Resuscitation fluids as drugs: targeting the endothelial glycocalyx

Guangjian Wang, Hongmin Zhang, Dawei Liu, Xiaoting Wang; Chinese Critical Ultrasound Study Group

Department of Critical Care Medicine, Peking Union Medical College Hospital, Peking Union Medical College & Chinese Academy of Medical Sciences, Beijing 100730, China.

Abstract

Fluid resuscitation is an essential intervention in critically ill patients, and its ultimate goal is to restore tissue perfusion. Critical illnesses are often accompanied by glycocalyx degradation caused by inflammatory reactions, hypoperfusion, shock, and so forth, leading to disturbed microcirculatory perfusion and organ dysfunction. Therefore, maintaining or even restoring the glycocalyx integrity may be of high priority in the therapeutic strategy. Like drugs, however, different resuscitation fluids may have beneficial or harmful effects on the integrity of the glycocalyx. The purpose of this article is to review the effects of different resuscitation fluids on the glycocalyx. Many animal studies have shown that normal saline might be associated with glycocalyx degradation, but clinical studies have not confirmed this finding. Hydroxyethyl starch (HES), rather than other synthetic colloids, may restore the glycocalyx. However, the use of HES also leads to serious adverse events such as acute kidney injury and bleeding tendencies. Some studies have suggested that albumin may restore the glycocalyx, whereas others have suggested that balanced crystalloids might aggravate glycocalyx degradation. Notably, most studies did not correct the effects of the infusion rate or fluid volume; therefore, the results of using balanced crystalloids remain unclear. Moreover, mainly animal studies have suggested that plasma may protect and restore glycocalyx integrity, and this still requires confirmation by high-quality clinical studies.

Keywords: Fluid resuscitation; Resuscitation fluid; Fluid therapy; Endothelial glycocalyx; Glycocalyx

Introduction

Clinicians have traditionally evaluated the hemodynamic state by macrovascular monitoring in critically ill patients.[1] However, macrovascular parameters cannot indicate what is occurring at the microvascular level under pathological conditions.[1,2] The degradation and shedding of the endothelial glycocalyx have been proposed as a mechanism that contributes to a poor prognosis in critically ill patients.[3] The endothelial glycocalyx is a layer that lines the luminal side of the endothelium and regulates vascular permeability, microcirculation perfusion, and leukocyte adhesion on the endothelium.[3] Shedding of the glycocalyx may result in local vasodilatation, thrombosis, and inflammation and is also thought to cause microcirculatory dysfunction in patients with sepsis.[4] Therefore, maintaining or even restoring the glycocalyx integrity may be a therapeutic strategy of high priority. Critical illnesses are often accompanied by glycocalyx degradation caused by an inflammatory reaction, hypoperfusion, shock, and so forth.[5] Fluid resuscitation is an essential clinical treatment strategy to improve tissue perfusion in critical illness,[6] and recent studies have shown that the type of resuscitation fluid used may significantly affect the glycocalyx integrity. Some resuscitation fluids can even restore the glycocalyx integrity and improve microcirculation perfusion.

Structure and Function of the Endothelial Glycocalyx

The endothelial glycocalyx is a 0.5- to 5.0-μm-thick gel-like layer lining the luminal side of the endothelium. It mainly consists of membrane-bound proteoglycans (PGs), glycoproteins, glycosaminoglycans (GAGs), and associated plasma proteins [Figure 1].[5] PGs contain many core proteins, such as perlecan, glypican, and syndecans (SDCs) (the most prominent component of PGs), and PGs can be connected by GAG side chains.[5] The GAG chains linked to PGs are the most common component in the glycocalyx and include heparan sulfate (HS), chondroitin sulfate (CS), hyaluronic acid (HA), dermatan sulfate, and possibly keratin sulfate.[3] In the standard vascular structure, the glycocalyx combines with plasma proteins (mainly albumin) to form the endothelial glycocalyx layer (EGL), maintaining the plasma composition and reducing exudation into the tissue spaces.

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Correspondence to: Prof. Xiaoting Wang, Department of Critical Care Medicine, Peking Union Medical College Hospital, Peking Union Medical College & Chinese Academy of Medical Sciences, 1# Shuai Fu Yuan, Dong Cheng District, Beijing 100730, China
E-Mail: icuting@163.com

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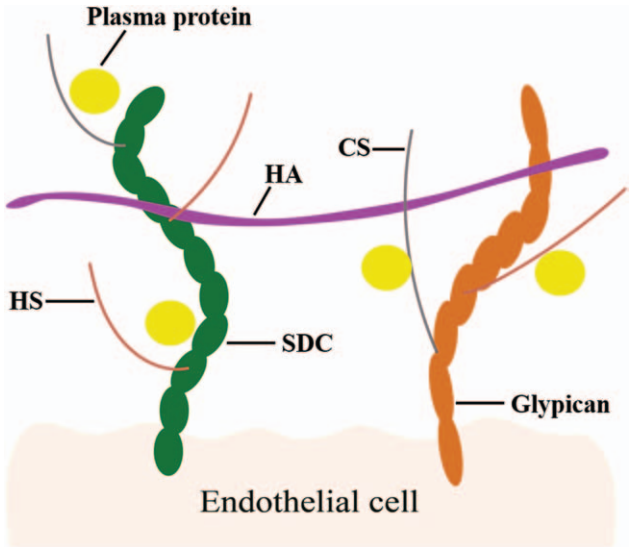

Figure 1: Structure of the endothelial glycocalyx. The endothelial glycocalyx mainly consists of PGs, GAGs, and plasma proteins. PGs mainly include glypican and SDCs. GAGs (including HS, CS, and HA) are linked to the PGs. CS: Chondroitin sulfate; GAG: Glycosaminoglycan; HA: Hyaluronic acid; HS: Heparan sulfate; PG: Proteoglycan; SDC: Syndecan.

As a critical structure of the EGL, the glycocalyx served as a barrier against vascular permeability and plays an essential role in avoiding interstitial edema caused by intravascular volume expansion during resuscitation.[3] Zhang *et al*[7] proposed that a vicious circle exists between endothelial glycocalyx impairment and endothelial cell dysfunction, which induces increased vascular permeability and thrombogenesis, mitochondriopathy and lysosomal dysfunction, microvascular rarefaction, impaired angiogenesis, and finally organ dysfunction. Therefore, the development and progression of many diseases, such as cardiovascular, renal, and metabolic diseases, are inextricably linked with the endothelial glycocalyx. The glycocalyx is also involved in several functions necessary for microcirculatory perfusion: (1) regulation of nitric oxide-mediated vasorelaxation through sensation and transmission of fluid shear force to endothelial cells, (2) provision of an anti-adhesive effect to protect endothelial cells from oxidative stress, and (3) provision of an anti-coagulant effect to inhibit microvascular thrombosis.[3] However, critical illnesses such as trauma, surgical ischemia, hemorrhagic shock, and sepsis often lead to inflammation, shock, and hypoperfusion, resulting in glycocalyx degradation,[8] and a high degree of degradation is associated with a poor prognosis in critically ill patients.[9] In addition, studies have shown that factors associated with intravenous fluid resuscitation, such as the volume of fluids administered and fluid overload, might affect the integrity of the endothelial glycocalyx.[10,11] In contrast, early restoration of the endothelial glycocalyx may improve the systemic inflammatory response, volume responsiveness, coagulopathy, and even prognosis of critically ill patients.[12]

Common Biomarkers of the Endothelial Glycocalyx

At present, the primary methods used to evaluate the glycocalyx integrity are direct bedside imaging techniques and the measurement of circulating biomarkers.[3] Orthogonal phase spectrometry and sidestream dark-field imaging are commonly used direct bedside imaging techniques that can be used to evaluate the glycocalyx integrity by measuring the sublingual microvascular thickness or perfusion boundary region.[13] However, the reliability of the measurement results and their relevance to the glycocalyx integrity remain questionable.[3] The most commonly used method for quantifying glycocalyx degradation in clinical practice is a measurement of the shedding glycocalyx components, such as SDC-1, HS, CS, and HA, in the plasma or serum of critically ill patients.[14] Among these components, SDC-1 is the most abundant PG, suggesting that the plasma concentration of SDC-1 may have a reasonably high correlation with glycocalyx degradation.[3] A systematic review conducted by Hahn *et al*[14] showed that SDC-1 was the most commonly used glycocalyx biomarker among 228 human studies, whereas HA, CS, SDC-4, and glypicans were rarely used. Rahbar *et al*[15] found that increased shedding of SDC-1 is associated with increased vascular endothelial permeability in trauma patients. Rodriguez *et al*[16] showed that an SDC-1 level of >40 ng/mL on admission is associated with significantly worse outcomes in trauma patients. Wu *et al*[17] proved that in the absence of SDC-1 synthesis, the effect of fresh frozen plasma (FFP) on improving pulmonary permeability disappeared in a mouse model of hemorrhagic shock. Together, these studies suggest that SDC-1 is a relatively well-recognized glycocalyx biomarker that may be used to guide therapy in clinical practice. However, caution is needed because these markers allow for only an indirect evaluation of glycocalyx degradation.

Common Factors of Fluid Resuscitation Affecting the Glycocalyx

The timing, volume, and rate of intravenous infusion as well as the type of resuscitation fluid selected may have different effects on the glycocalyx integrity. Hippensteel *et al*[10] found that a large fluid dosage during resuscitation increased the degree of glycocalyx degradation, confirming the observation in a preclinical study conducted by Byrne *et al*[18] that the intravenous fluid dosage was associated with glycocalyx degradation. Both studies suggested that the volume of resuscitation fluid may be independently associated with glycocalyx degradation. The release of atrial natriuretic peptide induced by hypervolemia may be an important cause of this phenomenon.[3] However, not all studies support this viewpoint.[19,20] Oscillatory shear stress caused by intravenous infusion may directly induce glycocalyx degradation,[10] indicating that the rate of intravenous infusion can also affect the glycocalyx integrity. However, recent studies showed no difference between intravenous infusion at a faster versus slower rate.[21,22] Furthermore, a clinical study conducted by Zampieri *et al*[23] showed that infusion at a slower rate did not reduce the 90-day mortality rate compared with an infusion at a faster rate. Few studies to date have focused on the timing of fluid resuscitation and glycocalyx degradation. Cooper and Silverstein[2] proposed that the timing of fluid resuscitation may also affect the microcirculation and glycocalyx integrity. Compared with early

fluid administration, intravenous infusion at a later stage may be harmful. In addition, more studies are now focusing on the effects of different types of resuscitation fluid on the glycocalyx integrity, which is an important part of our review.

Effects of Different Resuscitation Fluids on the Glycocalyx

Fluid resuscitation is a vital therapeutic strategy for critically ill patients, and the type of fluid used for resuscitation may significantly affect the glycocalyx integrity. Nevertheless, little attention has been paid to reducing glycocalyx degradation or restoring the glycocalyx integrity as the resuscitation target. Different fluid therapies may have different effects on the glycocalyx. In clinical practice, commonly used resuscitation fluids are divided into crystalloids and colloids.[24] Most crystalloids used in fluid resuscitation are isotonic solutions, including balanced crystalloids and normal saline (NS), whereas colloids include synthetic colloids (hydroxyethyl starch [HES], gelatin, and dextran) and natural colloids (albumin and plasma).[25]

Effects of NS and balanced crystalloids on the glycocalyx

Some studies have shown that resuscitation with a large amount of NS leads to hypernatremia, hyperchloric metabolic acidosis, and other complications such as renal function impairment.[26] The findings of several large unblinded, cluster-randomized, single-center trials have recently attracted much attention. Semler *et al*[27] showed that NS was associated with increased renal dysfunction and poorer outcomes than balanced crystalloids in critically ill adults. Self *et al*[28] found that NS was related to major adverse kidney events within 30 days in noncritically ill adults compared with balanced crystalloids. In contrast, Zampieri *et al*[29] found no significant difference between balanced crystalloids and NS in critically ill patients. Moreover, a trial conducted by Cheung-Flynn *et al*[30] showed that NS contributed to glycocalyx degradation in a pig model of a hemorrhagic shock compared with a balanced crystalloid (Plasma-Lyte). The same conclusion was reached in an *in vitro* study in which human endothelial cells were exposed to the cytokine tumor necrosis factor-α and then incubated with NS or a balanced crystalloid.[30] A preclinical study conducted by Byrne *et al*[18] suggested that NS resulted in the shedding of the glycocalyx in an ovine model of endotoxemia. Torres *et al*[31] found that NS was more closely associated with glycocalyx degradation than was lactated Ringer (LR) solution, 5% albumin, and FFP in a rat model of hemorrhagic shock, and this association may have been related to the loss of glycocalyx-adsorbed proteins and PGs. In addition, Martin *et al*[32] suggested that the glycocalyx degradation caused by NS may be due to hypernatremia. Thus, although NS is used worldwide, it may not be an ideal resuscitation fluid for restoring the glycocalyx.

Notably, studies have shown that compared with NS, resuscitation with balanced crystalloids reduces complications such as post-operative infection, acidosis, and acute kidney injury (AKI) after laparotomy.[33] Cheung-Flynn *et al*[30] and Torres *et al*[31] found that balanced crystalloids were superior to NS in reducing the shedding of the glycocalyx. Moreover, Ergin *et al*[34] and Guerci *et al*[35] showed that balanced crystalloids and NS were associated with glycocalyx degradation in animal studies. Unfortunately, these results may be affected by the volume or rate of intravenous infusion.[10] Overall, the effect of balanced crystalloids on the glycocalyx is not completely clear, and there is a lack of high-quality clinical studies in this regard.

Effect of synthetic colloids on the glycocalyx

Synthetic colloids usually include HES, gelatin, and dextran. Importantly, the guidelines do not recommend using synthetic colloids first for fluid resuscitation, especially HES,[6] possibly because synthetic colloids have several disadvantages. Resuscitation with HES can lead to AKI,[36] which may be related to the decreased glomerular filtration and interstitial inflammatory changes caused by the high oncotic pressure of HES.[37] HES is also associated with deterioration of coagulation function, which can be partially explained by hemodilution. Other mechanisms can also explain this deterioration of coagulation, such as detrimental influences of factor VIII, factor XIII, fibrinolysis, and von Willebrand factor.[38] Gelatin may cause allergic reactions, and large-scale randomized controlled trials proving its safety are lacking.[39] Dextran is rarely used for fluid resuscitation because of frequent adverse reactions such as coagulation dysfunction, renal function injury, and allergy.[39] However, Ergin *et al*[34] suggested that HES preserved the glycocalyx more effectively than balanced crystalloids in a rat model of acute normovolemic hemodilution. Zhao *et al*[40] confirmed that HES can protect the glycocalyx integrity and that this protective effect is associated with the down-regulated expression of heparinase, hyaluronidase, and neuraminidase. Li *et al*[41] speculated that 6% HES and albumin might protect the glycocalyx integrity in patients undergoing brain surgery, excluding the factor of fluid overload. Kaneko *et al*[42] also found that HES administration did not aggravate the glycocalyx degradation in patients undergoing abdominal surgery. Moreover, Smart *et al*[43] found that compared with fresh whole blood, fluid resuscitation with HES significantly decreased the plasma hyaluronan concentration 20 min after fluid administration in a canine model of hemorrhagic shock. In contrast, also compared with fresh whole blood, fluid resuscitation with 4% succinylated gelatin significantly increased the hyaluronan concentration 60 and 120 min after fluid administration. These findings suggest that fluid resuscitation with HES may have protective and restorative effects on the endothelial glycocalyx, whereas gelatin may lead to more severe shedding of the endothelial glycocalyx.[43] Nevertheless, as mentioned earlier, increasingly more studies are showing that HES can lead to serious adverse events such as AKI and coagulation deterioration, and this is leading to more limited use of HES for fluid resuscitation. Moreover, few trials have been performed to explore the effects of other synthetic colloids on the glycocalyx. Therefore, no clear conclusion can be drawn because of the limited evidence regarding the different effects of gelatin and dextran on the endothelial glycocalyx.[44]

Effect of albumin and balanced crystalloids on the glycocalyx

As the most widely used resuscitation fluids in clinical practice, albumin, and balanced crystalloids have been debated for decades. An early debate on whether to use balanced crystalloids or albumin for resuscitation can be traced back to 1998 when the Cochrane Injuries Group Albumin Reviewers published a meta-analysis.[45] They found that fluid resuscitation with albumin may increase mortality. However, the Saline versus Albumin Fluid Evaluation study of a heterogeneous population of patients in an intensive care unit refuted the above-mentioned conclusion. It indicated no significant difference in 28-day mortality between 4% albumin and NS for fluid resuscitation.[39] The Albumin Italian Outcome Sepsis (ALBIOS) study obtained the same results, producing no evidence that albumin is superior to balanced crystalloids.[39] These conflicting results have increased the difficulty of the debate between albumin and balanced crystalloids. As our understanding of the association between resuscitation fluid and the endothelial glycocalyx has deepened, further changes in this controversy have arisen.

In recent years, studies of the endothelial glycocalyx have made breakthroughs because of continuous innovations in staining techniques and observation methods.[46] The different effects of resuscitation fluids on the glycocalyx have gradually become important for comparing the advantages and disadvantages of albumin and balanced crystalloids. Unlike the unclear effects of balanced crystalloids on the glycocalyx, studies performed as early as 2014 have shown that a low plasma albumin concentration will lead to disruption and shedding of the endothelial glycocalyx, suggesting that albumin may play a crucial role in maintaining the structural integrity of the glycocalyx.[47] In addition, albumin is the main factor in maintaining the plasma colloid osmotic pressure and can regulate the inflammatory response and maintain the acid–base balance.[48] Many animal studies have demonstrated that albumin administration can restore the glycocalyx. Wong *et al*[49] established a mouse model and found that HES-containing solution damaged the endothelial and epithelial barriers whereas resuscitation with HES combined with albumin counteracted the adverse effects in the isolated perfused small intestine. These findings suggest that albumin may improve glycocalyx degradation. Notably, however, glycocalyx degradation is only one aspect of endothelial barrier damage. Such damage also involves many other mechanisms, such as damage to the endothelium, endothelial cell junctions, and basement membrane.[50,51] Damiani *et al*[52] found that infusion of 4% or 20% albumin restored microcirculation perfusion in a rat model of normotensive endotoxemia and that the effect of 20% albumin may be more stable. In a rat model of hemorrhagic shock, Torres *et al*[31] found that neither balanced crystalloids nor NS could restore the thickness of the EGL and that both significantly increased vascular permeability. In contrast, albumin partially restored the thickness of the EGL, decreased the plasma SDC-1 concentration to the baseline level, and improved vascular permeability. Smart *et al*[43] observed that fluid resuscitation with a large volume of crystalloids led to more significant shedding of the endothelial glycocalyx and a more severe inflammatory reaction than other fluids in a canine model of hemorrhagic shock.

Some clinical studies have also been conducted to explore the effect of albumin and balanced crystalloids on the glycocalyx. Li *et al*[41] suggested that albumin may protect the glycocalyx integrity in patients undergoing brain surgery. Suzuki and Koyama[53] found that 5% albumin could exert a protective effect on the glycocalyx integrity in patients undergoing hepatic or pancreatic surgery. A substudy of the ALBIOS study conducted by Piotti *et al*[54] showed that albumin administration was associated with a lower circulating concentration of vascular endothelial cadherin (endothelial cell junctions), suggesting that albumin may protect the EGL. A pilot study of patients with septic shock conducted by Hariri *et al*[55] showed that albumin infusion had beneficial effects on skin endothelial function and suggested that the antioxidant function of albumin may be the critical mechanism. Aldecoa *et al*[56] showed that albumin is an important transporter of sphingosine-1-phosphate, which plays a critical role in protecting the glycocalyx.

Nevertheless, some studies have led to different conclusions. For example, Pati *et al*[57] found that albumin had little effect on improving vascular permeability in a mouse model of vascular leakage. A clinical trial conducted by Yanase *et al*[58] suggested that albumin administration did not reduce the SDC-1 concentration on post-operative day one in patients undergoing abdominal surgery. Therefore, some clinicians have doubted the protective effect of albumin on the endothelial glycocalyx. In addition, because the volume of intravenous infusion also affects glycocalyx degradation (which may explain many of the above-mentioned study results), the effect of resuscitation with balanced crystalloids on the glycocalyx remains unclear. More rigorous studies are needed to elucidate the precise mechanism. At present, the guidelines still recommend crystalloids, mostly balanced crystalloids, as the first choice for fluid therapy in patients with sepsis and suggest using albumin combined with crystalloids only when patients require large amounts of crystalloids.[6]

Effect of plasma on the glycocalyx

Clinicians still reluctantly use plasma for fluid resuscitation because it often causes allergic transfusion reactions and other severe adverse events. Plasma administration is most commonly used in trauma patients and has improved the prognosis of such patients in multiple randomized controlled trials.[59] In addition, many animal trials have suggested that plasma can restore the endothelial glycocalyx. Nikolian *et al*[60] found that compared with NS, FFP improved the blood–brain barrier integrity by protecting the glycocalyx in a swine model of combined traumatic brain injury and hemorrhagic shock. Torres Filho *et al*[61] found that FFP more effectively restored the glycocalyx than did NS, balanced crystalloids, and albumin in a rat model. In a mouse model of hemorrhagic shock, Wu *et al*[17] found that FFP may restore the glycocalyx by promoting the synthesis of SDC-1 in a time- and dose-dependent manner. An animal study conducted by Vigiola

et al[62] showed that post-burn resuscitation with LR plus FFP improved vascular leakage in a rat model of large burns compared with LR only or LR plus albumin. A clinical study of critically ill patients showed that the concentration of SDC-1 significantly decreased after resuscitation with FFP, suggesting that FFP reduces the degree of shedding of the endothelial glycocalyx,[63] and this phenomenon may be associated with increased a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) and decreased large von Willebrand factor multimers. A single-center randomized controlled pilot trial is currently being conducted by Wei *et al*[64] to compare the effect of plasma versus balanced crystalloid resuscitation on the EGL in surgical and trauma patients with septic shock (NCT03366220); the results of this study are expected to be available soon.

Interestingly, not all plasma products have the same beneficial effects on the endothelial glycocalyx. Stensballe *et al*[65] found that compared with FFP, solvent-/detergent-treated pooled plasma (octaplasLG) reduced the severity of glycocalyx degradation in patients undergoing emergency surgery for thoracic aortic dissection. In contrast, Nelson *et al*[66] found that after correcting for the plasma volume difference caused by FFP, albumin, and Ringer acetate, there was no significant difference in the plasma concentrations of SDC-1 and HS. However, because of concerns about the severe adverse events of FFP, it is rarely used for fluid resuscitation. In addition, high-quality clinical studies regarding the protective effect of FFP on the endothelial glycocalyx are lacking.

Conclusion

Critical illnesses are often accompanied by glycocalyx degradation caused by an inflammatory reaction, hypoperfusion, and shock. This glycocalyx degradation may contribute to a poor prognosis in critically ill patients. Fluid resuscitation is an essential clinical therapeutic strategy to improve microcirculatory perfusion in patients with critical illness, and the type of fluid used may have beneficial or harmful effects on the endothelial glycocalyx. Many animal studies have shown that NS might be associated with glycocalyx degradation; however, clinical studies on this topic are lacking, preventing further confirmation. Recent studies have shown that HES may have a protective effect on the glycocalyx. However, clinicians must be aware that resuscitation with HES can lead to severe adverse events such as AKI and bleeding tendencies. Trials involving the effects of other synthetic colloids, such as gelatin and dextran, on the glycocalyx are

Table 1: Relevant studies of the effects of different fluids on the glycocalyx.

Experimental fluid	Study type	Author (year)	Control fluid	Effect
NS	Animal	Cheung-Flynn *et al* (2019)[30]	Balanced crystalloid	Harmful
NS	*In vitro*	Cheung-Flynn *et al* (2019)[30]	Balanced crystalloid	Harmful
NS	Animal	Byrne *et al* (2018)[18]	–	Harmful
NS	Animal	Torres *et al* (2017)[31]	LR, Albumin, FFP	Harmful
Balanced crystalloid	Animal	Ergin *et al* (2020)[34]	NS	Beneficial
Balanced crystalloid	Animal	Guerci *et al* (2019)[35]	NS	Harmful
HES	Animal	Zhao *et al* (2020)[40]	–	Beneficial
HES, albumin	Clinical	Li *et al* (2020)[41]	–	May be beneficial
HES	Clinical	Kaneko *et al* (2020)[42]	–	Uncertain
HES	Animal	Smart *et al* (2018)[43]	FWB	Beneficial
Gelatin	Animal	Smart *et al* (2018)[43]	FWB	Harmful
Isotonic crystalloids	Animal	Smart *et al* (2018)[43]	FWB	Harmful
Gelatin, dextran	–	Smart and Hughes (2021)[44]	–	Uncertain
HES	Animal	Wong *et al* (2016)[49]	–	Harmful
Albumin	Animal	Wong *et al* (2016)[49]	HES	Beneficial
20% Albumin	Animal	Damiani *et al* (2016)[52]	4% Albumin	More beneficial
NS, balanced crystalloid	Animal	Torres *et al* (2017)[31]	FFP, Albumin	Harmful
5% Albumin, HES	Clinical	Suzuki and Koyama (2020)[53]	–	Beneficial
Albumin	Clinical	Piotti *et al* (2021)[54]	–	Beneficial
Albumin	Clinical	Hariri *et al* (2018)[55]	–	Beneficial
Albumin	Animal, *In vitro*	Pati *et al* (2016)[57]	FFP	Little effect
Albumin	Clinical	Yanase *et al* (2021)[58]	–	No effect
FFP	Animal	Nikolian *et al* (2017)[60]	NS	Beneficial
FFP	Animal, *In vitro*	Wu *et al* (2017)[17]	–	Beneficial
LR plus FFP	Animal	Vigiola *et al* (2019)[62]	LR, LR plus albumin	Beneficial
FFP	Clinical	Straat *et al* (2015)[63]	–	Beneficial
Plasma	Clinical	Wei *et al* (2018)[64]	Balanced crystalloids	Uncompleted
OctaplasLG	Clinical	Stensballe *et al* (2018)[65]	FFP	More beneficial
FFP	Animal	Nelson *et al* (2016)[66]	Albumin, RA	No difference

FFP: Fresh frozen plasma; FWB: Fresh whole blood; HES: Hydroxyethyl starch; LR: Lactated Ringer solution; NS: Normal saline; OctaplasLG: Solvent-/detergent-treated pooled plasma; RA: Ringer acetate; -: Not available.

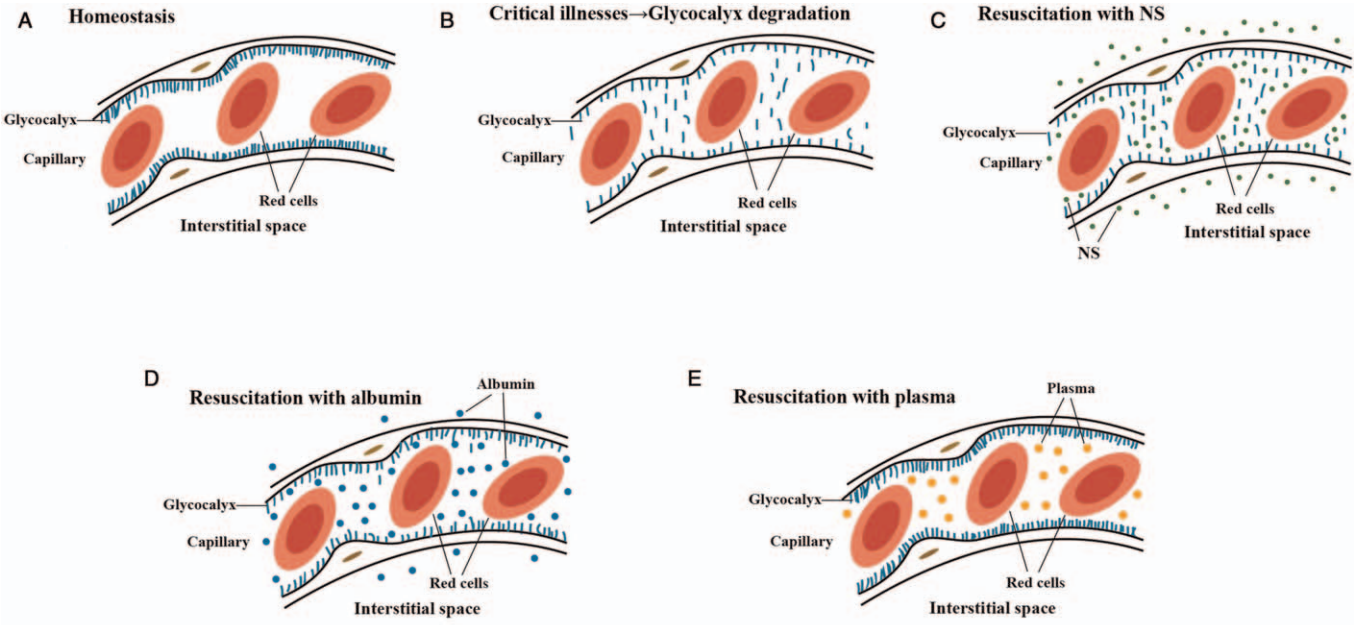

Figure 2: Effects of different resuscitation fluids on the endothelial glycocalyx. (A) The endothelial glycocalyx under homeostasis. (B) Critical illness causes glycocalyx degradation. (C) NS fails to restore the glycocalyx and instead increases exudation into the tissue spaces. (D) Albumin may restore the glycocalyx and reduce exudation into the tissue spaces. (E) Plasma can restore the endothelial glycocalyx. NS: Normal saline.

lacking. As a natural colloid, albumin is closely related to the protection and restoration of the glycocalyx integrity. Although some studies have suggested that balanced crystalloids might aggravate glycocalyx degradation, most studies did not correct for the effects of the infusion rate or infusion volume; therefore, the effects of balanced crystalloids remain unclear. Many animal studies have shown that plasma might protect and restore the glycocalyx, and this requires confirmation by high-quality clinical studies [Table 1 and Figure 2]. As a critical structure for regulating microcirculatory perfusion, the endothelial glycocalyx is also expected to become a new evaluation index and therapeutic target in the future, potentially leading to new changes in fluid therapy strategies.

Conflicts of interest

None.

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