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SYSTEMATIC REVIEW

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Accumulation of hydroxyethyl starch in human and animal tissues: a systematic review

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Abstract *Purpose:* To systematically review clinical and preclinical data on hydroxyethyl starch (HES) tissue storage. *Methods:* MEDLINE (PubMed) was searched and abstracts were screened using defined criteria to identify articles containing original data on HES tissue accumulation. *Results:* Forty-eight studies were included: 37 human studies with a total of 635 patients and 11 animal studies. The most frequent indication for fluid infusion was surgery accounting for 282 patients (45.9 %). HES localization in skin was shown by 17 studies, in kidney by 12, in liver by 8, and in bone marrow by 5. Additional sites of HES deposition were lymph nodes, spleen, lung, pancreas, intestine, muscle, trophoblast, and placental stroma. Among major organs the highest measured tissue concentration of HES was in the kidney. HES uptake into intracellular vacuoles was observed by 30 min after infusion. Storage was cumulative, increasing in proportion to dose, although in 15 % of patients storage and associated symptoms were demonstrated at the lowest cumulative doses (0.4 g kg^{-1}). Some HES deposits were extremely long-lasting, persisting for 8 years or more in skin and 10 years in kidney. Pruritus associated with HES storage was described in 17 studies and renal dysfunction in ten studies. In one included randomized trial, HES infusion produced osmotic nephrosis-like lesions indicative of HES storage ($p = 0.01$) and also increased the need for renal replacement therapy (odds ratio, 9.50; 95 % confidence interval, 1.09–82.7; $p = 0.02$). The tissue distribution of HES was generally similar in animals and humans. *Conclusions:* Tissue storage of HES is widespread, rapid, cumulative, frequently long-lasting, and potentially harmful.

Keywords Hydroxyethyl starch · Hetastarch · Storage · Accumulation · Uptake · Deposit

Introduction

The artificial colloid hydroxyethyl starch (HES) is administered intravenously to treat or prevent hypovolemia. While circulating in the plasma, HES exerts colloid osmotic pressure that causes water to remain in or to be drawn into the plasma to increase blood volume. Since its introduction in the 1970s, several HES products, differing in physicochemical properties such as molecular weight and degree and pattern of hydroxyethylation, i.e., substitution, have been used clinically. HES products are plant-derived polymers of glucose that have been chemically modified to resist degradation.

After infusion, HES exits the plasma over a matter of hours to days, depending upon its physicochemical properties. HES is either excreted in the urine or taken up

in tissues. In a recent meta-analysis we concluded that 26–42 % of HES may reside in human tissue at 24 h after infusion [1]. However, that meta-analysis dealt with whole-body tissue uptake derived from plasma persistence and urinary excretion data rather than direct observations of storage in biopsy or necropsy specimens.

Despite the widespread and long-standing use of HES for clinical fluid management, tissue uptake and storage of this artificial colloid remain poorly appreciated in humans and important questions remain unanswered. Evidence on its distribution in tissues and organs has not been systematically reviewed. The timing, dose-dependency, persistence, and functional consequences of HES tissue storage also remain unclear. We here present the first systematic review to address those questions.

Materials and methods

Search strategy

Published evidence, including clinical and preclinical data, on tissue deposition of HES was sourced from MEDLINE (PubMed). A search phrase was devised containing various terms related to HES and tissue accumulation (Table 1 in the Electronic Supplementary Material). In vitro studies, opinion-based articles (e.g., commentaries and editorials), and narrative, non-systematic reviews were not included in the search criteria. Letters were provisionally included as they might contain original data.

Selection of studies

The titles and abstracts of all articles retrieved by the search were assessed by CJW and MJ (without blinding to journal and authors) to identify relevant articles. Relevance was defined using the eligibility criteria as listed in Table 2 in the Electronic Supplementary Material. Relevant articles essentially comprised any studies appearing to report original data on whether or not HES was present in cells and tissues of humans or animals. Inclusion of studies was not restricted by any methodological criteria or language of reporting. Articles were excluded if they reported accumulation of HES in the serum/plasma only (e.g., pharmacokinetics studies) or if they reported effects of HES only on cell/tissue activation, function, adhesion, etc., with no indication in the title or abstract that data specifically on HES accumulation were also presented. In cases of uncertainty, the article was retained for full-text analysis. Any articles meeting exclusion criteria during full-text analysis were rejected from the evidence base. Reference lists were screened to identify studies not captured in the initial search.

Data extraction and assessment

For all articles that met the eligibility criteria, the full texts were examined and the following characteristics were extracted: type of study, study population/setting, protocol details, objectives, primary and comparator interventions (HES type, controls), results (histological findings, HES concentrations in organs, etc.), conclusions, and limitations. At this point, articles duplicating findings already reported elsewhere in the evidence base were removed. Study quality was assessed on the basis of investigational design, the use of specific methods for localizing or quantifying HES in tissues such as immunoelectron microscopy, immunohistochemistry, or enzymatic assays of tissue extracts, and supplementary evidence supporting the specificity of the observed HES storage.

Results

Search results

Our search yielded 700 records, of which 654 were excluded because they did not meet the inclusion criteria or matched at least one exclusion criterion. Forty-six full-text articles were then examined, including 12 identified from reference lists. A further ten articles were excluded because they did not contain original data on accumulation of HES, were performed in vitro, consisted of opinion-based commentaries, or were confounded by co-administration of dextran or cyclosporin A. Figure 1 shows the flow of information through the different phases of the systematic literature review, culminating in the selection of 48 articles on HES accumulation for inclusion in this review [2–49]. Those papers, which provided the evidence base for this review, described 37 human (Table 1) and 11 animal (Table 3 in the Electronic Supplementary Material) studies.

Human studies

With a combined total of 615 patients, the included human studies comprised two randomized controlled trials, six nonrandomized controlled studies, seven observational studies, and 22 case reports (Table 1). One nonrandomized controlled study encompassing both patients and a control group of six healthy volunteers was described in three publications [29, 50, 51]. Another nonrandomized controlled study [35] included a patient who had been the subject of a prior separate case report [52].

By far the most common indication for fluid infusion was surgery, including transplant procedures, which

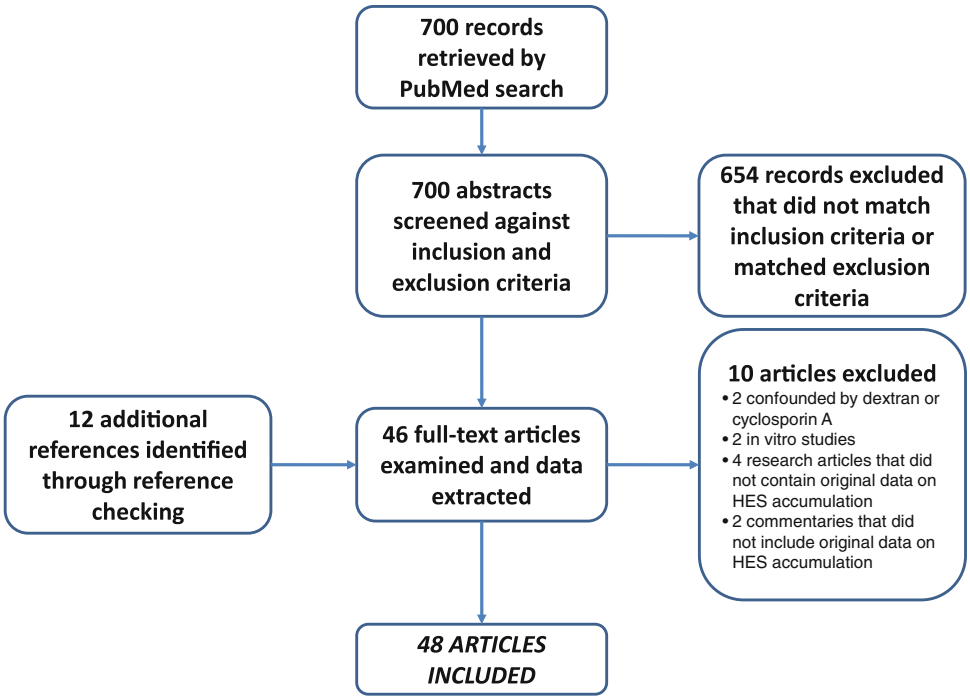

Fig. 1 Process of study selection

accounted for 282 patients (45.9 %) in 17 studies. The second most frequent was otologic disorder, composing 131 patients (21.3 %) in ten studies. Other indications investigated in multiple studies were trauma, plasma exchange, and dialysis (Table 1).

HES 70/0.5 was evaluated in 5 studies, HES 130/0.4 in 3, HES 200/0.5 in 14, HES 200/0.62 in 6, and HES 450/0.7 in 12. The type of HES solution was unspecified for eight studies. Investigated HES concentrations were 6 % in 20 studies, 10 % in 9, and unspecified in 13.

In seven studies the *cumulative* HES dose administered was below 1.2 g kg^{-1} and in ten studies below 2.0 g kg^{-1}. By comparison, the recommended *daily* maximum doses for HES 450/0.7, 200/0.5, and HES 130/0.4 are 1.2, 2.0, and 3.0 g kg^{-1}, respectively. Cumulative HES dose ranged from 2.0 to 10.0 g kg^{-1} in 16 studies and between 10.0 and 20.0 g kg^{-1} in five studies. Higher cumulative doses were administered in three studies: a nonrandomized controlled study of 16 plasmapheresis patients (30.2 g kg^{-1}) [35], an observational study of nine patients with liver dysfunction (30.5 g kg^{-1}) [27], and a plasma exchange patient (82.3 g kg^{-1}) [9].

Tissue localization of HES was assessed by light microscopy in 11 studies [10, 18, 20, 27, 33, 36, 37, 40, 42, 46, 48], electron microscopy in 3 [28, 32, 49], and both in 14 [4–7, 12, 14, 16, 17, 21, 23, 39, 41, 44, 47]. Specific anti-HES antibodies were employed in five studies for immunoelectron microscopy [14, 24, 26, 29, 35], as well as immunohistochemistry in two of those studies [14, 26]. Tissue HES was quantitated in biopsy or necropsy specimens by isolation, acid hydrolysis, and enzymatic assay in two studies [5, 25].

Immunoelectron microscopy, immunohistochemistry, and enzymatic assay of tissue extracts provide definitive evidence of HES storage. Other methods are potentially less specific. Therefore, in a number of included studies supplementary evidence was presented supporting the conclusion that the observed storage was indeed of HES. This evidence included lack of exposure to other colloids, heterologous blood products, radiocontrast agents, and drugs or of coexisting medical conditions that might mimic HES storage; the absence of storage in specimens secured prior to HES infusion or from control subjects unexposed to HES; the observation of a dose–response relationship between administered HES and observed storage; and the ability to discriminate morphologically between HES-laden vacuoles and those containing other materials [4, 7, 10, 20, 23, 27–29, 36, 37, 44, 46, 48].

Localization of HES in skin was demonstrated by 17 studies, in kidney by 12, in liver by 8, and in bone marrow by 5 (Table 1). Other sites of HES deposition were lymph nodes, spleen, lung, pancreas, intestine, muscle, trophoblast, and placental stroma. The highest concentration was found in kidney.

HES uptake into tissue was very rapid. Intracellular vacuoles were localized in Kupffer cells of the liver within 30 min after intraoperative infusion of 1.0 g kg^{-1} HES 450/0.7 [4]. Immunoelectron microscopy revealed HES-laden intracytoplasmic vacuoles in skin within 90 min after a single 0.4 g kg^{-1} infusion [29].

Table 1 Human studies of HES storage

Reference	*n*	Design	Indication	Solution	Dose[a]	Tissue distribution	Outcome
Jesch et al. [4]	12	OS	Surgery	6 % HES 450/0.7	1.0	Hepatic parenchymal, Kupffer and small bile duct cells, and interstitial histiocytes	–
Pfeifer et al. [5]	3	CR	Dialysis	6 % HES 70/0.5	6.8	Hepatic sinusoidal lining cells, hepatocytes, bile duct epithelia, endothelial cells, and fibroblasts in portal tracts; 44 mg/g HES measured biochemically in liver of one patient, and storage vacuoles occupied 40–45 % of entire tissue volume in that patient	Development of ascites
Dienes et al. [6]	2	CR	Dialysis	HES 200/0.5	10.4	Massive storage in all types of liver cells with morphologic resemblance to storage disease	Development of ascites with fatal outcome
Sirtl et al. [7]	11	NCS	Surgery	10 % HES 200/0.5 or 6 % HES 450/0.7	1.0	Kupffer and liver parenchymal cells and histiocytes; lymph nodes; skeletal muscle histiocytes and capillary endothelium; skin macrophages; bone marrow histiocytes; no differences between HES 200/0.5 and HES 450/0.7	–
Burgstaler and Pineda [9]	1	CR	Plasma exchange	HES 450/0.7	82.3	Lipid-laden macrophages in bone marrow	Anemia
Heilmann et al. [10]	60	RCT	IUGR or gestational hypertension	10 % HES 200/0.5	9.3	Grade I (light), II (moderate), or III (heavy) HES storage vacuoles in trophoblast among 59.3 % of patients; placental stroma among 45.8 %	Prolonged severe uterine bleeding in 17 % of patients
Gall et al. [12]	3	CR	Otologic disorder	6 % HES 70/0.5 or 6 % or 10 % HES 200/0.5	5.9	Dermal macrophages and endothelial cells and cutaneous nerve fibers	Pruritus
Jurecka et al. [14]	7	CR	Otologic or neurological disorder	HES 200/0.5 or HES 200/0.62	4.2	Skin of all patients, mainly in macrophages, blood, and lymph vessel endothelial cells, perineural cells, endoneural macrophages of larger nerve tracts, keratinocytes, and Langerhans cells	Pruritus
Legendre et al. [15]	90	NCS	Kidney transplantation	HES	–	Osmotic nephrosis-like lesions in 80 % of HES group vs 14 % of control group ($p < 0.01$)	Graft loss in 7 of 31 patients with osmotic nephrosis-like lesions vs zero of 55 patients without ($p < 0.001$)
Szeimies et al. [16]	1	CR	Otologic disorder	HES 200/0.5	3.6	Dermal macrophages and endothelial and perineural cells	Pruritus
Leunig et al. [17]	1	CR	Otologic disorder	10 % HES 200/0.5	8.6	Dermal macrophages	Pruritus
Cittanova et al. [18]	52	RCT	Kidney transplantation	6 % HES 200/0.62	1.8	Osmotic nephrosis of proximal and distal tubules in 3/3 HES recipients biopsied vs 0/6 control patients ($p = 0.01$)	Need for RRT in 33 % of HES group vs 5 % of control group ($p = 0.029$)

Table 1 continued

Reference	*n*	Design	Indication	Solution	Dose[a]	Tissue distribution	Outcome
Coronel et al. [19]	24	NCS	Kidney transplantation	HES	1.4	Osmotic nephrosis in 4/16 HES recipients vs 2/8 control patients	Urinary output 52.3 % lower in HES group ($p = 0.075$)
Cox and Popple [20]	1	CR	Surgery	6 % HES 450/0.7	6.5	Dermal macrophages	Pruritus, erythema, eyelid edema
Gall et al. [21]	10	OS	Otologic disorder	6 % HES 70/0.5 or 6 % or 10 % HES 200/0.5	5.6	Dermal endothelial cells and perivascular macrophages	Pruritus
Speight et al. [23]	3	CR	Surgery	6 % HES 450/0.7	0.7	Dermal edema, vessel dilatation, and increase in mast cell number; vacuolated macrophages around vessels and nerves throughout dermis	Pruritus
Kiehl et al. [24]	1	CR	Otologic disorder	HES 450/0.7	7.5	Periocular histiocytes, endothelial cells, basal keratinocytes, and small nerves	Periocular edema and pruritus
Lukasewitz et al. [25]	12	OS	ARDS	10 % HES 200/0.5	13.5	Kidney, spleen, lymph nodes, lung, liver, pancreas, and intestine	Multiorgan failure and death
Sirtl et al. [26]	26	NCS	Surgery, vascular disease, or chronic leg ulcer	HES 200/0.5, HES 200/0.62, and HES 450/0.7	3.5	Liver parenchymal or sinusoidal spindle-shaped cells, muscle interstitial histiocytes and macrophages, spleen reticular cells, intestine vascular endothelial cells and stromal macrophages, skin vascular endothelial cells and macrophages, perineural cells, endoneural connective tissue cells and Langerhans cells	Severe pruritus in 9/10 patients receiving >2 g kg^{-1} HES
Christidis et al. [27]	9	OS	Plasma exchange, paracentesis, or dialysis	6 % HES 200/0.62	30.5	Vacuolization of Kupffer cells in all patients and hepatocytes in 7/9; osmotic nephrosis in 2 patients with renal biopsies	Worsening of hepatic dysfunction with fatal outcome in 8/9 cases; development or worsening of renal dysfunction in 2 patients
de Labarthe et al. [28]	1	CR	Surgery	HES	0.5	Osmotic nephrosis-like lesions in proximal tubules	Oliguric acute kidney injury
Ständer et al. [29]	147	NCS	Otologic disorder, surgery, and other	HES 70/0.5, HES 200/0.62, or HES 450/0.7	5.2	Vacuolization of perivascular histiocytes in all skin biopsies; HES storage also observed in blood and lymphatic vessel endothelial cells, basal keratinocytes, epidermal Langerhans cells, and sweat gland epithelia	Pruritus in 39.5 % of patients exposed to HES
Weisshaar et al. [32]	1	CR	Trauma	HES	1.3	Dermal macrophages, blood vessel endothelial cells, nonmyelinated nerve cells, and Schwann cells	Severe persistent pruritus
Pillebout et al. [33]	26	OS	Orthotopic liver transplantation	6 % HES 200/0.62	$\leq$1.6	Osmotic nephrosis-like lesions in 61.5 % of patients	–
Ständer et al. [34]	1	CR	Trauma	HES	18.0	HES storage vacuoles in cutaneous macrophages, endothelial cells, and Schwann cells	Severe pruritus

Table 1 continued

Reference	*n*	Design	Indication	Solution	Dose[a]	Tissue distribution	Outcome
Auwerda et al. [35]	16	NCS	Plasmapheresis	6 % HES 200/0.5	30.2	Foam cells in bone marrow aspirates of all 5 HES recipients tested	Acquired lysosomal storage disease in 1 patient after 116 g/kg HES
Ebcioglu et al. [36]	1	CR	Kidney transplantation	6 % HES 450/0.7 in lactated electrolyte	1.1	Osmotic nephrosis-like lesions of proximal tubular epithelial cells	Delayed graft function
Schmidt-Hieber et al. [37]	1	CR	Trauma	6 % HES 130/0.4 and 6 and 10 % HES 200/0.5	17.1	Severe hyperplasia and hypertrophy of foamy portal macrophages and Kupffer cells and hepatocyte swelling; heavy infiltration of foamy cell degenerated macrophages throughout bone marrow accounting for 50 % of nucleated cells	Persistent thrombocytopenia and liver dysfunction with fatal outcome
Kamann et al. [39]	21	OS	Otologic, circulatory, and unspecified disorder	6 % and 10 % HES	4.3	Dermal macrophages, endothelium, and nerve cells	Pruritus
Chappell et al. [40]	1	CR	Otologic disorder	6 % HES 450/0.7	12.4	Bone marrow histiocytes	Subdural hematoma, bone marrow suppression, and pruritus
Haught et al. [41]	1	CR	Surgery	6 % HES	–	Dermal macrophages	Severe pruritus
Jamal et al. [42]	1	CR	Surgery	10 % HES 200/0.5	9.2	Renal tubular cells	Chronic renal failure
Hagne et al. [44]	1	CR	Sepsis	6 % HES 130/0.4	4.9	Proximal tubular epithelial cells	Severe renal insufficiency persisting ≥3 years
Zhao et al. [46]	1	CR	Hypovolemia	6 % HES	3.5	Severe inflammatory cell infiltrate in renal biopsy	Acute kidney injury
Aneja et al. [47]	1	CR	Surgery	6 % HES 450/0.7 in lactated electrolyte	0.5	Dermal macrophages	Pruritus
Kumar and Suneja [48]	1	CR	Surgery	6 % HES 450/0.7	0.7	Proximal tubular epithelial cells	Acute kidney injury
Ständer et al. [49]	70	OS	Otologic disorder, surgery, trauma, and other	HES 70/0.5, HES 130/0.4, and HES 200/0.5	4.3	Dermal macrophages in all patients and endothelial and/or nerve cells in 41 %	Severe pruritus

ARDS acute respiratory distress syndrome, *CR* case report, *HES* hydroxyethyl starch, *IUGR* intrauterine growth retardation, *NCS* nonrandomized controlled study, *OS* observational study, *RCT* randomized controlled trial, *RRT* renal replacement therapy

[a] Mean or individual patient cumulative dose (g kg^{-1})

HES tissue uptake was also cumulative, in that more extensive vacuolization was observed at higher cumulative doses (Fig. 2). For instance, light or moderate dermal HES deposits were found in 75 % of surgical patients receiving mean 0.8 g kg^{-1} HES, whereas storage was moderate or heavy in all ten patients of another group with vascular disease or chronic leg ulcer receiving a mean of 7.8 g kg^{-1} [26]. Nevertheless, HES storage and its sequelae often ensue after the lowest doses. In one study 15 % of patients displayed electron microscopy-proven dermal HES deposits and developed pruritus after receiving only 0.4 g kg^{-1} HES cumulatively [49].

Some HES deposits proved to be extremely long-lasting. Persistence in skin for longer than 4 years was documented by immunoelectron microscopy in two studies [26, 29]. In another study skin persistence for 8 years or more was shown by electron microscopy [39]. One patient suffered pruritus and disfiguring periocular edema with immunoelectron microscopy-proven HES deposition in periocular histiocytes, endothelial cells, basal keratinocytes, and small nerves [24]. There was no evidence that the deposits had subsided between 28 and 42 months after HES exposure, and the periocular edema had not resolved after 4.5 years. In a study of 26 orthotopic liver transplantation patients, osmotic nephrosis-like lesions remained on average at least 6.4 years after HES exposure up to a maximum of 10 years [33].

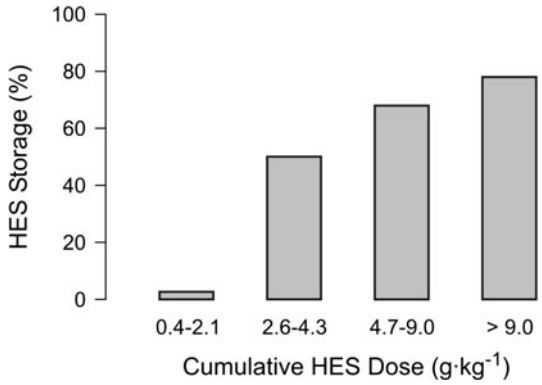

Fig. 2 Percentages of patients with moderate to heavy vacuolization of dermal histiocytes as a function of cumulative HES dose in a study of 115 patients receiving assorted HES solutions for otologic disorder, surgery, and other indications [29]. *HES* hydroxyethyl starch

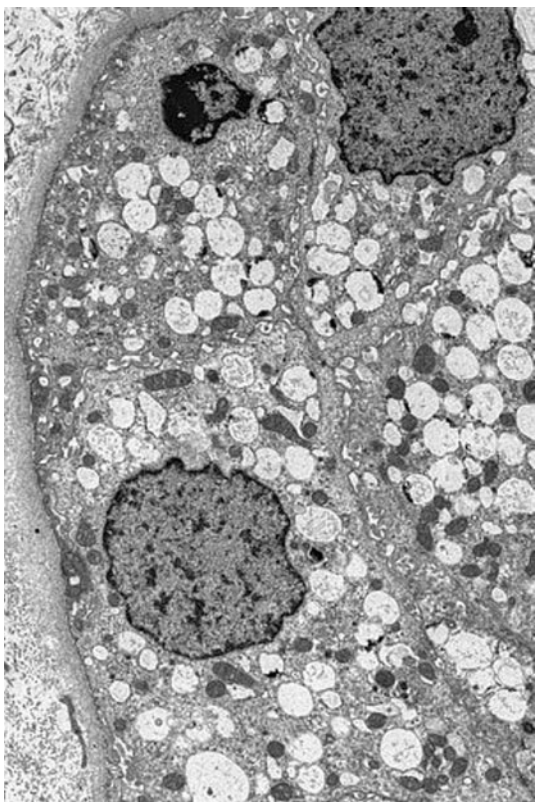

Fig. 3 Electron micrograph of osmotic nephrosis persisting 6 months after the development of acute kidney injury in a patient with septic shock who had received 6 % HES 130/0.4 at a cumulative dose of 4.9 g kg^{-1} [44]. Severe renal insufficiency continued ≥3 years after HES 130/0.4 exposure. *HES* hydroxyethyl starch

The most frequently encountered adverse event associated with HES storage was pruritus, which was reported in 17 studies (Table 1). Renal dysfunction was another common associated outcome, documented in ten studies (Table 1). Striking evidence of the association between HES storage in the kidney and poor renal outcomes was furnished by a randomized trial of 52 kidney transplant patients [18]. In that trial HES 200/0.62 increased the odds of needing renal replacement therapy nearly tenfold. All biopsied patients of the HES 200/0.62 group exhibited osmotic nephrosis, whereas none of those in the control group did. In some instances the renal dysfunction proved irreversible. Thus, chronic renal failure after HES exposure was reported in a patient with septic shock (Fig. 3) and a surgical patient [42]. Other reported poor outcomes associated with HES storage were liver dysfunction and bone marrow suppression (Table 1; Fig. 4).

Animal studies

Results of the included animal studies are summarized in Table 3 in the Electronic Supplementary Material. HES was generally localized in the same tissue types as humans although bone marrow deposition was not documented.

Discussion

This review of biopsy- or necropsy-proven cellular uptake of HES in humans demonstrates that after infusion HES is rapidly taken up by a wide spectrum of cells throughout the body. The review also documents that the accumulation of HES in cells and tissue is accompanied by serious complications such as renal, liver, and bone marrow failure and pruritus. Cellular HES accumulation was shown across a wide range of clinical indications and doses. Surgery patients comprised the largest group with demonstrated HES deposits. Cellular uptake can occur within minutes of exposure to HES, and repeated dose of HES can lead to increased accumulation. While the HES deposits may eventually disappear in some cases, they can persist for years in others.

Evaluation of semi-thin sections by light microscopy by multiple raters and assessment of inter-rater concordance were implemented in one included study [10]. However, reliance on multiple raters and blinding of the raters were not described in other studies. This is a limitation of the systematic review. The lack of pre-published study protocols was another limitation.

Because HES is a chemically altered plant-derived substance recognized by the body as foreign, phagocytic cells of the immune system avidly ingest it. HES has been identified not only in the circulating plasma macrophages and monocytes, but also in the tissue-resident macrophages, such as histiocytes in the skin, muscle, and bone marrow and Kupffer cells in the liver (Table 1). Moreover, HES has also been shown to be taken up by

epithelial and mesenchymal cells, such as keratinocytes, liver parenchyma cells, striated muscle cells, and peripheral nerve Schwann cells. There have been many reports of its presence in vascular endothelial cells (Table 1). This cellular uptake can lead to tissue accumulation and possible organ dysfunction.

The presence of HES in cells becomes problematic because it cannot be readily metabolized. The immune cells take up HES by phagocytosis and the other cell types are believed to ingest HES by pinocytosis. Both phagocytosis and pinocytosis are a form of endocytosis, a process of cellular ingestion by which the plasma membrane folds inward and pinches off to bring substances into the cells. These endosomes evolve and fuse to form lysosomes, specialized vesicles that contain digestive enzymes. In the plasma, HES can be metabolized by α-amylase. However, that enzyme is not present in cellular lysosomes. Acid α-glucosidase is the lysosomal enzyme that primarily breaks down starch and disaccharides to glucose. The processing of HES in lysosomes remains totally uncharacterized. The extent to which acid α-glucosidase can process HES remains unknown, but the long-lasting accumulation of HES in various cell types would indicate that it is very inefficient at best perhaps in part because HES has been chemically altered to be resistant to degradation. There have been no reports of acid α-glucosidase's ability to metabolize HES.

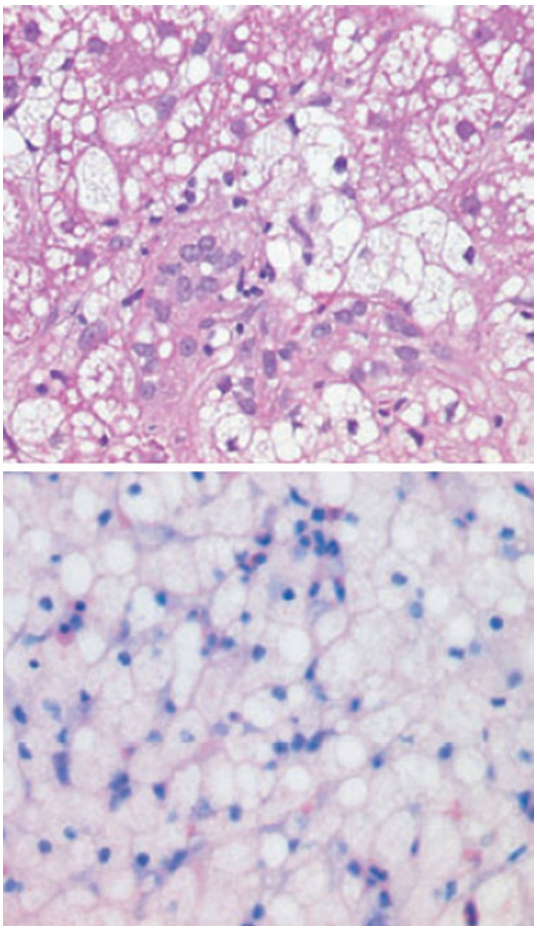

Fig. 4 Severe hyperplasia and hypertrophy of foamy portal macrophages and Kupffer cells and swelling of hepatocytes (*top*) and heavy infiltration of bone marrow with foamy cell degenerated macrophages, which accounted for approximately 50 % of nucleated cells, and marked depletion of fat cells (*bottom*) in a trauma patient who developed persistent thrombocytopenia and liver dysfunction and died after a 17.1 g kg^{-1} cumulative dose of 6 % HES 130/0.4 and 6 and 10 % HES 200/0.5 [37]. *HES* hydroxyethyl starch

The impact of storage in lysosomes can be amplified by the osmotic properties of HES. The HES molecules can create an oncotic gradient, leading to the accumulation of intracellular water, cytoplasmic swelling, lysosomal vacuolization, and disruption of cellular integrity. The osmotic nephrosis associated with HES use illustrates this phenomenon (Figs. 3, 4). The characteristic histological appearance is that of HES arrayed around the margins of the vacuole with an empty center that is believed to be aqueous. Large doses of HES can result in so much uptake by macrophages that they become "foamy", with resemblance to lysosomal storage disease [35].

Pruritus caused by storage of HES in the skin is the most studied and well-documented HES accumulation-related adverse event in part because of the relative ease in obtaining biopsies [53]. The pruritus associated with HES administration is typically severe, protracted, and refractory to treatment; it can last for years. It most often presents as a generalized pruritus without visible skin lesions weeks after exposure to HES. In a systematic review of 18 clinical studies with 3,239 total patients, pruritus was found to be frequent after routine doses in common clinical indications, with incidence rates of 13–34 % in the intensive care unit, 22 % in cardiac surgery, and 3–54 % in stroke [53]. Moreover, the reported prevalence of HES-induced pruritus is likely an underestimate because of the delayed onset of itching and failure to consider the diagnosis [47]. No effect of HES molecular weight or substitution on the occurrence of pruritus was apparent [53].

In one included study of 70 patients with electron microscopy-proven HES deposits 80 % of patients had severe or very severe pruritus, with a median latency between HES exposure and pruritus onset of 3 weeks and a median pruritus duration of 6 months [49]. Although the median cumulative dose of HES was 300 g, 15 % of patients developed pruritus after only 30 g, and the authors concluded that HES-induced pruritus may occur at any dose, molecular weight, or substitution.

HES deposits have been identified in a number of skin cell types: histiocytes, keratinocytes, Schwann cells, Langerhans cells, endothelial cells, and small nerves (Table 1). The mechanism of HES-associated pruritus remains poorly delineated but is thought to be related to

accumulation of HES in the epithelia of small peripheral nerves, especially Schwann cells [29, 50].

The effect of HES on renal function has become a serious clinical concern. Recent meta-analyses have concluded that HES use in critically ill patients is associated with significantly increased kidney injury and use of renal replacement therapy (e.g., [54, 55]). The kidney is a major site of HES tissue uptake. In a necropsy study of 12 patients who received repeated HES 200/0.5 infusions and died after protracted renal replacement therapy necessitated by acute kidney injury, the kidney contained the highest tissue concentration of HES in each individual patient compared with any of the other six major organs evaluated [25].

The primary site of HES uptake into renal tissue is in the luminal epithelial cells of the proximal tubules. Because of the glomerular filtration barrier, only HES molecules below 45 to 60 kDa pass through the kidney tubules where some are taken up by the proximal tubule cells through pinocytosis. The accumulation of these molecules in lysosomes results in a classic osmotic nephrosis, a morphological pattern with vacuolization and swelling of the renal proximal tubular cells (Figs. 3, 4) [56]. The presence of HES deposits in kidney tubular cells was demonstrated in 12 reports in this review. In a randomized trial, HES increased the odds of needing renal replacement therapy after kidney transplantation by almost tenfold, and all biopsied patients receiving HES showed osmotic nephrosis, whereas none in the control group did [18]. While the structural changes caused by osmotic nephrosis can be reversible and function restored, osmotic nephrosis resulting from HES infusion can be extremely long-lasting. During long-term follow-up after orthotopic liver transplantation, osmotic nephrosis attributable to HES persisted for on average at least 6.4 years in 61 % of patients [33].

Exposure of the proximal tubules to HES and therefore the potential for HES uptake may be greater for a lower molecular weight, less highly substituted HES solution. The average measured serum concentration of small HES molecules (<60 kDa) is 2.2 times higher over the first 24 h after infusion of HES 200/0.5 than of HES 450/0.7 [57]. The impact of molecular weight and substitution on HES uptake, storage, and processing in the kidney requires further study.

HES can be taken up into endothelial cells (Table 1). Currently, very little is known about the consequences of HES uptake in these cells. Since endothelial cells play important roles in both the coagulation and immune systems and since turnover rates of endothelial cells are rather low, accumulation of starch molecules could be relevant to various cell functions such as membrane recycling or other intracellular molecular trafficking. Further investigation into the effect of stored HES on endothelial cell function is needed.

Some evidence assembled in this systematic review also suggests deleterious effects of HES storage on the liver. In this connection one intriguing finding of a recently reported large randomized trial was increased liver failure in the group allocated to HES 130/0.4 [58].

This review underscores that HES cellular uptake has been much less investigated and reported than the plasma presence of HES. However, tissue accumulation may be an important determinant of HES safety and needs to be further elucidated. By its very nature, tissue uptake is much harder to investigate than the plasma volume-expanding effects of HES. The need for invasive multiple biopsies limits the type, size, and scope of studies that can realistically be conducted. The water-soluble HES granules are often difficult to identify in standard light microscopy approaches. The more advanced techniques of electron microscopy (especially immunoelectron microscopy with specific anti-HES antibodies), immunohistochemistry, and enzymatic assay are more demanding and often not readily available. Consequently, large randomized trials to address this issue have not been conducted and the barriers to such trials might be insurmountable. In any case, the evidence compiled systematically for the first time in this review suggests that the potential consequences of HES cellular uptake should be considered when selecting this artificial colloid for clinical fluid management.

Conflicts of interest CJW received fees for speaking and travel cost reimbursement from CSL Behring, Baxter, Kedrion, and the Plasma Protein Therapeutics Association, an organization representing the private sector manufacturers of plasma-derived and recombinant analogue therapies including albumin. MJ received speaker's honoraria from Baxter, Fresenius, Gambro, Orion Pharma, CLS Behring, and Braun Melsungen.

References

1. Bellmann R, Feistritzer C, Wiedermann CJ (2012) Effect of molecular weight and substitution on tissue uptake of hydroxyethyl starch: a meta-analysis of clinical studies. Clin Pharmacokinet 51:225–236
2. Thompson WL, Fukushima T, Rutherford RB, Walton RP (1970) Intravascular persistence, tissue storage, and excretion of hydroxyethyl starch. Surg Gynecol Obstet 131:965–972
3. Lindblad G, Falk J (1976) Konzentrationsverlauf von Hydroxyäthylstärke und Dextran in Serum und Lebergewebe von Kaninchen und die histopathologischen Folgen der Speicherung von Hydroxyäthylstärke. Infusionstherapie 3:301–303

4. Jesch F, Hübner G, Zumtobel V, Zimmermann M, Messmer K (1979) Hydroxyäthylstärke (HÄS 450/0,7) in Plasma und Leber: Konzentrationsverlauf und histologische Veränderungen beim Menschen. Infusionsther Klin Ernahr 6:112–117
5. Pfeifer U, Kult J, Förster H (1984) Ascites als Komplikation hepatischer Speicherung von Hydroxyethylstärke (HES) bei Langzeitdialyse. Klin Wochenschr 62:862–866
6. Dienes HP, Gerharz CD, Wagner R, Weber M, John HD (1986) Accumulation of hydroxyethyl starch (HES) in the liver of patients with renal failure and portal hypertension. J Hepatol 3:223–227
7. Sirtl C, Hübner G, Jesch F (1988) Zur Speicherung von hoch-und mittelmolekularer Hydroxyäthylstärke (HÄS) im menshlichen Gewebe. Beitr Anaesth Intensivmed 26:74–97
8. Sadek S, Owunwanne A, Abdel-Dayem HM, Yacoub T (1989) Preparation and evaluation of Tc-99m hydroxyethyl starch as a potential radiopharmaceutical for lymphoscintigraphy: comparison with Tc-99m human serum albumin, Tc-99m dextran, and Tc-99m sulfur microcolloid. Lymphology 22:157–166
9. Burgstaler EA, Pineda AA (1990) Hydroxyethylstarch as replacement in therapeutic plasma exchange. Prog Clin Biol Res 337:395–397
10. Heilmann L, Lorch E, Hojnacki B, Müntefering H, Förster H (1991) Die Speicherung von zwei unterschiedlichen Hydroxyäthylstärke-Präparaten in der Plazenta nach Hämodilution bei Patientinnen mit fetaler Mangelentwicklung oder Schwangerschaftshochdruck. Infusionstherapie 18:236–243
11. Parth E, Jurecka W, Szépfalusi Z, Schimetta W, Gebhart W, Scheiner O, Kraft D (1992) Histological and immunohistochemical investigations of hydroxyethyl-starch deposits in rat tissues. Eur Surg Res 24:13–21
12. Gall H, Kaufmann R, von Ehr M, Schumann K, Sterry W (1993) Persistierender Pruritus nach Hydroxyäthylstärke-Infusionen: retrospektive Langzeitstudie an 266 Fällen. Hautarzt 44:713–716
13. Hosgood G, Lewis DD, Hodgin EC, Church DF, Lopez MK (1993) Effect of deferoxamine-hydroxyethyl pentafraction starch on free, autogenous full-thickness skin grafts in dogs. Am J Vet Res 54:341–348
14. Jurecka W, Szépfalusi Z, Parth E, Schimetta W, Gebhart W, Scheiner O, Kraft D (1993) Hydroxyethylstarch deposits in human skin—a model for pruritus? Arch Dermatol Res 285:13–19
15. Legendre C, Thervet E, Page B, Percheron A, Noël LH, Kreis H (1993) Hydroxyethylstarch and osmotic-nephrosis-like lesions in kidney transplantation. Lancet 342:248–249
16. Szeimies R-M, Stolz W, Wlotzke U, Korting HC, Landthaler M (1994) Successful treatment of hydroxyethyl starch-induced pruritus with topical capsaicin. Br J Dermatol 131:380–382
17. Leunig A, Szeimies R-M, Wilmes E, Gutmann R, Stolz W, Feyh J (1995) Klinische und elektronenmikroskopische Untersuchung zur Hörsturztherapie mit der Kombination 10% HES 200/0,5 und Pentoxifyllin. Laryngorhinootologie 74:135–140
18. Cittanova ML, Leblanc I, Legendre C, Mouquet C, Riou B, Coriat P (1996) Effect of hydroxyethylstarch in brain-dead kidney donors on renal function in kidney-transplant recipients. Lancet 348:1620–1622
19. Coronel B, Mercatello A, Simone C, Xavier M, Moskovtchenko JF (1996) Hydroxyethylstarch and osmotic nephrosis-like lesions in kidney transplants. Lancet 348:1595
20. Cox NH, Popple AW (1996) Persistent erythema and pruritus, with a confluent histiocytic skin infiltrate, following the use of a hydroxyethylstarch plasma expander. Br J Dermatol 134:353–357
21. Gall H, Schultz KD, Boehncke WH, Kaufmann R (1996) Clinical and pathophysiological aspects of hydroxyethyl starch-induced pruritus: evaluation of 96 cases. Dermatology 192:222–226
22. Standl T, Lipfert B, Reeker W, Schulte am Esch J, Lorke DE (1996) Akute Auswirkungen eines kompletten Blutaustauschs mit ultragereinigter Hämoglobinlösung oder Hydroxyäthylstärke auf Leber und Niere im Tiermodell. Anästhesiol Intensivmed Notfallmed Schmerzther 31:354–361
23. Speight EL, MacSween RM, Stevens A (1997) Persistent itching due to etherified starch plasma expander. BMJ 314:1466–1467
24. Kiehl P, Metze D, Kresse H, Reimann S, Kraft D, Kapp A (1998) Decreased activity of acid α-glucosidase in a patient with persistent periocular swelling after infusions of hydroxyethyl starch. Br J Dermatol 138:672–677
25. Lukasewitz P, Kroh U, Löwenstein O, Krämer M, Lennartz H (1998) Quantitative Untersuchungen zur Gewebsspeicherung von mittelmolekularer Hydroxyethylstärke 200/0,5 bei Patienten mit Multiorganversagen. J Anaesth Intensivbeh 3:42–46
26. Sirtl C, Laubenthal H, Zumtobel V, Kraft D, Jurecka W (1999) Tissue deposits of hydroxyethyl starch (HES): dose-dependent and time-related. Br J Anaesth 82:510–515
27. Christidis C, Mal F, Ramos J, Senejoux A, Callard P, Navarro R, Trinchet JC, Larrey D, Beaugrand M, Guettier C (2001) Worsening of hepatic dysfunction as a consequence of repeated hydroxyethylstarch infusions. J Hepatol 35:726–732
28. de Labarthe A, Jacobs F, Blot F, Glotz D (2001) Acute renal failure secondary to hydroxyethylstarch administration in a surgical patient. Am J Med 111:417–418
29. Ständer S, Szépfalusi Z, Bohle B, Ständer H, Kraft D, Luger TA, Metze D (2001) Differential storage of hydroxyethyl starch (HES) in the skin: an immunoelectron-microscopical long-term study. Cell Tissue Res 304:261–269
30. Ständer S, Bone HG, Machens HG, Aberle T, Burchard W, Prien T, Luger TA, Metze D (2002) Hydroxyethyl starch does not cross the blood-brain or the placental barrier but the perineurium of peripheral nerves in infused animals. Cell Tissue Res 310:279–287
31. Leuschner J, Opitz J, Winkler A, Scharpf R, Bepperling F (2003) Tissue storage of ^{14}C-labelled hydroxyethyl starch (HES) 130/0.4 and HES 200/0.5 after repeated intravenous administration to rats. Drugs R D 4:331–338
32. Weisshaar E, Ständer S, Metze D, Diepgen TL (2004) Hydroxyethylstärke- (HES-)induzierter Pruritus als sekundäre Folge eines Arbeitsunfalls. Hautarzt 55:558–561
33. Pillebout E, Nochy D, Hill G, Conti F, Antoine C, Calmus Y, Glotz D (2005) Renal histopathological lesions after orthotopic liver transplantation (OLT). Am J Transplant 5:1120–1129
34. Ständer S, Evers S, Metze D, Schmelz M (2005) Neurophysiological evidence for altered sensory function caused by storage of hydroxyethyl starch in cutaneous nerve fibres. Br J Dermatol 152:1085–1086
35. Auwerda JJ, Leebeek FW, Wilson JH, van Diggelen OP, Lam KH, Sonneveld P (2006) Acquired lysosomal storage caused by frequent plasmapheresis procedures with hydroxyethyl starch. Transfusion 46:1705–1711
36. Ebcioglu Z, Cohen DJ, Crew RJ, Hardy MA, Ratner LE, D'Agati VD, Markowitz GS (2006) Osmotic nephrosis in a renal transplant recipient. Kidney Int 70:1873–1876

37. Schmidt-Hieber M, Loddenkemper C, Schwartz S, Arntz G, Thiel E, Notter M (2006) Hydrops lysosomalis generalisatus—an underestimated side effect of hydroxyethyl starch therapy? Eur J Haematol 77:83–85
38. Eisenbach C, Schönfeld AH, Vogt N, Wente MN, Encke J, Stremmel W, Martin E, Pfenninger E, Weigand MA (2007) Pharmacodynamics and organ storage of hydroxyethyl starch in acute hemodilution in pigs: influence of molecular weight and degree of substitution. Intensive Care Med 33:1637–1644
39. Kamann S, Flaig MJ, Korting HC (2007) Hydroxyethyl starch-induced itch: relevance of light microscopic analysis of semi-thin sections and electron microscopy. J Dtsch Dermatol Ges 5:204–208
40. Chappell D, Bruchelt W, Schenk W, Jacob M, Hofmann-Kiefer K, Conzen P, Kreimeier U, Rehm M (2008) Development of spontaneous subdural hematoma and bone marrow depression after hydroxyethyl starch administration. J Pediatr 153:579–581
41. Haught JM, Jukic DM, English JC 3rd (2008) Hydroxyethyl starch-induced pruritus relieved by a combination of menthol and camphor. J Am Acad Dermatol 59:151–153
42. Jamal R, Ghannoum M, Naud J-F, Turgeon P-P, Leblanc M (2008) Permanent renal failure induced by pentastarch. NDT Plus 5:322–325
43. Brandt S, Regueira T, Bracht H, Porta F, Djafarzadeh S, Takala J, Gorrasi J, Borotto E, Krejci V, Hiltebrand LB, Bruegger LE, Beldi G, Wilkens L, Lepper PM, Kessler U, Jakob SM (2009) Effect of fluid resuscitation on mortality and organ function in experimental sepsis models. Crit Care 13:R186
44. Hagne C, Schwarz A, Gaspert A, Giambarba C, Keusch G (2009) HAES in der Sepsis: ein Damoklesschwert? Schweiz Med Forum 9:304–306
45. Hüter L, Simon TP, Weinmann L, Schuerholz T, Reinhart K, Wolf G, Amann KU, Marx G (2009) Hydroxyethylstarch impairs renal function and induces interstitial proliferation, macrophage infiltration and tubular damage in an isolated renal perfusion model. Crit Care 13:R23
46. Zhao HJ, Chen HP, Meng ZY, Wang Q (2009) A case of acute renal failure due to hydroxyethyl starch. Clin Nephrol 71:329–332
47. Aneja S, Sood A, Taylor JS, McMahon JT, Billings SD, Bergfeld WF (2012) Generalized pruritus sine materia precipitated by exposure to hydroxyethyl starch. J Am Acad Dermatol 66:AB53
48. Kumar AB, Suneja M (2012) Hetastarch-induced osmotic nephrosis. Anesthesiology 117:647
49. Ständer S, Richter L, Osada N, Metze D (2013) Hydroxyethyl starch-induced pruritus: clinical characteristics and influence of dose, molecular weight and substitution. Acta Derm Venereol. doi: 10.2340/00015555-1639
50. Metze D, Reimann S, Szépfalusi Z, Bohle B, Kraft D, Luger TA (1997) Persistent pruritus after hydroxyethyl starch infusion therapy: a result of long-term storage in cutaneous nerves. Br J Dermatol 136:553–559
51. Reimann S, Szépfalusi Z, Kraft D, Luger T, Metze D (2000) Hydroxyethylstärke-Speicherung in der Haut unter besonderer Berücksichtigung des Hydroxyethylstärke-assoziierten Juckreizes. Dtsch Med Wochenschr 125:280–285
52. Auwerda JJ, Wilson JH, Sonneveld P (2002) Foamy macrophage syndrome due to hydroxyethyl starch replacement: a severe side effect in plasmapheresis. Ann Intern Med 137:1013–1014
53. Bork K (2005) Pruritus precipitated by hydroxyethyl starch: a review. Br J Dermatol 152:3–12
54. Mutter TC, Ruth CA, Dart AB (2013) Hydroxyethyl starch (HES) versus other fluid therapies: effects on kidney function. Cochrane Database Syst Rev 7:CD007594
55. Gattas DJ, Dan A, Myburgh J, Billot L, Lo S, Finfer S, CHEST Management Committee (2013) Fluid resuscitation with 6% hydroxyethyl starch (130/0.4 and 130/0.42) in acutely ill patients: systematic review of effects on mortality and treatment with renal replacement therapy. Intensive Care Med 39:558–568
56. Dickenmann M, Oettl T, Mihatsch MJ (2008) Osmotic nephrosis: acute kidney injury with accumulation of proximal tubular lysosomes due to administration of exogenous solutes. Am J Kidney Dis 51:491–503
57. Ferber HP, Nitsch E, Förster H (1985) Studies on hydroxyethyl starch. Part II: changes of the molecular weight distribution for hydroxyethyl starch types 450/0.7, 450/0.5, 450/0.3, 300/0.4, 200/0.7, 200/0.5, 200/0.3 and 200/0.1 after infusion in serum and urine of volunteers. Arzneimittelforschung 35:615–622
58. Myburgh JA, Finfer S, Bellomo R, Billot L, Cass A, Gattas D, Glass P, Lipman J, Liu B, McArthur C, McGuinness S, Rajbhandari D, Taylor CB, Webb SA (2012) Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med 367:1901–1911