complications after GI surgery.[11] While plasma albumin decreased postoperatively in all patients, those with normal recovery experienced a slight drop in albumin levels that quickly stabilised. In contrast, patients with complications and non-survivors had a more severe and prolonged decrease in albumin values.

This study suggests that hypoalbuminaemia after liver resection plays an important role in various biochemical and pathophysiologic correlations and that the degree of hypoalbuminaemia may reflect the severity of the illness.[11]

Liver transplant

Liver transplantation has always been the standard treatment for end-stage liver disease.[12] Hypoalbuminaemia plays a critical role in liver transplantation due to the compromised liver function of patients and the increased risk of internal environment imbalance and infection. Guidelines recommend the use of albumin in liver transplantation to manage ascites

and peripheral oedema, as well as to correct fluid imbalance caused by ascites., to promote homeostasis and postoperative recovery.[13]

Hypoalbuminaemia is common in patients with end-stage liver disease. It has been established as an independent risk factor for mortality in patients with end-stage liver disease in several studies, including a study by Bernardi and colleagues.[14] Albumin–bilirubin score, a logarithmic score combining albumin and bilirubin, has been recommended to assess liver function and predicting survival in patients with hepatocellular carcinoma.

The findings showed that both albumin-bilirubin grade 3 and low serum albumin levels were associated with worse overall survival outcomes in patients undergoing liver transplantation, while higher albumin levels correlated with decreased mortality (hazard ratio (HR), 0.6; p=0.002). ROC curve indicated that the albumin-bilirubin score was a stronger predictor of mortality than albumin levels alone, probably due to the synergistic effect of including bilirubin in the score.[14]

A recent retrospective analysis of living donor liver transplant patients showed that, in addition to albumin levels measured at specific time points, the cumulative postoperative change in albumin values is an important predictor of postoperative organ failure in patients undergoing liver transplantation.[15]

More specifically, patients with a smaller postoperative decrease in cumulative serum albumin level had a lower Sequential Organ Failure Assessment (SOFA) score on day 5 after surgery compared with those with a high decrease (p=0.005). The authors concluded that postoperative changes in serum albumin levels could serve as a predictor of organ failure in liver transplantation patients, although a prospective controlled trial is needed to validate the feasibility of this measurement.

Treatment of hypoalbuminaemia remains a matter of debate, along with the optimal timing and volume of albumin supplementation in liver transplantation.[15] A retrospective study found that continuous infusion of human albumin for seven days in liver transplant patients with hypoalbuminaemia improved organ function, particularly cardiovascular function.[16] Patients receiving albumin had significantly lower mean SOFA scores (p<0.001) and cardiovascular sub-scores, together with higher colloid osmotic pressure, serum albumin, and total protein levels, compared with the control group (p<0.001).

Abdominal surgery

Surgical interventions induce varying degrees of metabolic stress, which can impact complication rates, recovery duration, and the length of hospital stay. Changes in albumin levels early after abdominal surgery can indicate the surgical stress response, with decreases correlating with adverse clinical outcomes.[17]

In a prospective study of 70 abdominal surgery patients, albumin values dropped by approximately 1.0 g/dL immediately after surgery and showed a slow recovery. The ΔAlb was significantly larger in patients with complications and correlated with longer hospital stays, greater blood loss, longer surgery duration, and higher CRP levels. In addition, ΔAlb was greater in patients with major complications, with significant differences compared with those without complications.

A larger prospective study involving 138 patients undergoing major abdominal surgery[9] showed that ΔAlb correlated with the development of complications. A ΔAlb cut-off of 1 g/dL or more was associated with a three-fold increased risk of complications. Although perioperative albumin rapidly decreased after surgery in all patients, those with a significant albumin drop on the first day after surgery had higher rates of various complications, together with significantly longer hospital stays.[9]

More recent studies have further demonstrated that ΔAlb is associated with postoperative complications in patients undergoing both elective intestinal surgery and emergency laparoscopy.[18,19]

In a cohort of 105 intestinal surgery patients, including small bowel and colorectal procedures, ΔAlb on postoperative days 1 and 2 was significantly higher in those with major complications than those without major complications.[18] This study identified a ΔAlb cut-off of 27.3% on days 1 and 2 after surgery as predictive of high-grade morbidity.

Furthermore, in a study by Kumar et al, pre- and postoperative serum albumin levels were measured in 50 patients who underwent emergency exploratory laparotomy, with 62% having preoperative hypoalbuminaemia.[19] In this study, the mean ΔAlb percentage was significantly associated with postoperative complications, including poor wound healing, wound infection, acute respiratory distress syndrome, acute kidney injury, sepsis, anastomotic leaks, and ileus.

A retrospective study including 182 cases of laparoscopic bowel resection in patients with Crohn's disease showed, that ΔAlb could predict complications.[20] In particular, a ΔAlb threshold of 24% was identified as an independent predictor of postoperative complications (HR, 2.2; p=0.04). Patients who developed complications after surgery had significantly increased ΔAlb (p=0.03), while neither preoperative nor postoperative albumin levels correlated with outcomes when taken as absolute numerical values.

This suggests that ΔAlb is a more reliable prognostic marker for predicting complications after surgery in patients with Crohn's disease compared with absolute albumin levels.

Oesophageal surgery

Oesophagectomy still carries significant risks of complications and mortality.[21] Pulmonary infection and anastomotic dehiscence are the leading causes of postoperative mortality after surgery for oesophageal cancer, and both are related to malnutrition.[22] Early detection and treatment of complications are crucial, and albumin has become a potential biomarker for predicting perioperative complications in esophagectomy.

A retrospective study of 200 patients undergoing oesophagectomy for malignant disease reported that the risk of complications is doubled if the albumin level is below 2 g/dL on the first day after surgery (54% vs 28%, p<0.011).[3] These patients also had significantly higher rates of adult respiratory distress syndrome (22% vs 5%, p<0.001), respiratory failure (27% vs 8%, p<0.01), and in-hospital mortality (27% vs 6%, p<0.001). Low albumin concentrations were also associated with the need for further surgery and ICU readmission. The above data suggest that albumin levels on the first postoperative day are closely related to various clinical outcomes.

Similarly, a large subsequent multicentre study involving 1,046 oesophageal cancer surgery patients identified ΔAlb on postoperative day 1 as an independent predictor of major complications.[23] Oesophagostomy caused a rapid drop in albumin on postoperative day 1, which was followed by gradual recovery. A ΔAlb cut-off of 1.1 g/dL was determined as the optimal threshold for predicting complications and was significantly associated with rate of both major and overall complications. These results suggest that ΔAlb is a promising biomarker after esophageal cancer surgery, allowing early prediction of potential adverse outcomes. →

Gastric surgery

Gastric cancer is one of the most common cancers and the third leading cause of cancer-related deaths in China.[24] Surgery is the only curative option for patients with gastric cancer, but postoperative complications can significantly affect the short-term and long-term prognosis of gastric cancer patients. Over the past years, efforts have been made to identify predictors of complications after gastrectomy, including albumin levels.

Two retrospective studies have demonstrated a strong association between ΔAlb and complications after gastrectomy in patients with gastric cancer. In the first study, which enrolled 223 patients undergoing gastric cancer resection, compared with common indicators such as CRP and lymphocytes, ΔAlb is the strongest predictor of short-term postoperative complications.[24] Multivariate analysis confirmed that ΔAlb was an independent risk factor for complications and prolonged hospital stay ($p<0.001$).

The second study, which involved 193 gastric cancer patients with normal albumin levels before surgery, the ΔAlb was positively associated with postoperative complications (odds ratio, 14; $p<0.001$).[25] These findings suggest that ΔAlb is an independent risk factor for predicting short-term complications in patients with normal preoperative albumin levels and may be a better predictor for assessing postoperative risks compared with preoperative albumin levels alone.

Another study explored the correlation between hypoalbuminaemia and postoperative complications of gastric cancer. In patients undergoing laparoscopic-assisted gastrectomy, hypoalbuminaemia was identified as an independent risk factor for severe postoperative complications.[26] Multivariate analysis confirmed that after excluding common confounding factors such as nutritional risk and surgical time, hypoalbuminaemia ($p=0.004$) was an independent risk factor for postoperative complications.

Colorectal surgery

Postoperative complications after colorectal surgery can lead to prolonged hospital stays, higher treatment costs, and poorer long-term survival.[27] Colorectal cancer surgery is influenced by various factors. Reliable and easy-to-use markers are needed to predict these complications.

In a retrospective study of 626 patients undergoing colorectal resection observed that ΔAlb exceeding 15% within 2 days after surgery leads to an increased incidence of postoperative complications, prolonged hospital stay, and increased incidence of surgical site infections.[27] Multivariate analysis confirmed that ΔAlb of at least 15% was an independent risk factor for developing complications (odds ratio, 7.8; $p<0.01$). The study suggests that patients with ΔAlb exceeding 15% within 2 days after surgery should be closely monitored to detect complications as early as possible.

Another study retrospectively included 193 colorectal cancer patients who underwent laparoscopic colorectal resection and found that ΔAlb was an independent predictor of severe postoperative complications ($p<0.001$).[28] Multivariate logistic regression analysis showed that ΔAlb was the only independent factor associated with severe complications (odds ratio, 1.66; $p=0.003$).

Conclusions

In patients undergoing GI surgeries, perioperative hypoalbuminaemia is a significant predicting factor of poor outcomes, including increased mortality, longer hospital stays, and higher rates of postoperative complications. The ΔAlb after GI surgery has recently emerged as an important biomarker for assessing surgical stress and predicting adverse events. Studies show that a significant drop in albumin values in GI surgery patients correlates with postoperative complications across various types of GI surgeries, such as liver, abdominal, oesophageal, gastric and colorectal.

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Cost-effectiveness of albumin in the treatment of decompensated cirrhosis and severe sepsis

This article provides a comprehensive review of the cost-effectiveness data of human albumin in the treatment of critical illnesses such as decompensated cirrhosis and sepsis. It offers a pharmacoeconomic perspective supporting its use to enhance long-term clinical outcomes in chronic and critical care settings

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Human albumin (HA) is a multi-functional protein that plays a critical role in various physiological functions. Its key functions include correcting hypo-oncotic states, hypoalbuminaemia and hypovolaemia, and it has anti-inflammatory and antioxidant properties.[1] It is a plasma-derived product, so has a higher average cost than other fluids. Inefficient utilisation would result in waste and increase the economic burden on the healthcare system and patients themselves. At present, HA is listed as a nationally monitored drug to ensure its rational use in China.

HA has various application scenarios in treating critical and severely ill patients and has an important clinical value. Both domestic and international studies have shown that HA offers long-term clinical benefits in the treatment of decompensated cirrhosis and severe sepsis. Long-term albumin treatment for patients with decompensated cirrhosis improves survival rates, prevents complications such as acute-on-chronic liver failure and infections, simplifies ascites management, lowers hospitalisation rates and modifies disease progression.[2] Similarly, HA can improve haemodynamics and reduce mortality in patients with sepsis.[3]

Guidelines and consensus recommendations

The 2022 International Position Statement on the Use of Albumin Infusion for Cirrhosis-related Complications[4] recommends short-term infusion of HA for cirrhosis-related complications, including hepatorenal syndrome (HRS), large-volume paracentesis (LVP) and spontaneous bacterial peritonitis (SBP). Long-term infusion can be considered in certain circumstances.

The 2021 Surviving Sepsis Campaign Guidelines[5] recommend using HA in conjunction with large-volume crystalloid resuscitation in sepsis patients. The 2021 Expert Consensus on the Use of Human Serum Albumin in Critically Ill Patients[6] suggests that albumin may reduce mortality in septic shock patients when used during fluid resuscitation. It also suggests supplementation with albumin when using antibiotics with high protein-binding rates to enhance the pharmacokinetics and pharmacodynamics of the antibiotics.

The Chinese Expert Consensus on the Clinical Application Management of Human Albumin (2024)[7] identifies decompensated cirrhosis and its complications as the priority indications for HA, whereas sepsis is classified as a conditional indication for its use.

Randomised clinical studies and meta-analyses have demonstrated the efficacy of albumin in managing clinical complications of decompensated cirrhosis.[8] Consequently, international guidelines recommend the use of albumin for the treatment of cirrhosis-related complications, such as SBP and HRS, respectively.[7,9]

Economic aspects

The economic burden of HA therapy is a concern because it is often more expensive than alternative treatments. Similar concerns exist in the treatment of sepsis and septic shock. However, more recent studies have suggested that albumin therapy is cost-effective, especially in chronic and critical care settings such as decompensated cirrhosis and sepsis. While albumin therapy tends to be more expensive initially compared with alternative treatments, research consistently demonstrates its long-term clinical benefits, including reduced complications, improved survival outcomes, and shorter hospital stays, which can ultimately lead to lower overall healthcare costs.

Cost-effectiveness in liver cirrhosis

Cirrhosis of the liver is a major global cause of disability and death, responsible for more than 1.32 million deaths worldwide in 2017.[10] The prevalence of both decompensated and compensated cirrhosis is increasing, with 10.6 million and 112 million cases, respectively, reported globally in 2017. Decompensated cirrhosis, characterised by complications such as ascites, gastrointestinal bleeding, hepatic encephalopathy, and jaundice, has a poor prognosis with a median survival of approximately two years.[11]

Decompensated cirrhosis is associated with high healthcare costs, mainly due to frequent hospitalisations.[12,13] Known for its oncotic and non-oncotic properties, albumin has been extensively studied as a potential treatment for patients with ascites, which is the most common cause of decompensation, as well as SBP and HRS.[14] While most physicians in the US and Europe use HA for these complications, its long-term administration is considered costly.[8] However, the high costs of managing cirrhosis complications, including frequent hospitalisations, contribute to the overall financial burden and must be taken into account.

The human Albumin for the treatmeNt of aScites in patients With hEpatic ciRrhosis (ANSWER) trial was one of the first studies to estimate the clinical efficacy and cost-effectiveness of long-term albumin administration in patients with cirrhosis.[15] In this investigator-initiated study, 440 patients from 33 Italian hospitals were randomly assigned in a 1:1 ratio to receive either standard medical treatment (SMT) or SMT plus albumin for up to 18 months. The results showed that →

adding albumin to SMT significantly reduced hospital admissions by 35% and days spent in the hospital by 45%. Treatment with albumin was also associated with a significantly lower rate of paracentesis compared with SMT alone (12% vs. 29%, p<0.0001). Additional benefits of long-term albumin included a lower incidence of complications such as refractory ascites, bacterial infections including SBP, renal dysfunction, HRS type 1, and hepatic encephalopathy, while the rate of gastro-oesophageal variceal bleeding remained similar between the two treatment groups.

These clinical benefits were reflected in the cost-effectiveness analysis, which indicated that the additional cost of albumin (€2,488 per year) was counterbalanced by savings from fewer hospital admissions and paracenteses and reduced albumin use to treat complications.[15] The incremental health benefit in the SMT plus albumin group, measured as a mean quality-adjusted life-years (QALY) gain of 0.117(95% CI: 0.062–0.150), resulted in an incremental cost-effectiveness ratio (ICER) of €21,265 per QALY. A bootstrap analysis further demonstrated that long-term albumin use was cost-saving in 56% of 10,000 simulations compared with SMT alone. A total of 92.5% of all simulations presented an ICER of being under the threshold of €35,000 per QALY. Taken together, long-term albumin administration, traditionally expected to improve ascites management, is shown to be a cost-effective treatment for decompensated cirrhosis.

Another study showed that among 15 patients receiving long-term human serum albumin plus SMT, the total cost of treatment increased by £167,272 due to albumin administration compared with patients receiving SMT alone.[16] However, according to a model, albumin infusion avoided 28 hospitalisations, two cases of refractory ascites, and three deaths within 12 months, which resulted in an estimated overall cost-saving of £194,340 for patients those with SMT plus albumin versus SMT alone, an average of £1,805 per patient.

Following the ANSWER trial regimen, a Brazilian study evaluated the economic impact of albumin infusions in patients with decompensated cirrhosis from both public and private healthcare systems perspectives.[17] This analysis found that albumin use may result in cost savings. More specifically, the cost per patient per year was 118,759 Brazilian real (BRL) lower in the public system and 189,675 BRL lower in the private system for patients with SMT plus albumin versus SMT alone. The additional cost of albumin was offset by reduced complications, including fewer cases of refractory ascites, SBP, hepatic encephalopathy, renal dysfunction, and HRS, along with lower rates of non-liver-related hospitalisations and LVP. The primary factor contributing to the cost reduction was the decreased incidence of hepatic encephalopathy.

In summary, studies have demonstrated that long-term albumin administration in patients with decompensated cirrhosis is cost effective.

Cost effectiveness in complications of decompensated cirrhosis

The cost-effectiveness of albumin, in terms of lives saved and QALYs gained, in the management of decompensated cirrhosis associated with LVP, SBP or HRS was further shown in a study by Runken et al.[8] This study used a decision-tree economic model with a three-month time horizon to evaluate the cost-effectiveness of various treatments for the complications of decompensated cirrhosis from a hospital perspective in Germany, Spain and Italy (separately for each country).

LVP

In patients undergoing LVP, the overall treatment cost per patient was the lowest with albumin than with saline, gelatin, or no fluid in the three countries (Germany: albumin €2,088, vs. saline €2,518, gelatin €2,875, and no fluid €2,999; Spain: €992, vs. €1,105, €1,503, and €1,308; Italy: €1,352 vs. €1,616, €1,908, and €1,861).[8]

This cost-effectiveness was due to fewer complications, such as hyponatraemia, renal impairment and hepatic encephalopathy, along with reduced mortality (survival rate of the albumin group 97.9%, vs. saline 97.1%, gelatin 93.9%, and no fluid 96.2%) and more QALYs gained (albumin group 0.719, vs. saline 0.709, gelatin 0.686, and no fluid 0.701). As a result, albumin is considered the first-line treatment option for decompensated cirrhosis patients undergoing LVP, given its cost-effectiveness and improved clinical outcomes.

SBP

This study further showed that adding albumin to antibiotics improved clinical outcomes and quality of life and lowered treatment costs in patients with SBP.8 SBP is a bacterial infection of ascitic fluid with an incidence ranging between 7% and 30% in hospitalised patients with cirrhosis and ascites and is associated with poor outcomes.[18]

When considering pharmacy costs for SBP, together with inpatient medical costs for renal impairment and hospital stays, the total healthcare cost for treating SBP was lower with the combination of antibiotics and albumin compared with antibiotics alone in Germany (antibiotics + albumin: €13,598 vs. antibiotics: €15,268) and Italy (€6,969 vs. €7,058).[8] Treatment with antibiotics plus albumin versus antibiotics alone resulted in lower mortality (22% vs. 41%) and increased QALYs gained (0.351 vs. 0.266) in all three countries.

In Spain, where pharmacy and medical complication costs were lower, treatment with albumin plus antibiotics led to slightly higher costs (€288 more) but the ICER values (€1,516 per life saved and €3,369 per QALY gained) remained within acceptable cost-effectiveness thresholds.[8] Notably, these findings aligned with a study applying a US payer model. Albumin plus antibiotics lowered total medical costs ($7,628 vs. $7,682), and the improved survival resulted in a higher QALY (2.45 vs. 1.48) in patients using albumin in the treatment of SBP. This further highlighted the clinical and economic benefits of albumin as a guideline-recommended treatment for SBP.[9]

HRS

HRS is a rapid, progressive functional renal failure that occurs in patients with advanced liver disease, with a dismal prognosis and a 50% survival rate at one month after diagnosis.[20]

Albumin in combination with terlipressin was more effective at a lower cost than either terlipressin alone, albumin plus norepinephrine, or norepinephrine alone in patients with HRS.[8] The total cost per patient, including country-specific pharmacy and inpatient medical costs for renal complications, favoured albumin plus a vasoconstrictor then a vasoconstrictor alone, across Germany (albumin + terlipressin: €12,488 vs. terlipressin: €7,697; albumin plus noradrenaline: €8,354 vs. noradrenaline:$10,076), Spain (€3,264 vs. €2,798; €2,870 vs. €3,123) and Italy (€3,454 vs. €4,657; €3,622 vs. €4,035) despite the relatively high cost of albumin in the study.[8] This was mainly due to lower rates of renal impairment. Albumin plus terlipressin provided more QALYs than terlipressin alone (0.439 vs. 0.093), while albumin plus noradrenaline resulted in more QALYs than noradrenaline alone (0.352 vs. 0.093).

Taken together, the lower total costs and improved clinical outcomes with the combination of albumin and

vasoconstrictors in managing patients with HRS support this regimen as the guideline-recommended treatment option for these patients.[9]

Cost-effectiveness in sepsis

Sepsis is a life-threatening condition caused by a dysregulated response to infection, which can lead to organ dysfunction and, if untreated, death.[21] In 2017, sepsis accounted for 48.9 million cases and 11 million deaths globally, representing 19.7% of all deaths worldwide. Sepsis is a leading cause of hospital mortality and represents a significant economic burden to healthcare systems. In the US alone, sepsis is the most common cause of in-hospital deaths and costs over US$24 billion annually.

As a treatment for patients with severe sepsis, albumin has been investigated in many clinical studies, including the large Saline vs. Albumin Fluid Evaluation (SAFE) and Albumin Italian Outcome Sepsis (ALBIOS) studies.

The prospective, randomised SAFE study included approximately 1,200 adult patients with severe sepsis admitted to the intensive care unit (ICU).[22,23] Half of these patients received 4% albumin as resuscitation fluid, and the other half received normal saline. The results showed that albumin was associated with a 13% lower risk of death during the 28-day study period compared with saline (unadjusted odds ratio (OR) 0.87).[22] After adjusting for baseline characteristics and potential confounders, the adjusted OR was 0.71 (p=0.03).[23] Notably, patients treated with albumin had a significantly lower heart rate on days 1 and 3, the greatest difference being on day 1 (95.2 beats per min (bpm) in the albumin group vs. 99.0 bpm in the saline group, p=0.002). Central venous pressure was highest on days 1–3, the biggest difference being observed on day 2 (albumin 12.8 mmHg vs. saline 11.1 mmHg, $p < 0.005$, $p<0.00$), indicating some haemodynamic benefits with albumin.

In the ALBIOS study, 1,818 adult patients with severe sepsis were randomly assigned to receive either 20% albumin and crystalloid solution or crystalloid solution alone.[24] Although no significant difference was reported in survival outcomes between the two treatment groups, patients receiving albumin experienced several clinical benefits during the first seven days of treatment. These included a significantly lower heart rate (on day 1: 94±21 bpm in the albumin group vs. 99±22 bpm in the crystalloid group, $p<0.001$), higher mean arterial pressure (after 6 hours of administration: 79 ±14 mmHg in the albumin group vs. 77 ±13 mmHg in the saline group, $p<0.001$), and a lower daily net fluid balance ($p<0.001$).[24] Despite these positive findings, the types of fluids used in sepsis for resuscitation are often governed by guidelines where cost is a consideration, particularly for albumin.[25]

Cost-effectiveness vs. hydroxyethyl starches and crystalloid

Hydroxyethyl starches (HES) have been used in various clinical settings for decades due to their lower cost. However, meta-analyses have suggested that HES products increase the risk of haemostatic and renal complications, prompting authorities in the US and Europe to restrict their use.[26] In contrast, several analyses have shown that albumin improves survival rates and reduces total medical costs in the treatment of sepsis compared with HES.

Due to the lack of large, high-quality, randomised trials directly comparing albumin and HES, several meta-analyses have been performed to indirectly compare these therapies by integrating available clinical data. One such study by Farrugia et al used a decision-analytic model to assess the cost-effectiveness of albumin versus HES for the treatment of sepsis.[25]

This study found that albumin was not only more effective, with higher survival rates, but also less costly per life year gained compared with HES. Albumin also proved more cost-effective when all the medical expenses associated with therapy-related adverse events were considered, such as renal replacement therapy. Albumin is associated with increased survival at lower costs compared to HES (life-years gained: 0.84 vs. -0.69, total medical cost: $20,403 vs. $48,488).[25] The authors concluded that simple per-unit cost assessments by hospitals are inadequate for decision-making in this context.

A follow-up study by the same group confirmed these findings.[26] This network meta-analysis used a model to compare the effects of crystalloid, albumin and HES solutions in severe septic patients from hospital admission to 90 days in ICU from a US payer perspective.

Albumin was more clinically effective than crystalloid, with a gain of 0.21 life years, representing an 11% increase in life expectancy relative to standard practice, as predicted by the model. Treatment with HES resulted in a loss of 0.85 life years compared with crystalloid. Although the total cost of crystalloid ($20,133) was slightly lower than albumin ($20,403), albumin showed the lowest cost per life year saved (albumin $9,253 vs. crystalloid $10,036 vs. HES $24,363).[26] Albumin was also more cost-effective than HES, which was associated with higher costs due to complications, particularly the need for renal replacement therapy. Albumin remained cost-effective in 56% of scenarios at a threshold of $10,000 per life year gained, followed by crystalloids with 40% of the iterations and HES in less than 5% of iterations.[26]

The cost-effectiveness of albumin versus crystalloid was also evaluated in the large COASST study, which included more than 11,000 patients with severe sepsis and septic shock admitted to the ICU in France.[1]

Based on data from the SAFE study,[22] this analysis modelled a 4.6% reduction in mortality in the albumin arm (during the 28-day study period), which resulted in 513 fewer deaths with albumin use compared with treatment without it.[1] Among these surviving patients, the difference in survival between →

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the albumin-treated and crystalloid-treated patients was 5,017 years in favour of albumin.

The authors calculated that with a mean cost of albumin of €218 per patient, there would be an additional cost of €3,097,200 if the entire population had been treated with albumin. The cost per life saved was estimated at €6,037, and the cost per life-year gained at €617.7. This analysis also revealed that the mortality rate was the primary cost driver. Overall, these findings suggest that albumin therapy for ICU patients with severe sepsis is cost-effective.

Cost-effectiveness in septic shock

Septic shock is a severe form of sepsis, characterised by profound circulatory, cellular and metabolic dysfunction, and is associated with a higher risk of mortality than sepsis alone.[27] According to current guidelines,[5,7] albumin is suggested for adults with sepsis or septic shock who have received large volumes of crystalloids over using crystalloids alone.

The efficacy of adding albumin to crystalloid was assessed in the ALBIOS trial, which included patients with septic shock and severe sepsis.[24] Although no overall mortality benefit was observed in the sepsis group, the septic shock group experienced a significant reduction of 13% in 90-day mortality (RR 0.87; p=0.003). Similarly, a meta-analysis of five clinical trials reported a significantly reduced 90-day mortality with albumin compared with crystalloid in septic shock patients (OR 0.81; p=0.03).[28]

Albumin may be considered costly, but research has shown that it is more cost-effective than crystalloid and HES when considering total medical costs and associated complications.[24,26,29] This was supported by the French EMAISS study, which compared 20% albumin plus crystalloid versus crystalloid alone in 6,406 septic shock patients using cost-effectiveness simulation.[29]

This study used a decision tree model to estimate ICU costs and health outcomes with albumin plus crystalloid versus crystalloid alone in patients with septic shock, from ICU admission and over a lifetime horizon. Based on the relative risk reduction of 0.87 from the ALBIOS study,[24] the addition of albumin led to a mean increase of 0.49 years in survival.[29] The incremental cost of albumin was €480, which resulted in an estimated cost per life-year gained of €974.[29] With willingness-to-pay thresholds of €20,000 or €30,000 per life-year saved, the probability of albumin being cost-effective was 95% or 97%.[29] These results confirmed that albumin is a cost-effective treatment option compared with crystalloid in patients with septic shock.

Conclusion

In summary, HA plays a crucial role in the clinical treatment of chronic and severe illnesses, including decompensated cirrhosis and severe sepsis. Decompensated cirrhosis is a significant global health problem, associated with poor outcomes and high healthcare costs. Studies from various countries show that despite its higher treatment cost, long-term albumin therapy leads to overall cost savings due to reduced complications, hospitalisations, and mortality rates. These findings support the use of albumin as a guideline-recommended treatment for SBP and HRS. Albumin is cost-effective in terms of lives saved and QALYs gained in managing decompensated cirrhosis associated with LVP, SBP or HRS.

Sepsis is a life-threatening condition caused by organ dysfunction, which accounts for millions of deaths worldwide each year. Albumin has been demonstrated as a more cost-effective treatment for severe sepsis and septic shock compared with alternatives such as HES.

Given the variability in cost data across countries, it is recommended that cost-effectiveness evaluations be conducted in Chinese healthcare settings. The results of cost-effectiveness analyses of HA in the treatment of decompensated cirrhosis and severe sepsis will provide evidence to support its rational clinical use in China. Furthermore, incorporating recommendations from relevant Chinese guidelines and conducting additional cost-effectiveness research will strengthen the evidence base for the optimal use of HA in these conditions.

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