Guideline and Consensus

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Chinese expert guidance on critical care hemoadsorption (2025)

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ABSTRACT

Hemoadsorption (HA) has become an important adjunctive therapy in critical care, with potential benefits in managing sepsis, severe acute pancreatitis (SAP), poisoning, and rhabdomyolysis (RM). However, significant heterogeneity in clinical evidence, the diversity of adsorption devices, and lack of standardized protocols hinder its widespread and rational use. To address these issues, the Critical Care Nephrology Quality Control Subcommittee of the National Center for Healthcare Quality Management in Critical Care Medicine convened a multidisciplinary expert panel to develop a national consensus. This expert consensus summarizes current evidence, defines core concepts, categorizes HA materials and modes, and outlines indications, timing, operational procedures, anticoagulation strategies, and safety considerations. It also provides expert recommendations for the use of HA in various clinical scenarios based on collective clinical experience and literature review. The aim is to promote standardized, safe, and effective HA practices across critical care settings in China.

Key words: hemoadsorption, expert consensus, critical care, extracorporeal blood purification, sepsis, acute pancreatitis, poisoning, rhabdomyolysis, inflammatory mediators

INTRODUCTION

In recent years, hemoadsorption (HA), an important technology in the field of extracorporeal blood purification, has shown unique value in the treatment of severe clinical conditions, such as sepsis, severe acute pancreatitis (SAP), poisoning, and rhabdomyolysis (RM). However, with the continuous expansion of clinical applications, HA is facing many challenges. First, there are various types of adsorption materials, significant differences in the mechanisms of action and removal efficiencies, and a lack of unified standards for clinical selection. Second, the existing research results are highly heterogeneous. On the one hand, some randomized controlled trials (RCTs) have failed to confirm a beneficial effect of HA in terms of mortality. On the other hand, findings from observational studies have mostly suggested that HA can reduce levels of inflammatory mediators and improve hemodynamics. For different diseases/conditions, the timing, type of membrane materials, and anticoagulation strategy are not standardized.

To promote the standardized application of HA, in March 2024, the Critical Care Nephrology Group, Critical Care Medicine Branch, Chinese Medical Association and the Critical Care Nephrology Quality Control Subspecialty Group of the National Medical Quality Control Center for Critical Care Medicine Specialties jointly organized a group of Chinese experts in the field of critical care medicine. Based on the latest research results and clinical practice experience, after a systematic review of the relevant literature on HA in China and abroad and multiple rounds of in-depth discussions based on their existing treatment experience, these experts finally formed this guidance after one year. This guidance is divided into two parts: the general monograph and monographs. The general monograph covers the basic concept of HA, the classification of materials, the clinical application modes, the operational procedures, the anticoagulation therapy strategies, and the management measures for complications; the monographs include the potential value of HA in clinical scenarios, such as sepsis, SAP, poisoning, and RM. The purpose of this guideline is

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to provide clinical workers with scientifically rigorous operating specifications and treatment references.

GENERAL MONOGRAPH

The concept and principles of HA and the factors affecting the adsorption efficiency

The concept of HA

HA is a treatment technique that involves removing a patient's blood from the body, removing harmful substances in the blood (such as toxins and inflammatory mediators) through a specific adsorption device, and then returning the treated blood back to the body.[1] With the development of materials science, adsorption materials are gradually shifting from natural materials (such as activated carbon) to synthetic resins and novel high-porosity materials. With the application of novel adsorption materials, HA has demonstrated a wide range of application potential in the regulation of inflammation and the immune response, and its application fields have been extended to severe clinical conditions, such as sepsis, SAP, and RM.[1]

Adsorption principle

Blood or separated plasma passes through adsorbents in the adsorption column; adsorbents bind to harmful substances in the blood (such as toxins and inflammatory mediators) through physical adsorption, chemical adsorption, or ion exchange; and these substances are then removed. The most common adsorption forces include the following: (1) hydrophobic bonds—the hydrophobic affinity between the adsorbent and the target molecule; (2) Ionic bond—the electrostatic attraction between positive and negative ions; (3) Van der Waals force—the weak interaction force between molecules.

The porous structure of the adsorbent has a major effect on the type and size range of the adsorbed molecules. For example, the size and spatial distribution of the pores affect the adsorption efficiency, while the adsorption material used also determines the adsorption capacity for a specific solute.

Factors affecting adsorption efficiency

The factors affecting the adsorption efficiency include the following: (1) adsorption material and porous structure—the adsorption material (such as resin or activated carbon) used and the size and distribution of the pores affect the adsorption capacity; (2) blood flow velocity and contact time—the longer the blood or plasma remains in the adsorbent, the better the adsorption effect; (3) solute concentration—the higher the solute concentration in the blood, the higher the adsorption efficiency; (4) molecular size and properties of the solute—different adsorbents have different adsorption capacities for small molecules, middle-sized molecules and macromolecules; usually, small molecules are more easily adsorbed through diffusion.

Classification of adsorption materials and solute removal

The earliest adsorption materials were natural adsorbents (zeolite, porous carbon, *etc.*), and the development of adsorption materials can be roughly divided into three stages: from activated carbon to inorganic porous materials to polymer materials.[2] At present, the adsorption materials commonly used in clinical practice are mostly synthetic polymer materials, such as ion exchange resins, adsorption resins, and immunoadsorbents. These adsorption materials can be divided into nonspecific adsorption materials and specific adsorption materials, and they have different solute removal activities and efficiencies.[3]

Nonspecific adsorption materials

Nonspecific adsorption materials are adsorption materials that have nonselective and broad-molecular-spectrum adsorption properties. Their materials include natural and synthetic polymers, such as activated carbon and resins.

Activated carbon

Activated carbon, one of the most studied adsorption materials, was used to treat drug poisoning as early as 1964, and it is prepared from plants rich in cellulose and lignin. The adsorption performance of activated carbon is related to its high specific surface area and intermolecular forces. The specific surface area of activated carbon can reach 500-1400 m^2/g, which results in high adsorption performance over a wide range but low selectivity, and activated carbon is typically used for substances with relative molecular weights from 0.1 to 5.0 kDa. Early activated carbon materials had poor biocompatibility; therefore, techniques to coat activated carbon were developed to reduce roughness. However, after coating, the pores of activated carbon are blocked, thereby reducing the adsorption performance.

Resins

Resins are synthetic polymer microspheres that are porous and have a high surface area. The physicochemical properties of resins are stable, and resins have strong adsorption capacity. Different types of nonspecific adsorption materials can be prepared by changing the physical properties and chemical polarity of the molecular structure of the resin. Neutral macromolecular resins made of styrene-divinylbenzene copolymers are commonly used in China. The molecular weights of solutes removed by resins with different pore sizes vary. The molecular weight range of solute removal is 0.5-40.0 kDa for HA130, 0.2-10.0 kDa for HA230, and 0.5-60.0 kDa for HA330.

Carbonized resins

Carbonized resins have the characteristics of resins and activated carbon, have a specific surface area of 1000-1600 m^2/g, and have broad-spectrum molecular weight adsorption characteristics.

Polysaccharides

Polysaccharides are natural polymers, such as agarose, chitosan, and cellulose, with good biocompatibility. Polysaccharides can be used as nonselective adsorbents or as good selective adsorbents through self-modification. Chitosan is considered one of the most promising adsorption materials, with the main advantage being that there are adjustable sites in its chemical structure so that the stability and adsorption capacity can be increased through modification.

Poly (styrene-divinylbenzene)

An adsorption column composed of poly (styrene-divinylbenzene) is used to remove substances from whole blood *via* pore capture and surface adsorption, and the effective molecular weight range of targets is wide (approximately 5-60 kDa). With a total surface area of more than 40,000 m^2, poly (styrene-divinylbenzene) has excellent adsorption efficiency for various inflammatory cytokines (such as tumor necrosis factor-α [TNF-α], interleukin-1β [IL-1β], IL-6, IL-8 and IL-10).[4] Common poly (styrene-divinylbenzene) cytokine adsorbents include CytoSorb (CytoSorbents, USA), CYT-860-DHP, CTR-001, MPCF-X, and CA330.

Specific adsorption materials

Positive ion adsorbents

Adsorbents with modifications of surface cationic functional groups (the carrier can be resins or polysaccharides) can selectively adsorb solutes or cell components containing anions in the blood. Polymyxin B is a cationic cyclic peptide antibiotic that has antibacterial activity against gram-negative bacteria and the ability to bind to endotoxins. The polymyxin B adsorption column from Toray Company, Japan, has been used in clinical applications.

Immunoadsorbent

Adsorbents that bind antigens and antibodies are referred to as immunoadsorbents. Agarose derivatives, cellulose, polyvinyl alcohol, *etc*., are used as carriers of immunoadsorbents; the commonly used adsorbents are *Staphylococcus aureus* protein A, synthetic peptides, anti-immunoglobulin antibodies, dextran, *etc*. Different specific solutes can be adsorbed according to the specificity of the antibody.[5]

Solute removal effects of different adsorption materials

According to the characteristics and mechanism of action of different adsorption materials, substances with different physicochemical properties and different sizes can be adsorbed, and the solute removal abilities of different adsorption materials are significantly different.[4-8] The solute removal activities of commonly used clinical adsorption materials and commonly used adsorption columns are shown in Table 1.

Safety of the adsorption materials

Adsorption materials should have good biocompatibility, adsorption selectivity, and mechanical properties (*i.e*., strength and thermal stability), and their clinical safety and effectiveness are closely related to the survival of patients.[4,9-12] The biocompatibility of an adsorption material refers to the ability of the material to contact the human body without causing an inappropriate host response. Technological progress in the development of HA materials has improved their biocompatibility, leading to a significant reduction in inflammation, coagulation activation reactions, cytotoxicity, and the influence of adsorption materials on immune cells.

Contact of the adsorption material with blood may activate the coagulation system and cause platelet adhesion and aggregation on the surface of the adsorbent, resulting in the consumption of coagulation factors, a reduction in the platelet count, and an increased risk of bleeding in patients, especially those with preexisting coagulation disorders. During HA therapy, patient coagulation function and platelet count need to be closely monitored. In addition, some patients may have allergic reactions to the materials or adsorbents of the adsorption column and may experience symptoms, such as rash, itching, difficulty breathing, and decreased blood pressure. Severe allergic reactions can be life-threatening.

Technological advancements in adsorption materials have improved their biocompatibility. The early naturally activated carbons used in adsorption columns had poor biocompatibility, and their impact on platelets was especially strong. However, the carbonized resin used in recent years is a synthetic activated carbon, which is designed to have an activated carbon adsorbent with a macropore structure and adjustable pore size distribution through embedding or coating formation technologies. Based on the improved adsorption performance, carbonized resin has good mechanical strength, which overcomes the disadvantages of activated carbon, such as particle shedding and poor hemocompatibility, supporting the clinical application of carbonized resin adsorption columns. Biocompatibility and cytotoxicity evaluation experiments of a series of HA columns (HA130, HA230, HA330 and HA380) with resin adsorption materials revealed that these types of adsorption columns have good biocompatibility, and the dynamic and static experiments have not shown increased nuclear cell necrosis and apoptosis or decreased viability.[10]

The CytoSorb® adsorption column is composed of poly (styrene-divinylbenzene) and is clinically shown to have good biocompatibility and safety. The polymyxin B adsorption column specifically adsorbs endotoxin, and clinical studies have shown that the incidence of serious adverse events (SAEs) in patients receiving HA therapy with the polymyxin B adsorption

Table 1

Adsorption materials and columns commonly used in clinical practice in critical care medicine

Adsorption material	Adsorption column	Molecular weight (kDa)	Solute removal
Resin	HA130	0.5-30.0	Molecular protein-bound toxins in patients with uremia
Resin	HA230	0.2-10.0	Hydrophobic or protein-bound exogenous substances
Resin	HA330/380	0.5-60.0	Cytokines, complement, free hemoglobin
PEI	oXiris	5.0-100	Cytokines, endotoxin
Poly (styrene-divinylbenzene)	CytoSorb, CA330	5.0-60.0	Cytokines, microbial toxins, free hemoglobin, bilirubin, activated complement, drugs, and various inflammatory mediators
Positive ion adsorbent	Polymyxin B adsorption column	5.0-100	Endotoxin

PEI, Polyethyleneimine; HA, hemoadsorption; CA, Cytokine adsorption column.

column is not greater than that in patients who do not receive HA therapy.[11] HA therapy with activated carbon or resin adsorption columns has been safely and effectively used in the clinical treatment of patients with poisoning (with, *e.g.*, organophosphorus pesticides, antiepileptic drugs, antipyretic and analgesic drugs, sedative drugs, or anticoagulant drugs).[13] HA therapy is also used in the treatment of autoimmune diseases (for the removal of antibodies) and patients with acute liver failure (for the removal of bilirubin and bile acids).[14-16] HA therapy has some clinical benefits for patients with trauma, burns, severe pancreatitis, and various cytokine release syndromes and those undergoing cardiac surgery (observational studies), but large-scale RCTs are lacking.[17,18]

The clinical application of HA therapy in sepsis is currently the area of greatest concern. Early exploratory RCTs have shown the efficacy of HA therapy for patients with severe infection or septic shock (enrolled in the emergency department after abdominal infection), but subsequent large-sample studies have not confirmed that HA therapy can increase the likelihood of survival in patients with septic shock.[19-23] HA can adsorb inflammatory mediators and regulate the immune-inflammatory response. Several small clinical studies have shown that HA can significantly reduce the levels of inflammatory cytokines, reduce blood lactic acid, increase mean arterial pressure, and improve hemodynamics and organ function in septic patients, but large-scale RCTs to confirm the clinical efficacy are still lacking.[24-42]

HA mode and hybrid blood purification technology

HA mode

The HA mode refers to the method by which plasma or blood contacts the adsorbent through the adsorption device. The initial mode of HA mainly refers to the adsorption of plasma or blood through contact with the adsorbent through the adsorption column. With the progress in the development of hemofilter/dialyzer membrane materials for renal replacement therapy (RRT), some filters with adsorption properties have been applied in clinical practice. The 30th acute disease quality initiative (ADQI) working group expert consensus[4] includes RRT with adsorptive hemofilters/dialyzers as a mode of HA. HA models can be classified according to the blood components that contact the adsorbent device or the adsorption device.

On the basis of the blood components that contact the adsorption device, HA can be divided into two modes: Whole-blood HA and plasma adsorption

During whole-blood HA [Figure 1], blood directly passes through the adsorption column. During plasma adsorption, blood first passes through the plasma filter, and the separated plasma then flows through the adsorption column. During whole-blood HA, the blood flow rate through the adsorption column is generally 150-200 mL/min. The high blood flow rate during whole-blood HA leads to insufficient adsorption. At the same time, the blood directly contacts the adsorbent, which may result in excessive protein deposition on the adsorbent surface of the adsorption column and the activation of immune cells, leading to high requirements for adsorption column biocompatibility. During plasma adsorption [Figure 2], the flow rate of plasma through the adsorption column is generally 20-40 mL/min, which means that the contact time with the adsorbent is longer, and the adsorption efficiency is greater. Moreover, the cellular components in the blood do not directly contact the adsorbent, and it is difficult to damage these components.[43,44] The plasma adsorption mode, which requires an additional plasma separator, has an ideal adsorption effect and few side effects. Some selective plasma component adsorption columns can be used only in plasma adsorption mode, such as plasma bilirubin adsorption columns[45] and plasma antibody adsorption columns.[46]

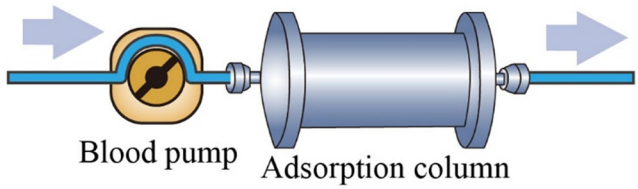

Figure 1. Hemoadsorption.

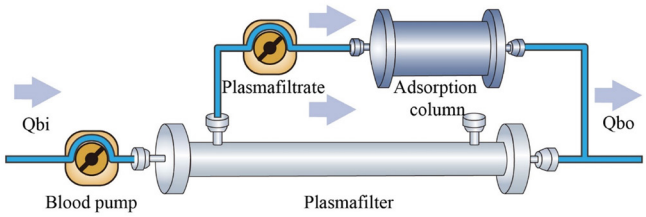

Figure 2. Plasma adsorption. Qbi, Blood flow at the inlet of the units; Qbo, Blood flow at the outlet of the units.

On the basis of the adsorption device, HA can be divided into adsorption column adsorption and RRT adsorption modes

The adsorption column adsorption mode is performed through a specialized adsorption column. In RRT adsorption mode, a hemofilter/dialyzer with an adsorption membrane is used to purify blood through adsorption during RRT. Commonly used membranes with good adsorption performance include polymethyl methacrylate (PMMA) membrane,[47] AN69-surface-treated (ST) membrane[48] and the AN69-polyethyleneimine (PEI)-heparin membrane.[49] When continuous renal replacement therapy (CRRT) adsorption mode is used, although the hemofilter can be continuously used for up to 72 h, when the cytokine levels remain continuously high and there is a cytokine storm, in order to prevent membrane saturation caused by adsorption, it is recommended to replace the hemofilter once every 12 to 24 h. The specific replacement frequency should depend on the patient's condition and saturation of the hemofilter/dialyzer adsorption membrane: when the patient's condition is unstable and inflammation is severe, the replacement frequency should be appropriately increased to ensure a sufficient adsorption effect; when the patient's condition tends to be stable and inflammation is significantly reduced, the use time can be appropriately extended.[50-52]

Hybrid blood purification technology including HA

Sometimes in the treatment of complex clinical diseases, more than one target substance needs to be removed in HA therapy, and blood purification and organ function support often need to be taken into consideration. Therefore, a hybrid blood

purification technology that is based on the combination of multiple adsorption columns and a hybrid application of HA combined with extracorporeal organ support (ECOS) has been developed.[53,54]

Hybrid blood purification technology based on a combination of multiple adsorption columns

Hybrid blood purification technology, which is based on a combination of multiple adsorption columns, is mainly used to treat acute liver failure.[55] Liver dysfunction leads to the accumulation of various toxins in the circulation. These toxins can be roughly divided into water-soluble toxins (such as ammonia) and albumin-bound toxins (such as bilirubin and bile acids). Hybrid blood purification technology, which is based on a combination of multiple adsorption columns, removes toxins bound to albumin through adsorption and removes small-molecule water-soluble toxins in combination with hemofiltration/dialysis as needed. Common combination methods include the following: double plasma molecular adsorption system (DPMAS), molecular adsorbent recirculating system (MARS), and plasma component separation and adsorption system (Prometheus system). The MARS and Prometheus systems require specific machinery, equipment and consumables, the combinations are relatively fixed, and the prices are relatively high. In this expert guidance, the DPMAS is taken as an example.

The DPMAS is suitable for the blood purification of patients with hyperbilirubinemia and acute liver dysfunction,[56] and the process generally lasts for approximately 3-4 h. In this mode, blood first passes through the plasma filter, and then the filtered plasma flows through two adsorption columns placed in series: an anion exchange resin adsorption column (*e.g.*, BS330) and a neutral macroporous resin adsorption column (*e.g.*, HA330-II; Figure 3). The former is a specific adsorbent for bilirubin and bile acids, whereas the latter is a broad-spectrum adsorbent for medium and macromolecular inflammatory mediators and toxins. The two-column combination can remove bilirubin and inflammatory mediators from the circulation in patients with acute liver failure and improve liver function.

Hybrid application of HA combined with ECOS

Common combinations include HA + RRT, HA + extracorporeal membrane oxygenation (ECMO), and HA + cardiopulmonary bypass (CPB). Multiple studies[40,42,57,58] have confirmed that HA + CPB can be safely performed during cardiac surgery and can reduce cytokine levels. This expert guidance is focused on the hybrid application of HA + RRT and HA + ECMO used in the intensive care unit (ICU).

a. HA + RRT

HA can be combined with CRRT and hemodialysis (HD). In critically ill patients, the HA + CRRT mode, while performing RRT, removes medium and macromolecular substances from the circulation that cannot be filtered by traditional CRRT, such as inflammatory cytokines, through HA.[59-61] In patients with end-stage renal disease (ESRD), HA + HD is mainly used for the additional removal of middle-molecular-weight uremic toxins (such as β2-microglobulin).[62,63]

HA + RRT can also be divided into two modes: whole-blood

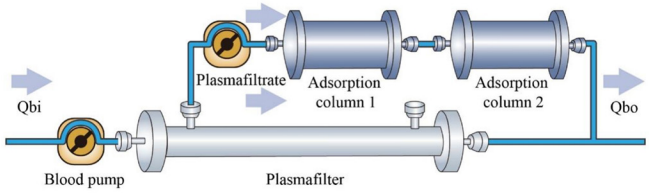

Figure 3. The DPMAS. DPMSA, double plasma molecular adsorption system; Qbi, blood flow at the inlet of the units; Qbo, blood flow at the outlet of the units.

HA and plasma adsorption. In whole-blood HA mode, the hemofilter/dialyzer and the adsorption column are connected in series, and the adsorption column is usually placed after the hemofilter/dialyzer [Figure 4]. On the one hand, it is more convenient to add the adsorption column after the hemofilter/dialyzer in currently used CRRT machines. On the other hand, the service life of the adsorption column can be extended to the maximum extent, and premature saturation of the adsorption column can be avoided. Sometimes, the adsorption column is also placed before the dialyzer, the possible temperature or other abnormalities (such as acidosis) that may be caused by the adsorption column are corrected by HD.[4,44] HA + CRRT in plasma adsorption mode, that is, coupled plasma filtration adsorption (CPFA) technology, involves a plasma adsorption loop and a hemofiltration loop in series [Figure 5]. The blood first passes through the plasma filter, and the separated plasma then flows through the adsorption column to adsorb and remove cytokines, inflammatory mediators, and toxins/poisons. The plasma is purified by the adsorption column, mixed with blood cell components, reinfused, and then passes through a hemofilter for CRRT to remove small- and medium-molecule toxins and regulate blood volume. First, CPFA was used mainly for patients with sepsis and septic shock, but later, it has also been used to treat liver failure, RM, severe autoimmune diseases and poisoning.[43,64,65] A multicenter RCT (COMPACT study) on septic shock[66] showed that CPFA neither reduced the mortality of patients with septic shock nor affected other important clinical outcomes. However, the subgroup analysis revealed that when a large amount of plasma was treated by HA, CPFA could reduce mortality. Therefore, a multicenter adaptive RCT of high-dose CPFA in septic shock, the COMPACT-2 study, was conducted,[67] but because CPFA had some harmful effects in patients with septic shock, the study was terminated early. An unplanned analysis revealed that in septic shock patients who did not have severe kidney injury and did not require RRT, the mortality of the CPFA group was significantly greater than that of the control group. Therefore, CPFA is not currently recommended for the treatment of patients with septic shock who do not meet the indications for CRRT.

b. HA + ECMO

> Existing evidence does not support routine use in sepsis patients without CRRT indications. Mandate careful risk-benefit assessment prior to implementation. Recommend exclusive use in multidisciplinary teams (*e.g.*, ECMO centers) with dynamic cytokine monitoring.

ECMO can provide a longer period of organ support for patients with respiratory and/or circulatory dysfunction. The treatment process may induce nonspecific inflammation mediated by cytokines,[68] and the patient's primary disease needs to be treated; therefore, it is necessary to implement the HA + ECMO mode.

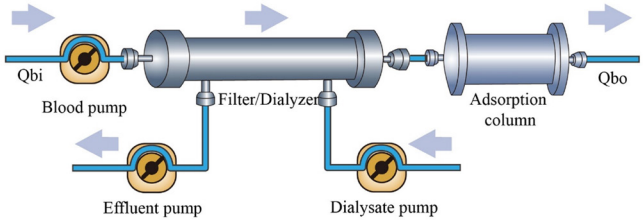

Figure 4. HA + RRT. HA, hemoadsorption; RRT, renal replacement therapy; Qbi, blood flow at the inlet of the units; Qbo, blood flow at the outlet of the units.

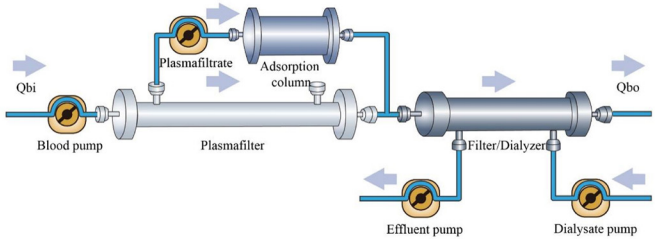

Figure 5. CPFA. CPFA, coupled plasma filtration adsorption; Qbi, blood flow at the inlet of the units; Qbo, blood flow at the outlet of the units.

The principle for the connection of HA to ECMO tubing is as follows: the HA blood access tube should be placed in the high-pressure area of the ECMO tube (after the ECMO centrifugal pump) before the oxygenator [Figure 6A] or after the oxygenator [Figure 6B] to guide the blood. The HA blood return tube should be placed in the low-pressure area of the ECMO tube (before the ECMO centrifugal pump). This connection prevents air embolism and veno-arterial shunting,[68] but the issue of recycling needs to be taken into consideration.

The clinical data concerning the ideal blood flow rate required for adsorption tubing during HA + ECMO treatment are limited. A sufficient blood flow rate is needed for full adsorption while avoiding interference with the ECMO circuit. The blood flow rate recommended by the manufacturer is between 150 and 500 mL/min.[59]

Compared with HA + CPB, clinical studies on HA + ECMO are more limited, with conflicting results, which may be related to the confounding factors of different diseases and different ECMO modes. The CYCOV study,[69] a single-center RCT on the use of HA + ECMO in patients with severe coronavirus disease 2019 (COVID-19), revealed that early initiation of cytokine adsorption did not reduce serum IL-6 levels and had a negative effect on the survival rate, and combined use of cytokine adsorption was not recommended for COVID-19 patients within the first few days of receiving ECMO. However, the CYCOV study has limitations of a small sample size and an excessive effect size. A systematic review of the use of HA combined with veno-venous ECMO (V-V ECMO) for patients with severe acute respiratory distress syndrome (ARDS) revealed that the use of CytoSorb could reduce inflammation and increase the survival rate of ARDS patients treated with V-V ECMO.[70] Owing to the limited overall clinical data on HA + ECMO, HA + ECMO is not approved for use in some countries in the European Union (*e.g.*, Germany).[4]

Operating procedures and precautions for HA

Plasma adsorption

Since different types of adsorption columns and different treatment modes are used for plasma adsorption, the operating procedures also differ. Please refer to the relevant instruction manuals for different treatment methods, different adsorption columns, and different machinery and equipment. The main procedures are as follows.

Pretreatment evaluation

Plasma adsorption should be performed in a hospital with corresponding qualifications. Routine examinations, including routine blood examinations and tests of coagulation indicators, serum albumin, serum globulin, electrolytes, liver function, renal function, and specific indicators associated with the primary disease, should be performed before treatment. The plasma adsorption treatment mode and the adsorption column used are determined according to the condition of the patient, the procedure is explained to the family or patient, and informed consent is signed.

Formulating treatments

Generally, the dose of a single adsorption treatment is 2-3 times the plasma volume, and the duration of treatment is preferably 2-3 h. If necessary, the adsorption column could be replaced once to continue the adsorption, or the adsorption could be performed periodically. The selection of the adsorption column is based on the treatment purpose, and the specific course of treatment should be evaluated based on the levels of pathogenic factors, such as the patient's pathogenic antibodies and immunoglobulin. The patient's estimated plasma volume can be calculated on the basis of their sex, hematocrit and weight according to the following formula: plasma volume = (1 - hematocrit) × (b + [c × body weight]). Please note that the unit of plasma volume is milliliters and that of body weight is kilograms. The b value is 1530 for males and 864 for females. The c value is 41 for males and 47.2 for females.

Item preparation and verification

(1) Items to prepare: plasma filter, plasma component adsorption column, special plasma adsorption tubing (with model numbers and expiration dates checked), puncture needles, sterile treatment towels, normal saline, povidone-iodine and cotton swabs, tourniquets, and disposable gloves.

(2) Equipment to prepare: HA machine, HD machine, hemodiafiltration machine, or CRRT equipment.

(3) Routinely prepare emergency drugs and equipment, such as an electrocardiogram (ECG) monitoring system, a blood oxygen monitoring system, dexamethasone, and epinephrine.

Operating procedure

(1) Check the patient's bed number and name; inform the patient of the treatment purpose; evaluate the patient's level of consciousness, degree of cooperation, and status of vascular access; and measure and record the patient's vital signs.

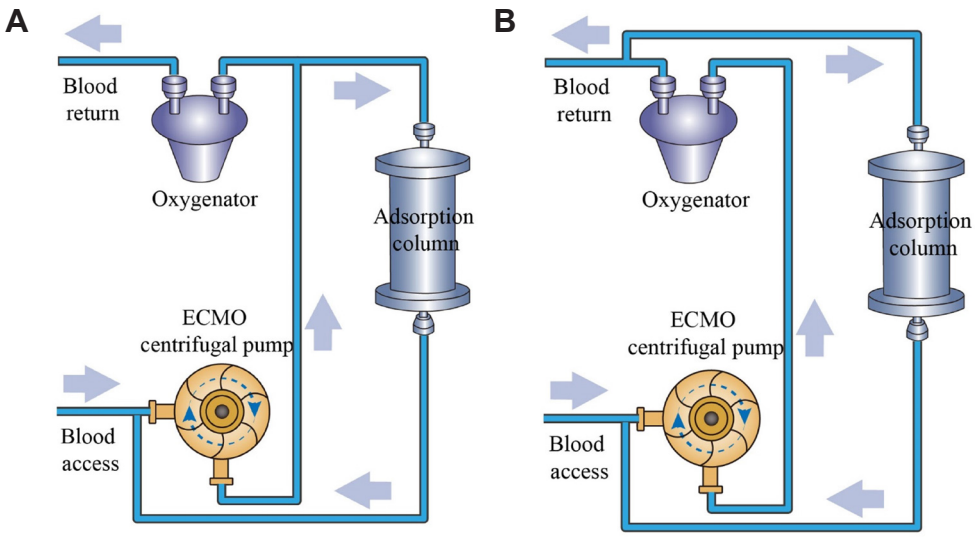

Figure 6. HA + ECMO. (A) The HA tube is placed before the oxygenator. (B) The HA tube is placed after the oxygenator. HA, hemoadsorption; ECMO, extracorporeal corporeal membrane oxygenation.

(2) Check whether the connection of the power cord of the machine is normal and then turn on the master switch of the machine to complete the inspection.

(3) Check the plasma filter, plasma component adsorption column and tubing for damage, and whether the packaging is intact; check the expiration date and model number; install and connect tubes according to the treatment modes, product instructions of the machine and various consumables; and automatically preflush the tubes, plasma filter and plasma component adsorption column.

(4) Set parameters for plasma adsorption treatment, including the flow rates of the blood pump, plasma pump, waste liquid pump and heparin pump; the target volume for plasma processing; the temperature; and various alarm parameters.

(5) When the CPB machine is connected, whole-blood self-circulation for 5 to 10 min is performed, and the treatment procedure is started after the patient's condition is observed to be normal. The operation of the machine, including changes in the whole-blood flow rate, plasma flow rate, arterial pressure, venous pressure, and transmembrane pressure, is closely monitored.

(6) At the beginning of treatment, the blood flow rate generally increases gradually from 50-80 mL/min to 100-150 mL/min, and the separated plasma passes through the adsorption column at a flow rate of 25-50 mL/min and then returns to the body.

(7) The condition of the filters and the color of the plasma are closely monitored, and the presence of hemolysis is monitored. If a membrane ruptures, the corresponding filter should be replaced in a timely manner. The vital signs of the patient, including blood pressure, heart rate, respiration, and pulse, are closely monitored every 30 min to determine the patient's condition.

(8) After the therapeutic dose is reached, or according to the procedure. The patient's vital signs and changes in condition and the treatment parameters, process, and results should be monitored and recorded.

HA

The operating procedures are different because of the different types of adsorption columns used for HA. The main procedures are as follows.

Pretreatment evaluation

HA should be performed in a hospital with corresponding qualifications. Routine examinations, including routine blood examinations and tests of coagulation indicators, serum albumin, serum globulin, electrolytes, liver function, renal function, and specific indicators associated with the primary disease, should be performed before treatment. The adsorption column and treatment time for HA are determined on the basis of the patient's condition, the procedure is explained to the family or patient, and informed consent is signed.

Determine the time and frequency of treatment

The adsorption capacity and saturation rate of the adsorption material in the adsorption column affects the duration of each adsorption treatment. The adsorption of most solutes by commonly used resins and activated carbon adsorbents generally reaches saturation within 2 h. If clinically necessary, the adsorption column can be replaced every 2 h, but the duration of one continuous adsorption treatment generally does not exceed 6 h. For some drugs or poisons with greater fat solubility, after the end of treatment, the related substances in the adipose tissue are likely released into the blood, and the adsorption treatment can be performed again after a certain interval according to the characteristics of different substances.

Item preparation and verification

(1) Items for preparation: HA column, tubing, puncture needle, sterile treatment towels, normal saline, and disinfection items such as povidone iodine and cotton swabs, tourniquets, and disposable gloves.

(2) Equipment preparation: HA machine, HD machine, hemodi-

afiltration machine, or CRRT equipment.

(3) Routinely prepare emergency drugs and equipment, such as an ECG monitoring system, a blood oxygen monitoring system, dexamethasone, and epinephrine.

Operating procedure

(1) Check the patient's bed number and name; inform the patient of the purpose of treatment; evaluate the patient's level of consciousness, degree of cooperation, and status of vascular access; and measure and record vital signs.

(2) Check whether the connection of the power cord of the machine is normal and then turn on the master switch of the machine to complete the inspection.

(3) Check the plasma filter, plasma component adsorption column and tubing for damage and determine whether the packaging is intact; check the expiration date and model number; install and connect the tubes according to the treatment modes, product instructions for the machine and various consumables; and automatically preflush the tubes, plasma filter and plasma component adsorption columns.

(4) Set parameters for plasma adsorption treatment, including the flow rates of the blood pump, plasma pump, waste liquid pump and heparin pump; the target volume for plasma processing; the temperature; and various alarm parameters.

(5) Heparinization of the adsorption column. 1) Dynamic heparinization: according to the product instructions. 2) Static heparinization: according to the doctor's instructions, heparin is injected into the adsorption column, mixed evenly and left to stand for 20-30 min before use. Strict aseptic techniques are used in the treatment preparation room. The specific operation methods are as follows: ① A 5 mL disposable syringe is used for the heparin injection (100-200 mg); ② After the adsorption column is gently tapped, the protective cap at the upper end of the adsorption column is opened; ③ Place the opened protective cap in the sterile treatment towel; ④ Remove the needle from the syringe with the heparin injection and directly inject the heparin into the preservation solution in the adsorption column; ⑤ Take the protective cap out from the treatment towel and tighten it; ⑥ Ensure the name, dose, and time of anticoagulant injection are indicated on the adsorption column; ⑦ Slowly turn the adsorption column up and down (180°) for 10 times (approximately 20 s); ⑧ Place the adsorption column in a sterile treatment towel, immerse the resin completely in the liquid, and let it stand for 30 min before use.

(6) Priming of the adsorption column and tubing. 1) The blood tube at the arterial end is connected to the system, filled with normal saline and then correctly connected to the arterial end of the adsorption column, while the blood tube at the venous end is connected to the venous end of the adsorption column. 2) Blood pumping is started at a rate of 200-300 mL/min. The total volume of preflushed saline is generally 2000-5000 mL, or the recommended volume of the relevant product. If free adsorbent particles are washed out during the preflushing process or the adsorbent capsule is damaged, the HA column must be replaced. 3) Before the end of dynamic preflushing, the tubing and filter are soaked in 4% heparin-based normal saline (the preparation method is as follows: add 2500 U [20 mg] of unfractionated heparin into 500 mL of normal saline; the value can be adjusted according to the clinical situation), the tubing and filters are soaked for 30 min, and a saline flush of not less than 500 mL should be given before the machine is started. However, heparin is contraindicated in patients with heparin allergy or a history of heparin-induced thrombocytopenia (HIT). If the patient is in shock or a hypovolemic state, extracorporeal priming can be performed before the start of adsorption therapy. Priming fluid can be normal saline, a plasma substitute, fresh plasma, or 5% albumin to reduce the impact of CPB on the patient's blood pressure.

Precautions: Before connecting the adsorption column, exhaust the air in the tubing at the arterial end in advance. During the exhausting period, the liquid remains in the flowing state. If there are some residual air bubbles that are difficult to exhaust, the side of the nut at the venous end can be tapped horizontally to exhaust the residual air bubbles. The air exhaustion completion criteria are as follows: there are no air bubbles in the adsorption column, and the diameter of residual single air bubbles at the venous end is < 5 mm.

(7) Connection to the CPB system. The tubing at the arterial end of the device is connected to the patient's central tubing to establish CPB. Blood pumping is started, preferably at a rate of 50-100 mL/min, and then gradually adjusted to a rate of 100-200 mL/min. When the blood passes through the adsorption column and is about to reach the outlet at the venous end, the blood tube at the venous end of the device is connected to the patient's central tubing. The suitable blood flow rate for HA is generally 100-200 mL/min. Studies have shown that the blood flow rate in CPB is significantly correlated with the treatment effect. If the blood flow rate is too high, the treatment time could be long, while if the blood flow rate is too low, the treatment time is relatively short; however, if the blood flow rate is too low, there is a tendency for coagulation to occur.

After the treatment time is reached, blood is returned to the body according to the procedure. The patient's vital signs, changes in condition, treatment parameters, treatment process, and results should be monitored and recorded.

What are the complications related to HA? How can they be solved?

Hypotension

Hypotension is a common complication of adsorption therapy. Hypotension may be related to the decrease in blood volume caused by CPB, and the incidence of this complication may be higher in patients with preexisting hypovolemia. Notably, in some patients, hypotension resulting from decreased vasotension due to allergies needs to be ruled out. For patients with hypovolemia, supplementation with the necessary colloid or crystalloid solution before HA could be performed to reduce the incidence of hypotension during the adsorption process.

Bioincompatibility and treatments

The main clinical manifestations of adsorbent biocompatibility are chills, fever, chest tightness, difficulty breathing, and a transient decrease in the percentages of white blood cells or

platelets (which could be as low as 30%-40% of the adsorption level) within 0.5-1.0 h after the start of adsorption treatment. In general, there is no need to stop adsorption therapy, and an intravenous injection of dexamethasone and oxygen inhalation therapy can be administered. If symptoms are not relieved after the treatments and vital signs are seriously affected, adsorption therapy should be terminated in a timely manner.

Adsorbent particle embolism

After the start of treatment, if patients develop progressive difficulty breathing, chest tightness, and a decrease in blood pressure, the presence of adsorbent particle embolism should be considered. Once it occurs, treatment must be stopped, and oxygen inhalation or hyperbaric oxygen therapy should be administered, together with corresponding symptomatic treatment.

Coagulation disorders

Coagulation disorders caused by adsorption therapy may be associated with various factors: adsorption therapy may be accompanied by the adsorption of coagulation factors, causing the consumption of coagulation factors; a large amount of platelet aggregation and activation may occur during treatment, leading to the development of coagulation disorders; and insufficient heparin usage, insufficient blood flow, and low ambient temperature can lead to coagulation disorders. Therefore, during adsorption therapy, coagulation factors and platelets should be closely monitored, the anticoagulant regimen should be optimized, and the occurrence of insufficient blood flow and excessively low temperature should be avoided.

Air embolism

Air embolism occurs when air is not completely removed from the CPB machine before adsorption therapy, blood returns to the body with air inside, or air enters the body due to weak or broken blood tube connections during treatment. Affected patients may present with sudden difficulty breathing, chest tightness, shortness of breath, cough, and, in severe cases, cyanosis, decreased blood pressure, and even coma. Once the diagnosis of air embolism is confirmed, the adsorption treatment must be stopped immediately, high-concentration oxygen therapy should be administered, and symptomatic treatment should be administered according to the diagnosis and treatment standards for air embolism.

Anticoagulant therapy during adsorption

How to choose the anticoagulant used in adsorption therap?

(1) The anticoagulants used in HA therapy should be selected and adjusted on an individual basis according to the treatment mode and the specific conditions of the patient. Compared with CRRT, the duration of HA therapy is shorter, but the requirements for anticoagulation are higher, and the coagulation function of patients needs to be monitored more closely.

(2) Sodium citrate should not be used for anticoagulation in patients with HA alone, plasma adsorption alone, or double plasma exchange to avoid hypocalcemia and metabolic complications.

(3) Unfractionated heparin or low-molecular-weight heparin (LMWH) are usually the preferred anticoagulants for HA, and they are suitable for patients without significant bleeding risk.

(4) For patients at high risk of bleeding, argatroban anhydrous or nafamostat mesylate can be considered.

(5) For HA + CRRT, sodium citrate can be used as a local anticoagulant, but electrolyte levels and acid-base status should be closely monitored.

Anticoagulant therapy for HA is based on the assessment of the coagulation status of the patient; the selection of the appropriate anticoagulant and dose for the patient; and continuous monitoring, evaluation and adjustment to maintain the blood state of flow in the circuit device and to ensure the smooth implementation of HA.[71,72] Compared with traditional blood purification therapy, the time of HA therapy is shorter, the requirements for anticoagulation therapy are greater, and the coagulation function of patients needs to be monitored more closely.

Selection and recommended dose of anticoagulant drugs

Unfractionated heparin is suitable for patients with no risk of bleeding disorders; with hyperlipidemic or abnormal bone metabolism; with a plasma antithrombin III activity percentage greater than 50%; and with a normal platelet count, activated partial thromboplastin time (APTT) or activated clotting time (ACT), thrombin time (TT), international normalized ratio (INR), and D-dimer level. Unfractionated heparin should not be used as an anticoagulant drug for patients with a history of allergies, a clear bleeding tendency, or HIT. The first dose of unfractionated heparin is typically 62.5-125 U/kg (0.5-1.0 mg/kg),[73] and the maintenance dose is typically 1250-2500 U/h (10-20 mg/h).[71]

LMWH is suitable for patients who have no active bleeding disorders, who have a plasma antithrombin III activity percentage above 50%, and whose platelet count is essentially normal; however, patients with severe abnormalities in lipid metabolism and bone metabolism, a prolonged partial thromboplastin time (APTT) and prothrombin time (PT), or a potential risk of bleeding due to an increased INR, an intravenous injection of 60-80 IU/kg is usually given.[71]

Nafamostat mesylate: This compound is a serine protease inhibitor that is mostly degraded and removed by blood purification during CPB, and a small amount is rapidly degraded after entering the body, with a half-life of 3-5 min. The effect of nafamostat mesylate on coagulation function is small; therefore, it is suitable for use as an anticoagulant in patients with bleeding tendencies. Before HA preflushing, the adsorption column is soaked with 50 mg of nafamostat mesylate for 20 min and then preflushed with 2 L of solution containing 40 mg/L nafamostat mesylate, and the initial dose is 45 mg/h. For plasma adsorption preflushing, 2 L of solution containing nafamostat mesylate at 20 mg/L is used, and the initial dose is 40 mg/h. The dose should be adjusted on the basis of the risk of coagulation, the anticoagulant effect on the adsorption column and the coagulation function in the body.[74]

Argatroban anhydrous: This compound is a direct thrombin inhibitor suitable for patients with active bleeding or a high risk of bleeding, with heparin allergy, or with previous HIT. Typically, the first dose is 250 μg/kg, and any additional dose is 1-2 μg/(kg·min) for continuous prefilter administration.[71]

Citrate: Sodium citrate anticoagulant acts through calcium chelation. If 1.0 mmol of citrate is used for anticoagulant therapy, then 3.0 mmol of sodium, 1.5 mmol of calcium and 3.0 mmol of bicarbonate are added to the body, and patients are at risk of citrate accumulation, producing metabolic complications such as hypocalcemia and metabolic acidosis; therefore, sodium citrate is not recommended for use as an anticoagulant in HA alone. However, regional citrate anticoagulation has been confirmed to be safer than systemic heparin anticoagulation in terms of reducing the risk of bleeding, and the incidence of metabolic complications and symptomatic hypocalcemia is low; therefore, sodium citrate can be used for anticoagulation in HA + CRRT. The concentration of sodium citrate is 4%, the pump rate (mL/h) = 1.3 - 1.6 × the blood flow rate (mL/min), and the sodium citrate enters through the arterial end; the pump rate of 10% calcium gluconate (mL/h) = 7.7% of the blood flow rate (mL/min), and the sodium citrate enters from the venous end behind the membrane. During treatment, the free calcium concentration inside and outside the body is monitored every 30 min, and the free calcium concentration in the body is dynamically evaluated and maintained at 1.0-1.2 mmol/L.[71,75]

No anticoagulant: For patients with no contraindications to heparin, before blood purification, preflushing with heparin-based saline at 500 U/dL (4 mg/dL) is performed, and then after 20 min, rinsing with 500 mL of normal saline is performed; for patients with contraindications to heparin, only adequate rinsing with normal saline is performed.[71]

Monitoring of anticoagulant therapy

The coagulation status of the patient should be monitored before, during and after anticoagulant therapy, and the dose of anticoagulant drugs should be adjusted on the basis of the monitoring results. When heparin, nafamostat mesylate, or argatroban anhydrous are used as anticoagulants, ACT or APTT monitoring is recommended. When LMWH is used as an anticoagulant, the activity of plasma anticoagulant factor Xa should be monitored. When sodium citrate is used as an anticoagulant, the free calcium concentration after the filter and in the patient should be monitored, and ACT or APTT can also be monitored.[71]

Anticoagulant therapy under special conditions

Liver failure

Patients with liver failure often have coagulation dysfunction. Therefore, evaluating the coagulation status of patients before and after treatment and observing and monitoring coagulation function in patients during treatment is particularly important. The APTT is usually controlled to be 1.5-3.0 times the upper limits of normal (ULN) or the ACT is controlled to be 150-200 s; when APTT > 3 × ULN or ACT > 200 s or 30 min after the end of treatment, the anticoagulant drugs could be stopped. During the purification process, the patient's coagulation and *in vitro* tubing status should be evaluated every 30 min.[76] If there is active bleeding, anticoagulant allergy, extracorporeal coagulation, *etc*., anticoagulant drugs should be adjusted in a timely manner, or the blood purification treatment should be stopped.[77]

(1) Heparin: The first dose of 15-60 U/kg, generally not more than 2500 U (20 mg), is given through the arterial end of the tubing, followed by maintenance administration of 7.5-30.0 U/(kg·h) to control the APTT to be 40%-80% greater than the ULN. For patients with liver failure with 20% $\leqslant$ plasma thromboplastin antecedent (PTA) $\leqslant$ 40%, APTT $\leqslant$ 87 (2 times the ULN), and platelet count $\geqslant$ 50 × 10^9/L, an anticoagulation regimen of 0.2 g/kg of heparin for the first dose without maintenance doses can be adopted.[78-80]

(2) LMWH: Dosed at 60-80 U/kg (no more than the volume of a single vial) or at the volume of a single vial while controlling the anti-Xa level at 0.3-0.5 U/mL.[77]

(3) Nafamostat mesylate: The first dose of nafamostat mesylate (3-20 mg) is given through the arterial end of the tubing, the maintenance dose is administered at 1-25 mg/h, the APTT is controlled to be (1.5-3.0) × ULN, or the ACT is controlled to be 150-200 s.

(4) Argatroban anhydrous: For patients with liver failure, the first dose is 40-65 μg/kg, the maintenance dose is 9-30 μg/(kg·h), the APTT is (1.5-3.0) × ULN, or the ACT is 150-200 s.

(5) Regional citrate anticoagulation: Sodium citrate is pumped into the arterial end of the catheter, and 10% calcium gluconate or calcium chloride is pumped into the venous end. The pumping rate is adjusted on the basis of the results of blood gas analysis to maintain the postfilter Ca-ion concentration between 0.2 and 0.4 mmol/L to achieve an anticoagulant effect *in vitro*, and the Ca-ion concentration in the body is maintained at 1.0-1.2 mmol/L to ensure that there is no anticoagulant in the body.[80-82]

(6) No anticoagulant: For patients at high risk of bleeding, anticoagulants should be avoided whenever possible. Patients with high bleeding risk are those who meet one of the following conditions: 1) within 3 days of surgery; 2) significant bleeding; 3) prothrombin time $\geqslant$ 50 s; 4) APTT $\geqslant$ 3 × ULN; 5) platelet count < 50 × 10^9/L; and 6) the thromboelastography R value (time to initial clot formation and coagulation index [CI] reveal a hypercoagulable state).[77]

Disseminated intravascular coagulation (DIC)

There is little evidence-based medicine for the plasma adsorption of patients with DIC, and a consensus has not yet been reached. However, during the plasma adsorption, different anticoagulation strategies should be used according to the different states of DIC (hypercoagulable state, consumptive hypercoagulable state, and secondary hyperfibrinolytic state).

Hypercoagulable state: In the early stage of DIC, various factors lead to the activation of the coagulation system, increased generation of thrombin, the formation of many microthrombi, and a hypercoagulable state of the blood. During this period, systemic heparinized anticoagulant therapy can be used in blood purification.[83]

Consumptive hypercoagulable state: Coagulation factor levels and platelet counts are reduced due to massive depletion by the formation of thrombin and microthrombi, and the blood is in a hypercoagulable state because of the increased function of the secondary fibrinolytic system. To avoid increasing the risk of bleeding, regional citrate anticoagulation therapy should be administered.

Secondary hyperfibrinolytic state: Thrombin and XIIa activate the fibrinolytic system, turning a large amount of plasminogen into plasmin, which, together with the formation of fibrin degradation products (FDPs), further strengthens the fibrinolytic and anticoagulant effects. In addition to heparin treatment, an appropriate amount of fibrinolysis inhibitor can be given.[84]

In these anticoagulation states, the conditions of patients, such as the ACT, APTT, fibrinogen level, AT III level, and platelet counts, should be continuously and dynamically monitored, and the anticoagulant dose should be adjusted on the basis of the test results.

MONOGRAPH

Application of HA in sepsis

The current evidence is not sufficient to prove that HA is directly associated with a reduction in the sepsis mortality rate, and more large-scale clinical studies are still needed for verification.

HA therapy may benefit patients with uncontrolled inflammation due to severe infection from the perspective of stabilizing hemodynamics and improving organ function.

The timing of HA treatment for sepsis should be based on a comprehensive assessment of organ functional status (refer to the sequential organ failure assessment [SOFA] score or the usage of vasoactive drugs) and inflammatory indicators (such as IL-6 or PCT), and treatment should be administered as soon as possible.

Description of evidence

Although some retrospective studies have shown that HA can reduce the mortality rate of patients with septic shock,[85-87] significant heterogeneity exists across study findings, and several high-quality studies have failed to replicate these results.[23,29,88-92] Relevant meta-analyses demonstrate varied evidence grades regarding polymyxin B hemoperfusion (PMX) for sepsis mortality reduction (with some low-quality evidence); current evidence remains insufficient to support the routine clinical use of PMX, highlighting the urgent need for validation through large-scale RCTs.[19,93]

A number of studies from different countries (the United States, Germany, China, and Japan) have shown that with the administration of HA therapy for sepsis patients, the dose of vasoactive drugs can be reduced, and a reduction in the SOFA score can be observed.[85,86,88,94-100] A number of studies have shown that HA can significantly reduce the levels of inflammatory cytokines (IL-6, IL-8 and IL-10).[96,97,99-101] Two studies have shown that HA could reduce the levels of inflammatory factors while reducing the dose of vasoactive drugs used.[96,100] Two single-center retrospective studies on HA therapy for children with sepsis have revealed that CytoSorb-HA is associated with a decrease in the levels of inflammatory cytokines, such as IL-6 and IL-10.[98,102] Therefore, we speculate that for patients with uncontrolled inflammation due to severe infection and impaired hemodynamic stability, HA may stabilize hemodynamics and improve organ function by weakening uncontrolled inflammation. However, some studies have not revealed similar results. A multicenter RCT on the effect of HA on IL-6 removal in septic patients revealed that the adsorption of IL-6 by CytoSorb did not lead to a decrease in the serum concentration, but this result may be related to the short duration of HA therapy.[103] One meta-analysis on the application of CytoSorb that included 34 studies revealed that, in the sepsis subgroup, there were no significant differences between the HA group and the control group in terms of the levels of norepinephrine, mean arterial pressure, or SOFA score, but all of the observational studies had a moderate to severe risk of bias.[104]

For septic patients, if the condition is not stabilized or shows a worsening trend after receiving initial bundle treatment, HA therapy should be considered.[105] The organ function assessment of patients should meet any of the following criteria: a SOFA score $\geqslant$ 10, a SOFA score increase of $\geqslant$ 2 within 6 h, or the use of vasoactive drugs (such as norepinephrine $\geqslant$ 0.4 μg/kg/min or other equivalent drugs).[5,106,107] Moreover, the inflammatory indicators of patients should meet any of the following criteria: an IL-6 concentration > 500 ng/L or an increase in the IL-6 concentration of more than 100% within 6 h. In the case of bacterial infection, a PCT $\geqslant$ 10 μg/L can be used as a criterion.[5,106,107] Patients who meet these conditions should receive HA therapy as soon as possible.

For the comparison of membrane materials in the HA treatment of sepsis, no study has clearly demonstrated the superior performance of one membrane material. Individual studies on the effects of various membrane materials on sepsis are also inconsistent, whether PMX use in HA therapy for sepsis is beneficial is unclear,[19,93] and most studies of CytoSorb have revealed that CytoSorb has no significant effect on inflammation or mortality in septic patients.[88,90,92,102,108,109] Although studies on HA[94,95] or oXiris[87,96,97,99,100] have shown improved hemodynamics of septic patients, most of these studies are single-center retrospective studies with small sample sizes; therefore, the quality of the evidence is low.

Administration of HA in SAP

The existing evidence is not sufficient to prove that HA is directly related to the improvement in clinical outcomes of patients with SAP, and large multicenter RCTs are still needed for verification.

HA may benefit SAP/hypertriglyceridemia (HTG)-acute pancreatitis (AP) patients by removing inflammatory mediators and improving organ function and hemodynamics.

The timing of HA therapy initiation for SAP patients should be based on a comprehensive evaluation of inflammation, organ function and hemodynamics.

The early pathophysiological process of SAP is characterized by systemic inflammatory response syndrome. The excessive release of inflammatory mediators triggers multiorgan failure

through the cascade effect, posing a main risk of early death. The targeted removal of inflammatory mediators has become an important research direction for stopping the progression of SAP.

Findings from a number of international and Chinese studies have suggested that HA may improve the organ function, inflammatory factor levels and length of ICU stay of SAP patients.[110-113] The PACIFIC study (a single-center, small sample size, single-arm study) conducted in Germany showed that, compared with the historical control group, the CytoSorb group had improved renal function, more stable hemodynamics, and lower levels of inflammatory cytokines such as IL-6; however, the nonrandomized design limits the reliability of the conclusions.[108] In traditional blood purification technologies, continuous veno-venous hemofiltration (CVVH) removes inflammatory mediators through filters with adsorption functions, such as PMMA membranes and AN69 ST membranes. Therefore, combined blood purification regimens (such as HA combined with high-flow hemofiltration) have gradually received increasing attention. A number of Chinese single-center retrospective studies have shown that the use of an HA-330 adsorber combined with other blood purification regimens may increase the removal of inflammatory mediators and improve renal function synergistically.[110-112] Although some observational studies and small-sample exploratory RCTs have suggested that SAP patients may benefit from HA, significant heterogeneity exists among the studies, and the overall quality of evidence is still low. The current Chinese and international guidelines for the diagnosis and treatment of SAP (International Association of Pancreatology [IAP]/American Pancreatic Association [APA], American College of Gastroenterology [ACG], *etc.*) do not include HA as the recommended treatment.[108,110-119] Although SAP is listed as an indication for HA in the *Blood Purification Standard Operating Procedure (SOP)*,[120] the evidence is mainly from observational studies. Therefore, there is an urgent need to clarify the role of HA in treating SAP through rigorously designed large-sample clinical studies.

In the subgroup of patients with HTG-AP, HA has unique dual removal properties. An early exploratory study confirmed for the first time that HA combined with hemofiltration could significantly reduce triglyceride (TG) and IL-10 levels as well as APACHE II scores.[113] Findings from a subsequent exploratory study conducted by Sun *et al.* further suggested that HA combined with hemofiltration might shorten the length of ICU stay.[112] However, at present, all relevant studies are single-center and small-sample explorations, but the clinical efficacy still needs to be verified in multicenter RCTs.

There are currently no studies on the optimal timing of HA therapy for SAP patients, and the optimal starting time remains unclear. By analyzing the initiation timing of HA in the studies showing that HA can reduce the inflammatory response and improve organ function and hemodynamics in SAP patients, and based on the pathogenic mechanism that the cascade of inflammation responses in SAP patients tends to occur in the early stages, we recommend performing a comprehensive assessment of the inflammatory response, organ function, and hemodynamic status of SAP patients, and HA should be initiated as early as possible if the treatment indications are met.

Administration of HA in severe poisoning

For severe poisoning by fat-soluble or highly protein-binding poisons (such as organophosphorus pesticides, paraquat, toxins, *etc.*), it is recommended to start HA therapy in the early stage (within 2-4 h) of poisoning; especially when complicated with multiorgan dysfunction or the blood concentration of toxicant is high, combined HD/filtration can be considered.

At present, further investigation of the optimal timing of starting HA, the selection of adsorption materials, and the effect on long-term prognosis in the treatment of severe poisoning is still needed.

The treatment of acute drug or toxin poisoning should follow the principle of early and rapid intervention. As an important treatment for the removal of fat-soluble or highly protein-binding poisons, HA has been widely used in the rescue treatment of severe poisonings with multiple substances, including valproic acid,[121,122] carbamazepine,[123,124] organophosphorus pesticides,[125] paraquat,[126] diquat,[127] and mushrooms.[128] The first RCT examining HA for the treatment of critically ill patients with suspected organophosphorus poisoning, conducted by Omar *et al.*, revealed that HA230 adsorption shortened the length of ICU stay and reduced the 28-day mortality rate and the incidence of serious complications.[129] A prospective cohort study of 260 patients further confirmed that the HA330 adsorption could accelerate the recovery of cholinesterase activity and reduce the incidence and mortality of intermediate syndrome.[130] A retrospective study by Shi *et al.* revealed that HA230 adsorption significantly affected the removal of poison from patients with acute paraquat poisoning and repeated HA therapy effectively inhibited the rebound phenomenon.[131] A retrospective study of 149 patients revealed that HA330 adsorption combined with HD might improve the likelihood of survival.[132] With respect to the treatment of severe poisoning by HA, a consensus, based on the clinical practice experience in China and abroad, has been reached. In the *Clinical Guideline for the Diagnosis and Treatment of Acute Organophosphorus Pesticide Poisoning (2016)*,[133] it is recommended that HA therapy be administered as soon as possible for patients with severe organophosphorus pesticide poisoning, and the combination of HD or CRRT should be considered for patients with renal dysfunction and multiple organ dysfunction syndrome (MODS). In the 2013 Expert Consensus on the Diagnosis and Treatment of Acute Paraquat Poisoning, it is recommended that HA be performed as soon as possible after oral paraquat poisoning, and the effect is better if it is performed within 2-4 h.[134] The EXTRIP workgroup published the recommendation for the use of blood purification therapy for poisonings with common drugs or poisons on its website (http://www.extrip-workgroup.org/recommendations), including overall opinions, indications, timing of termination, and selection of blood purification methods. However, most of the existing evidence is from low-quality observational studies (case studies/cohort studies), and large multicenter RCTs are still needed to optimize treatment strategies and explore long-term benefits.

Administration of HA in patients undergoing cardiac surgery

HA has certain curative effects in cardiac surgery, especially for the

inflammation response caused by CPB. By reducing the levels of inflammatory factors (such as IL-6 and IL-8), HA helps to relieve postoperative inflammation and improve hemodynamics. However, although some studies have shown that HA is helpful for reducing postoperative cytokine levels and short-term prognosis, more large-scale clinical studies are still needed to verify the long-term effect.

CPB can induce a cytokine storm and is an important factor for organ failure in patients after cardiac surgery. Currently, the application of HA in CPB is still controversial, and several RCTs have revealed inconsistent results. In a multicenter RCT (the REMOVE study) conducted by Diab *et al.*, 282 patients with infective endocarditis undergoing cardiac surgery were enrolled and randomly assigned to the CytoSorb and control groups, and the results indicated that HA cannot reduce the likelihood of postoperative organ failure, and although HA reduced the levels of IL-1β and IL-18, it did not affect clinically relevant prognostic indicators.[35] Two other single-center pilot studies revealed that there were no statistically significant differences in postoperative inflammatory factor levels or clinical outcomes between CytoSorb treatment and conventional treatment after CPB.[40,57] He *et al.* implemented a single-center RCT and enrolled 60 patients who underwent valve replacement surgery, and the results indicated that an HA column (HA380) could significantly reduce the levels of IL-6, IL-8, and IL-10; the dose of vasoactive drug used; the mechanical ventilation time; and the length of ICU stay.[135] A single-center pilot study revealed that the use of HA380 could reduce the incidence of acute kidney injury (AKI) after CPB.[18] Currently, clinical studies on the use of HA380 in CPB are limited. We look forward to prospective RCTs with large sample sizes to reveal the clinical efficacy of HA380 in treating CPB.

Application of HA in RM

In the treatment of RM, HA mainly can rapidly remove myoglobin from the blood, reduce the incidence of complications such as kidney damage, and improve the clinical status of patients. In clinical practice, the timing and duration of treatment should be reasonably selected according to the specific conditions of the patient (such as myoglobin level, renal functional status, *etc.*) to maximize the treatment effect.

RM is the release of substances, such as myoglobin and creatine kinase (CK), into the blood due to muscle cell damage, which may cause serious complications, such as AKI and DIC.[136,137] Myoglobin has a relatively large molecular weight (approximately 17 kDa), and excessive accumulation in the blood directly damages renal tubular epithelial cells. Because conventional RRT has a limited effect on the removal of myoglobin, HA has become an effective means to remove myoglobin.[136,138,139] A review of 111 patients revealed that HA combined with CRRT (CRRT + HA380) significantly reduced the ICU mortality and in-hospital mortality of patients with RM and AKI and clearly removed CK, without significantly increasing the occurrence of AEs.[138] A number of studies have shown that CytoSorb can rapidly reduce the levels of myoglobin and CK and improve the recovery of renal function, and CytoSorb has shown good safety in multiple studies.[5,140] According to the HRTF consensus combined with clinical experience, for patients with RM, if the serum myoglobin level exceeds 10,000 μg/L (for patients complicated with AKI, the myoglobin level is > 5000 μg/L), HA therapy should be performed as soon as possible, preferably within 24 h of hospitalization. If myoglobin cannot be measured or is limited by the upper limit of detection (such as 3000 μg/L), but the patient has significantly increased CK levels and is accompanied by typical symptoms and abnormal renal function, HA can also be considered.[136] However, owing to the lack of large-scale clinical trial data, further study of the optimal application of HA is still needed.[136,141]

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Changsong Wang is an Editorial Board Member of the journal. The article was subject to the journal's standard procedures, with peer review handled independently of the editor and the affiliated research groups.

Data availability statement

All data supporting the findings of this study are included within the paper and its supplementary file. The summary tables of evidence-based medical evidence are provided as Supplementary Material, https://links.lww.com/JTCCM/A34.

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