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Clinical application of artificial liver and blood purification: expert consensus recommendations

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Introduction

Artificial liver therapy is a type of blood purification, which can remove harmful substances, supplement essential substances, improve the internal environment, and temporarily replace some functions of the failed liver through an in vitro mechanical, physical, chemical, and biological device. Artificial liver therapy can create conditions for hepatocyte regeneration and liver function recovery, or allow for opportunities to receive liver transplantation [1–3]. The role of artificial liver in patients with liver failure has been well established [4], and has expanded clinical applications in other diseases. This technology has been used for decades in many provincial regions in China. However, there are still considerable disparities at the practical level in terms of timing of treatment, choice of the treatment model, establishment of the vascular access, use of anticoagulants, handling of common machine alarms, flow, and management of treatment and even layout of artificial liver treatment rooms. China has promulgated the *Guidelines for the Diagnosis and Treatment of Liver Failure (2018 Edition)* and the *Standard Operating Procedures for Blood Purification (2021 Edition)*, which are important guidelines for standardizing and improving clinical diagnosis and treatment. It is, however, still necessary to study the characteristics of severe liver disease and indications for artificial liver to address the current clinical problems, and further highlight challenges in clinical practice, thereby contributing to the enhancement of this technology. This consensus aims to highlight the key points of artificial liver and blood purification technology, standardize clinical application, and enhance artificial liver and blood purification technology. Due to the complexity of liver failure and the emergence of new artificial liver blood purification technology, this consensus cannot cover all the issues involved. It only provides basic norms to facilitate the development of reasonable clinical protocols based on disease characteristics, principles of artificial liver blood purification, as well as the accessibility of medical resources. However, this consensus will continue to be updated as artificial liver technology improves and matures.

Indications, relative contraindications, and timing of artificial liver therapy

Indications

(1) Pre-, early, and mid-stage liver failures due to various reasons; patients with advanced liver failure may also be treated, but the complications increase, the risk of treatment is high, and the benefits to the patient may be reduced. Clinical physicians should weigh the pros and cons and proceed with caution while actively seeking liver transplantation opportunities. (2) Patients are waiting for liver sources prior to liver transplantation for end-stage liver disease, patients with liver transplant rejection, and

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patients with a non-functional stage of the transplanted liver. (3) Patients with severe cholestatic liver disease, and severe hyperbilirubinemia due to various causes [1]. (4) Other diseases: For example, sepsis or multiple organ dysfunction syndrome (MODS) with severe liver injury, acute poisoning and refractory severe immune diseases, thrombotic thrombocytopenic purpura, myasthenia gravis, etc. Please refer to Sect. 3 for more details on the specific indications for different artificial liver models.

Relative contraindications

(1) Severe active bleeding or diffuse intravascular coagulation; (2) severe allergy to blood products or drugs used in treatment such as plasma, heparin, and protamine; (3) hemodynamic instability; (4) non-stable stage of cardiac or cerebral infarction [1].

Timing selection

The timing of artificial liver treatment is determined in conjunction with various factors such as the pathophysiological characteristics of the disease, indication for artificial liver model, and the treatment objectives for the patient, in line with the "early diagnosis and early treatment" principle [5, 6].

For patients with subacute liver failure and acute-on-chronic (subacute) liver failure at the pre, early, and mid-stage, artificial liver therapy is recommended as early as possible to stop the progression of the disease and to promote recovery of liver function, based on the treatment of etiology and causative factors. Given general complications, poor overall prognosis and high risk of artificial liver treatment, the risks need to be assessed in detail for the above-mentioned advanced-stage patients. Also, adequate preparations (including various contingency plans) should be made prior to treatment, while actively seeking liver transplantation opportunities. Acute liver failure, with hepatic encephalopathy progresses rapidly, and it is recommended to initiate artificial liver therapy as early as possible, while the prognosis is dynamically evaluated. Furthermore, liver transplantation opportunities can be actively sought if necessary. Specific treatment modalities may be selected in accordance with the patient conditions. The frequency of treatment should be determined in accordance with the type of liver failure and the rate of progression of the disease.

For patients with liver failure who are awaiting liver transplantation, active artificial liver support therapy is recommended to prevent complications, prolong survival time, and create conditions for successful transition to liver transplantation. For patients developing liver transplant rejection, early initiation of artificial liver therapy is recommended if the results are still poor after adjusting the treatment regimen after transplant rejection. Artificial liver is also recommended in patients with non-functional transplanted liver.

Artificial liver therapy is recommended in patients with severe cholestatic liver disease and those with severe hyperbilirubinemia, if the bilirubin level remains high with general treatment, except in cases of obstructive jaundice.

The prognosis of patients after treatment with artificial liver should be gauged on the basis of symptoms, laboratory indicators such as bilirubin, prothrombin activity (PTA), complication control, end-stage liver disease model score, liver failure grading and dynamic assessment staging methods [7]. Artificial liver treatment can be stopped if the patient's conditions improve significantly.

Establishment of artificial hepatic vascular access

Common methods for establishing artificial hepatic vascular access include central venous cannulation, peripheral vascular puncture, and a combination of both. The central venous cannulation method is often selected as it has a higher success rate, allows for sufficient and stable blood flow, and satisfies all the artificial liver treatment criteria compared to the peripheral vascular puncture method [8].

Central venous cannulation

The main central venous cannulae commonly used for artificial liver include internal jugular and femoral venous cannulae [9]. Primarily, a high-flow double-lumen catheter without a tunnel or polyester sleeve is used. Ultrasound localization or ultrasound-guided puncture placement is recommended. Following internal jugular vein cannulation, chest radiographs are done to understand the position of the catheter. There are no absolute contraindications to central venous cannulation, however, relative contraindications include extensive vena cava system thrombosis, local infection at the puncture site, coagulation dysfunction, as well as patient non-cooperation.

Internal jugular vein cannulation is mostly chosen for the right internal jugular vein puncture, and the commonly used puncture point is the tip of the sternocleidomastoid triangle (the triangle formed by the clavicular head, sternal head and clavicle of the sternocleidomastoid muscle), 3–5 cm from the upper edge of the clavicle and anterolateral to the common carotid artery. Catheter length of 12–15 cm is selected for the right side (15–19 cm for the left side). The catheter is typically retained for no more than 4 weeks. There is a risk of complication such as pneumothorax and hemopneumothorax. The femoral vein is generally placed

1–3 cm below the inguinal ligament and 0.5–1 cm medial to the femoral artery. The catheter is at least 19–20 cm long and is generally retained for no longer than 2 weeks. The incidence of catheter-associated infection and blockage is higher than that of internal jugular vein placement due to the immobility of the patient, proximity of the catheter to the perineum, and the slow blood flow rate. No differences were observed between the two types of central venous cannulation in terms of treatment outcome. Subclavian vein puncture is relatively rarely employed in artificial liver treatment due to its difficulty in operation, compression hemostasis, and high incidence of thrombosis and stenosis.

Peripheral vascular puncture

To ensure adequate and stable blood flow, peripheral arteries (radial artery, brachial artery, dorsalis pedis artery) are generally selected as the arterial end, while peripheral veins (median elbow vein, cephalic vein, noble vein) are selected as the venous end, or the venous–venous approach may also be selected. A 16G–20G internal fistula needle or a tube indwelling needle is used for puncture.

The peripheral vascular puncture method has relatively smaller number of complications. The vascular outlet and return circuit are placed separately, therefore, the blood circulation rate is not affected. It satisfies most of the artificial liver treatment models, and is single-use and inexpensive. However, it is affected by peripheral vascular conditions, especially arterial puncture, which is affected by slightly greater number of factors. The blood flow is also unsatisfactory, making it suitable for models with less demanding blood flow requirements and shorter treatment time. Complications are rarer, with mainly petechiae, pseudoaneurysms, etc.

Major complications, prevention, and treatment

(1) Bleeding or hematoma at the puncture site: local compression for hemostasis; in case of intraoperative bleeding, observe for excessive anticoagulation. If the bleeding is extensive or hematoma is suspected, perform ultrasound examination if necessary to determine or monitor the bleeding situation; hemostatic drugs may be used to assist in treatment. (2) Incorrect arterial puncture: remove the needle immediately, apply pressure for at least 10 min, with adequate pressure to prevent hematoma. (3) Infection: remove the catheter immediately after the diagnosis is confirmed and perform bacterial culture to choose appropriate antibiotic treatment. (4) Pneumothorax and hemopneumothorax: when central venous puncture is done, the puncture point should be prevented from being too low and the skin expander should not enter too deep. If it occurs, the treatment is similar to pneumothorax.

Care of indwelling catheters

Catheter care is performed in accordance with the ISO 9001 Nursing Quality Management System, with emphasis on the following areas: (1) During and after treatment with artificial liver the presence of local bleeding, hematoma, infection, extubation, and blockage should be observed. Also, pain, swelling, color change and arterial pulsation of the limb on the side of the tube, fixation of the indwelling catheter and whether it has loosened or dislodged, and the presence of rupture or switch failure of the catheter should all be observed. Catheter slippage should be scored when the catheter is retained, the patient and his/her family members should be informed of the precautions to be taken, and a restraint band should be applied to assist in fixation, if necessary. (2) With an indwelling catheter, large movement of the head or thighs should be avoided to prevent local bleeding. Lying on the side of the indwelling catheter during sleep should also be avoided to prevent the catheter from loosening and falling off due to friction. (3) Appropriate massage and instructions should be provided to patients for active and passive functional exercises of the limbs, to ensure adequate blood circulation and reduce the risk of thrombosis. (4) Active prevention of infection by keeping skin clean and dry at the puncture site and changing the dressing every other day. (5) Performing catheter patency check and care every other day: During nursing, the sealing solution in the catheter should be taken out, presence of blood clots should be observed, and then the tube should be flushed and sealed after confirming that it is smooth and free of blood clots. To avoid embolism, it is strictly prohibited to inject directly when there is a blood clot.

Treatment modality with artificial liver and related instructions

Plasma exchange/selective plasma exchange (PE/SPE)

Application highlights

The main replacement solutions used in PE include fresh frozen plasma, albumin solutions, and other plasma substitutes. Different replacement solutions should be selected as per the specific conditions of the patient. For example, when the patient's PTA is normal or drops insignificantly, part of the albumin solution may be used instead of fresh frozen plasma. When the patient's PTA drops significantly and the amount of fresh frozen plasma is insufficient, plasma substitutes (less than 1/4 of the total amount of replacement) may be used first, followed by fresh frozen plasma [10–12].

Attention must be paid to setting the plasma fractionation ratio following the characteristics of different plasma separators/plasma component separators and the erythrocyte-specific volume of the patient. This is to avoid the plasma fractionation ratio being higher than the upper limit of the plasma separator and resulting in membrane rupture or the plasma fractionation ratio being too high and causing excessive blood concentration, resulting in erythrocyte destruction and line blockage.

The frequency of PE treatment should be individualized based on patient condition. Factors to be considered include the volume of distribution of the causative agent in the body, the half-life of the causative agent, the severity of the primary disease (e.g., the baseline level of serum bilirubin and the magnitude of rebound in patients with liver failure), etc.

Citrated fresh frozen plasma is alkaline, and the colloid osmotic pressure is generally lower than the patient's plasma colloid osmotic pressure. Hence the PE may aggravate hepatic encephalopathy. Therefore, PE mode alone is not recommended for patients with existing significant hepatic encephalopathy. For these patients, other modes (or in conjunction with PE) are recommended.

Advantages and disadvantages and applicable population

Advantages: easy operation, broad-spectrum rapid, and efficient removal of various toxins, supplementation of fresh frozen plasma components (such as coagulation factors), shorter treatment time, acceptable patient tolerance, etc. Compared to membrane PE, centrifugal PE requires a lower blood flow rate and the possibility of performing it through peripheral vascular puncture, thereby avoiding the complications and risks associated with central venous cannulation.

Disadvantages: limited by plasma sources as well as poor clearance of water-soluble toxins, there may be aggravation of hepatic encephalopathy, plasma allergy, risk of infection associated with blood products, and water and sodium retention after treatment. The disadvantages of centrifugal PE also include the possibility of mixing cellular components in the separated plasma, relatively complicated procedure, inability to perform SPE, etc.

Intended population: patients with hepatic failure, prehepatic failure, hyperbilirubinemia; patients with other diseases that include macromolecules or pathogenic mediators bound to albumin in the blood, such as cryoglobulinemia, Guillain–Barré syndrome, thrombotic thrombocytopenic purpura as well as myasthenia gravis.

Hemoperfusion (HP)/plasma perfusion (PP)

Application highlights

HP tends to destroy blood-formed elements, therefore, PP is recommended in patients with poor coagulation and low platelets, such as those with liver failure [13–15]. During HP treatment, care should be taken to use the appropriate blood flow rate. A rapid blood flow rate can reduce the adsorption efficiency, while a sluggish flow rate can easily cause clotting of the perfuser. Changes in pressure should be closely monitored during treatment, especially arterial and venous pressure in HP mode, and transmembrane pressure and secondary membrane inlet pressure in PP mode. Abnormal elevation of pressure must be detected in a timely manner and additional anticoagulation should be used when necessary. To avoid allergic reactions, various filters and lines must be adequately primed before treatment. Depending on patient's condition, HP/PP can be used in conjunction with other artificial liver models.

Advantages, disadvantages, and applicable population

Advantages: wide range of adsorption, relatively high clearance of medium and large-molecule and protein-bound substances, without reliance on plasma. PP may avoid the destruction of blood-formed elements like blood cells. Specific bilirubin adsorption could specifically adsorb bilirubin and small amount of bile acid.

Disadvantages: inability to regulate water, electrolytes, acid–base balance, loss of some albumin and coagulation factors, easy destruction of blood-formed elements by HP.

Applicable population: patients with liver failure and hepatic encephalopathy, liver failure with systemic inflammatory reaction syndrome (SIRS), hyperbilirubinemia, endotoxemia, acute poisoning, autoimmune diseases, etc. HP is not recommended in patients with liver failure and poor coagulation.

Double plasma molecular adsorption system (DPMAS)

Application highlights

This model features a large extracorporeal circulation volume, and the patient is prone to hypotension during the initial treatment period. Therefore, monitoring should be strengthened. In case of hypotension, rehydration, and volume expansion therapy should be given in a timely manner, and if necessary, the plasma separator

and adsorber may be primed with colloidal fluid upon completion of heparin saline priming.

This model of extracorporeal circulation pipeline is relatively complex, and the adsorption column also has certain effects on anticoagulants. Therefore, attention must be paid to appropriately increase the dose of anticoagulants in the initial stage of treatment, especially within the first 30 min. Changes in pressure should be closely monitored during treatment, especially the transmembrane and secondary membrane inlet pressure, to detect abnormal elevation of pressure in a timely manner and to provide additional anticoagulants when necessary. The frequency of treatment depends on the severity of the primary disease and the effectiveness of treatment.

Advantages, disadvantages, and applicable population

Advantages: rapid removal of bilirubin, inflammatory mediators, etc., without requiring exogenous plasma, and continuous intensification of treatment if necessary by switching to a new set of adsorption columns.

Disadvantages: inability to replenish coagulation factors; if necessary, it can be used in conjunction with a model containing exogenous plasma supplementation; it also has a certain adsorption effect on albumin and coagulation factors, which should be supplemented accordingly if necessary, after treatment; the volume of extracorporeal circulation is relatively large, and hypotension is prone to occur during the initial treatment period.

Intended population: patients with liver failure, prehepatic failure, hyperbilirubinemia from various causes, also applicable to those with hepatic encephalopathy, perioperative treatment of liver transplantation, and MODS with jaundice or sepsis [16–18].

Plasma diafiltration (PDF)

Application highlights

The main replacement solutions used in PDF include fresh frozen plasma, albumin solutions, and other plasma substitutes. Different replacement solutions must be selected according to the patient's condition. It may be either all fresh frozen plasma or plasma and a certain percentage of plasma substitute (e.g., 4–5% albumin solution). The dialysis solution can be selected as a finished product or configured according to the actual conditions. Electrolyte, blood sugar levels and the acid–base balance should be monitored during treatment.

Plasma component separators of different specifications must be selected according to specific patient's conditions. Attention should be paid to avoid excessive concentration of blood due to excessive filtration fraction during the treatment process, which may result in red blood cell destruction and line blockage. Treatment frequency is the same as PE.

Advantages, disadvantages, and applicable population

Advantages: it can simultaneously remove protein-bound and water-soluble toxins, while replenishing the lack of coagulation factors and bioactive substances in the body, and maintaining electrolyte and acid–base balance. This prevents the rebound of toxins in the blood, which is relatively less after treatment, thereby avoiding possible complications like imbalance syndrome and tissue edema. Compared to PE, less plasma is required (30%–50% savings in plasma), resulting in less risk of allergy and infection that may occur with the application of more plasma, and contributing to the maintenance of hemodynamic stability. Flexible selection is available between intermittent (4–8 h) or continuous treatment, depending on clinical demands [19].

Disadvantages: subject to plasma sources, there are risks of plasma allergy, blood product-related infections, relatively long treatment time, high anticoagulation requirements, etc.

Intended population: patients with liver failure (especially combined with hepatic encephalopathy), renal insufficiency, SIRS, poisoning, electrolyte and/or acid–base balance disorders, etc.

Hemofiltration (HF)/hemodialysis (HD)/HDF

Application highlights

Given the complex composition of toxins in patients with liver failure, HF/HD/HDF are now commonly used in combination with other blood purification models. In clinical practice, the temperatures and flow rates of dialysate and replacement fluid formulations are individually adjusted according to the volume, cardiopulmonary function, electrolyte and/or acid–base imbalance, etc., of the patient. Protein loss may increase during HF/HDF treatment, in which case, supplementation is required.

For HF and HDF models, when setting the blood flow rate and replacement fluid speed, the filtration fraction is generally required to be controlled within 25–30%, to avoid over-concentration alarm. When the blood pump slows down, the replacement fluid speed should also be adjusted downward, to maintain an appropriate filtration fraction [20–22].

Advantages, disadvantages, and applicable population

Advantages: high efficiency in removing medium and small molecules, rapid correction of volume overload, accurate regulation of electrolyte and acid–base imbalance.

Disadvantages: low clearance of large-molecule toxins, protein-bound toxins, etc. Preferably used in conjunction with other artificial liver models in the treatment of liver failure. The treatment features a large change in content or electrolyte concentration per unit of time, which can easily cause hypotension and imbalance syndrome.

Intended population: patients with liver failure, prehepatic failure or other types of diseases with disorders of water, electrolyte, and acid–base balance that are difficult to cure; patients with renal insufficiency; liver failure combined with cerebral edema, and hepatic encephalopathy; toxic liver disease; SIRS, etc.

Couple plasma filtration adsorption (CPFA)

Application highlights

Generally, a dedicated blood purification device with CPFA mode is required to perform CPFA treatment. For the treatment of liver failure, an adsorption column with bilirubin adsorption capability is required for the plasma adsorption portion of CPFA.

When there is no dedicated blood purification device with CPFA model, two blood purification devices may be clinically connected in series for CPFA treatment, of which one performs plasma adsorption and the other performs HF/HD treatment. Adsorbers should be selected according to the therapeutic purpose, such as perfusion devices or cytokine adsorbers with broad-spectrum adsorption function in sepsis; bilirubin adsorbers or dual adsorption in liver failure.

Advantages, disadvantages, and applicable population

Advantages: the CPFA integrates plasma adsorption therapy and HF/HD in an organic manner, simultaneously removing protein-bound and water-soluble toxins and features broad-spectrum and continuous removal of pathogenic solutes from the blood, as well as simultaneous adjustment of water-electrolyte and acid–base balance, to maintain a stable internal environment. Among them, the plasma adsorption part may be flexibly selected as a perfusion device, cytokine adsorber, or bilirubin adsorber, based on the therapeutic purpose without the need for plasma or albumin. The HF/HD fraction removes medium and small molecular weight water-soluble toxins such as ammonia and creatinine and is capable of volume regulation and renal support.

Disadvantages: CPFA has higher equipment requirements, complex procedures, and high treatment cost, and may cause complications if not properly applied. Therefore, the indications for CPFA should be strictly controlled.

Intended population: patients with liver failure due to various causes, also patients with renal insufficiency and hyperammonemia, rhabdomyolysis, burns, severe autoimmune diseases, poisoning, etc. [23–26].

Double filtration plasmapheresis (DFPP)

Application highlights

The main replacement solutions used in DFPP include fresh frozen plasma, albumin solutions, and other plasma substitutes. Different replacement solutions are selected in accordance with the specific conditions of the patient, for example, when the patient's PTA is normal or declines insignificantly, an albumin solution or other plasma substitute may be used instead of fresh frozen plasma. When there is a more significant decline in the PTA, fresh frozen plasma should be used. During treatment, the blood pump speed is gradually increased, and filtration is started after a period. The filtration volume is increased gradually to avoid drastic changes.

During treatment, the speed ratio of the plasma disposal pump to the plasma fractionation pump is adjusted in accordance with the inlet pressure of the plasma component separator, to avoid excess inlet pressure and to continue treatment. The ratio of the plasma disposal pump to the plasma fractionation pump should not be too high, else it can result in excess plasma loss, necessitating the need to replenish more replacement fluid.

Advantages, disadvantages, and applicable population

Advantages: selective removal of large molecules of pathogenic substances from plasma, reduces the loss of albumin and the need for fresh frozen plasma, as also reduces the incidence of cross-infection and allergic reactions.

Disadvantages: loss of a part of coagulation factors, with relatively complicated operations.

Applicable population: patients with diseases requiring removal of disease-causing macromolecules in the blood, such as severe autoimmune diseases, hypercholesterolemia, systemic lupus erythematosus, neurological diseases (such as myasthenia gravis) as well as skin diseases (such as common aspergillosis) [27–33].

Molecular absorbent recirculating system (MARS)

Application highlights

Due to the inability of this model to replenish coagulation factors, the risk of bleeding in the treatment of patients with severe coagulation impairment should be assessed. The treatment time is relatively prolonged, and patients should be fully informed prior to treatment to ensure excellent compliance. Generally, MARS is safe and stable. In rare

cases, imbalance syndrome, hypotension, allergic reaction, bleeding, coagulation, and hypocalcemia may occur, which require close observation and timely management during the treatment process.

Advantages, disadvantages, and applicable population

Advantages: effective removal of protein-bound and water-soluble toxins; ability to regulate water, electrolyte and acid–base balance disturbances and maintain a stable internal environment; excellent biocompatibility; relatively safe and reliable treatment with few adverse effects.

Disadvantages: relatively high price of consumables; requires mainframe to work with dialysis machine or hemofilter; cannot supplement coagulation factors.

Applicable population: patients with acute severe liver injury or liver failure due to various causes, including combined hepatic encephalopathy, hepatorenal syndrome, MODS, primary transplanted liver non-function, etc. [34].

The characteristics of various models of artificial liver are detailed in Table 1.

Artificial liver combination models

In cases where patients suffer from significantly elevated bilirubin levels or face multiple problems (e.g., hyperbilirubinemia, renal insufficiency, water/electrolyte/acid–base imbalance) requiring resolution, or when plasma sources are inadequate, a combination model is recommended. In practical clinical application, various factors such as the disease status of the patient, characteristics of each artificial liver model, actual equipment conditions, the amount of plasma available, as well as the economic situation of the patient should be taken into consideration to select the most suitable artificial liver combination model and to combine and increase the effectiveness or avoid the shortcomings, so as to obtain a better therapeutic effect and reduce the occurrence of adverse reactions and complications. When the patient presents with significantly elevated bilirubin levels, two models that clear medium and large molecules may be combined. When the patient presents with low PTA, the combined model should contain a treatment model using exogenous plasma, such as PE and PDF. When the patient presents with relatively obvious hepatic encephalopathy, a combination model is recommended to include DPMAS, PDF, or HDF; when the patient presents with renal insufficiency and electrolyte/acid–base imbalance, the combination model is recommended to include HDF or PDF; when the patient requires dehydration, the combination model is recommended to include HF or HDF; the following are some of the commonly used combination models.

DPMAS + PE

Application highlights Generally, the single treatment dose of DPMAS is 2–3 times the plasma volume, which is sequenced with the regular treatment volume of PE or half volume of PE. DPMAS is recommended for patients with relatively low PTA but still $\geq 20\%$, followed by PE or SPE with plasma as the replacement solution; for patients with PTA $< 20\%$, it is recommended that PE or SPE should be performed with plasma as the replacement solution, followed by DPMAS; for patients with normal PTA, PE may be performed with plasma substitutes, such as albumin solution, as the replacement solution, followed by DPMAS. The frequency of treatment is dependent on the severity of the primary disease, the effectiveness of treatment, and the molecular weight and plasma concentration of the cleared pathogenic factors. Furthermore, individualized treatment protocols should be developed.

Advantages, disadvantages, and applicable population Advantages: DPMAS can specifically adsorb bilirubin as well as remove inflammatory factors and other toxins without losing autologous plasma, while the combination of PE replenishes coagulation factors and albumin, improves the small amount of depletion of coagulation substances and albumin due to DPMAS, and alleviates the lack of plasma resources. Compared with the application of DPMAS or PE alone, it may increase the removal of toxins such as bilirubin and obtain better therapeutic results.

Disadvantage: inability to improve kidney function. Hepatic encephalopathy may be aggravated when performing PE with plasma as the replacement fluid.

Intended population: indicated for patients with various causes of liver failure, prehepatic failure, and hyperbilirubinemia, especially those with total bilirubin levels > 500 μmol/L.

PE + HDF

Application highlights In sequential treatment, it is recommended that PE should be preceded by HDF to facilitate water, electrolyte, and acid–base balance disturbances and plasma osmolality changes that may be associated with PE. When both models are implemented simultaneously, the extracorporeal circulation blood volume is relatively large, therefore, HDF treatment can be performed first, and then PE can be performed, after ensuring the stability of the patient's vital signs.

Advantages, disadvantages, and applicable population Advantages: the main functions of PE are to remove large molecular weight toxins from plasma, while

Table 1 Characteristics of various artificial liver models

Artificial liver model	Advantages	Disadvantages	Precautions
Models containing exogenous plasma			
PE/SPE	Easy to operate, broad-spectrum toxin removal and plasma replenishment	Subject to plasma sources, it has poor clearance of water-soluble toxins, plasma allergy, and there is risk of blood product-related infections	PE/SPE model alone is not recommended for patients with significant hepatic encephalopathy and may be used in conjunction with other models
PDF	Removes protein-bound and water-soluble toxins, replenishes plasma components, and regulates electrolyte and acid–base balance	Subject to plasma sources, plasma allergy may occur and there is risk of blood product-related infections	Plasma component separators of different specifications must be selected based on the specific conditions of the patient
DFPP	Selective removal of large-molecule pathogenic substances with a low requirement of exogenous plasma	Loss of a part of coagulation factors, with relatively complicated procedures	Different replacement fluids should be selected in accordance with the patient condition, and the appropriate ratio of the disposal pump to the fractionation pump speed should be established
Models not containing exogenous plasma			
HP/PP	Wide adsorption range, without reliance on plasma	Inability to replenish plasma components, with partial loss of albumin and coagulation factors	PP is recommended as compared to HP in patients with liver failure. HP is indicated for the treatment of various toxicities
DPMAS	Wide toxin removal (including inflammatory mediators), plasma-independent, and available for intensive treatment	Inability to replenish plasma components, with partial loss of albumin and coagulation factors	Recommended to be used in conjunction with a model containing exogenous plasma supplementation in patients with poor coagulation
HF/HD/HDF	High efficiency in removing medium and small molecules, ability to regulate water, electrolytes, and acid–base balance	Inability to replenish plasma components, low efficiency in the removal of large-molecule toxins, protein-bound toxins, etc.	Indicated for patients with water/electrolyte/acid–base balance disorders, renal insufficiency, cerebral edema, hepatic encephalopathy, SIRS
CPFA	Removes protein-bound toxins and water-soluble toxins and regulates water/electrolyte/acid–base balance	Inability to replenish plasma components, high equipment requirements, and complex procedure	Different adsorbers are selected according to the specific conditions of the patient
MARS	Removes protein-bound toxins and water-soluble toxins and regulates water/electrolyte/acid–base balance	Inability to replenish plasma components, high equipment requirements, and relatively high cost of consumables	Relatively prolonged treatment time, requiring adequate communication with patients to improve compliance

the ability to remove medium and small molecular weight toxins such as blood ammonia and creatinine is relatively weak. Such toxins may be easily distributed widely in tissues through blood vessel walls, and may accumulate in nerve cells through the blood–brain barrier, resulting in brain edema and aggravating the symptoms of hepatic encephalopathy. HDF compensates for this deficiency, and combined with PE, can remove toxins of various molecular weights, effectively correcting water and electrolyte balance disorders, while improving renal insufficiency and hepatic encephalopathy, thus maintaining the stability of the internal environment.

Disadvantages: PE is dependent on a relatively large amount of plasma and cannot be implemented when plasma resources are limited. Therefore, SPE may be considered. HDF treatment is of relatively longer duration, and some patients may not tolerate prolonged prone positioning.

Intended population: patients with liver failure, accompanied with renal insufficiency and water/electrolyte/acid–base imbalance, as well as those suffering from hepatic encephalopathy.

HDF + DPMAS

Application highlights Both models can be implemented simultaneously or sequentially. When both models are used simultaneously, the extracorporeal volume circulating is relatively large, therefore, HDF treatment can be performed first, and then DPMAS later, once the patient is stabilized.

Advantages, disadvantages, and applicable population Advantages: this combination model requires no plasma, and can be performed even when plasma resources are limited. It reduces the risk of allergy and infection caused by exogenous plasma products. Furthermore, it has a strong ability to remove bilirubin, inflammatory mediators, endotoxins, and small and medium-sized water-soluble toxins, and can effectively delay the occurrence of SIRS and MODS, while creating favorable conditions for liver function recovery, and rapidly improving jaundice symptoms in patients.

Disadvantages: DPMAS has a partial adsorption and depletion effect on beneficial substances such as albumin and coagulation factors, and this combination model cannot supplement coagulation factors on its own. HDF treatment is relatively prolonged, and some patients may not tolerate prolonged prone positioning.

Intended population: patients with severe liver disease with hyperbilirubinemia as the main manifestation, combined with severe infection, renal insufficiency, hepatic encephalopathy, and patients with severe drug toxicity. It should be cautiously used in patients with severe bleeding tendency and hypoalbuminemia.

PDF + PP

Application highlights Generally, PDF is required continuously for 4–6 h or even longer, while patients with liver failure have insufficient coagulation function. Hence, appropriate anticoagulation protocols are required to ensure the stability of blood flow and the absence of bleeding and clotting events.

Both models can be performed simultaneously or sequentially. Simultaneously implemented, the extracorporeal circulation blood volume is relatively large, therefore, PDF treatment can be performed first, followed by PP after ensuring patient stability.

Advantages, disadvantages, and applicable population Advantages: PDF can simultaneously remove large, medium, and small toxin molecules and replenish coagulation factors. Compared to PE, it can retain more coagulation factors in the body and requires less plasma for treatment. Prolonged PDF treatment enhances toxin clearance, reduces post-treatment rebound of toxins, and is more conducive to maintaining hemodynamic stability. PDF and PP combined is more effective in removing bilirubin and other large toxin molecules.

Disadvantages: patients with severe liver disease suffer from poor coagulation, and this combination model features prolonged treatment time. Reasonable anticoagulation therapy and monitoring should be conducted to ensure smooth treatment and reduce the risk of bleeding in patients. Also, some patients may not tolerate prolonged prone position.

Intended population: patients with severe liver disease with acute kidney injury, hepatorenal syndrome, SIRS, or electrolyte/acid–base imbalance.

PE + PP + HDF

Application highlights Generally, two devices are required, one for sequential PE and PP, the other for HDF. This combination model features relatively large extracorporeal circulation blood volume, therefore, HDF treatment can be performed first, followed by PE, once the patient is stable.

Advantages, disadvantages, and applicable population Advantages: this combination model can effectively compensate for the shortcomings of the individual models, has an excellent ability to remove large, medium, and small toxin molecules, and is capable of regulating disorders of water, electrolytes, and acid–base balance, while replenishing coagulation factors.

Disadvantages: PE requires a relatively large amount of plasma, and the development of this model is limited when plasma resources are limited, therefore, SPE may

be considered. The extracorporeal circulation line is complicated with prolonged treatment time. Therefore, a reasonable anticoagulation protocol must be established and monitoring must be conducted to ensure the smooth treatment and reduce the risk of bleeding in patients.

Applicable population: patients with severe liver disease with acute kidney injury, hepatorenal syndrome, SIRS, or water/electrolyte/acid–base imbalance.

Anticoagulation for artificial liver therapy

Heparin anticoagulation

Principle

The most important mechanism by which unfractionated heparin (UFH) works as an anticoagulant is by binding to antithrombin to form a complex that catalyzes the inactivation of several coagulation factors, including thrombin and coagulation factors Xa, IXa, XIa, and XIIa. Other mechanisms may include activation of Heparin Cofactor II and promotion of tissue factor pathway inhibitor release. The individual variations in the pharmacokinetics of unfractionated heparin are relatively large, with a non-linear relationship between anticoagulant strength, duration, and increasing dose. Compared to unfractionated heparin, low molecular weight heparin (LMWH) features higher utilization and longer half-life, specifically inhibiting coagulation factor Xa, and reduces the risk of bleeding in patients to a certain extent. As patients with liver failure suffer from coagulation disorders of varying degrees, the dose of heparin should be individualized based on the patient's coagulation status. The general principle is to apply the possible smallest dose of heparin while ensuring smooth treatment [35–38].

Indications and contraindications

Indicated for patients without clear active bleeding or with low risk of bleeding, or a hypercoagulable blood state. Heparin anticoagulation is not recommended in patients with a history of prior heparin allergy, previously diagnosed heparin-induced thrombocytopenia, and current clear active bleeding.

Application solutions

Systemic UFH anticoagulation Administer the first dose of UFH for systemic heparinization, followed by a maintenance dose of continuous pre-filter pumping, and discontinue UFH 30 min before the expected end. Two administration strategies are currently available, depending on the pre-treatment condition of the patient.

(1) Adjust the UFH dose based on body mass. Generally, the first dose is 62.5–125.0 U/kg (0.5–1.0 mg/kg) and the maintenance dose is 1,250–2,500 U/h (10–20 mg/h).
(2) Adjust the UFH dose based on coagulation function. For PE, PTA < 20%, UFH-free anticoagulation can be applied; for PTA 20–40%, only the first dose of 625–1250 U (5–10 mg) can generally be administered; for PTA 40%–80%, the first dose of 1250–2500 U (10–20 mg) and the maintenance dose of 312.5–625.0 U/h (2.5–5.0 mg/h); for PTA > 80%, refer to the method of adjusting UFH dose according to body mass. For DPMAS, the dose may be increased appropriately, with individualized adjustments made based on platelet count and antithrombin activity.

In vitro *UFH anticoagulation* UFH is continuously pumped at the arterial end of the vascular pathway, to maintain blood in a heparinized state in the extracorporeal pathway, while protamine is administered at the venous end to neutralize the UFH.

UFH-free anticoagulation method This anticoagulation model may be selected for patients requiring PE with PTA < 20% and no contraindications to heparin-based drugs. Priming with UFH saline is done prior to treatment, and saline is used to prime the tube periodically during treatment.

LMWH anticoagulation method Generally, 60–80 U/kg is administered intravenously, and the dose is increased or decreased according to the coagulation function. No maintenance dose is required to be administered for PE or DPMAS.

Monitoring and adjustment Activated clotting time of whole blood (ACT) and activated partial thromboplastin time (APTT) are commonly monitored indicators in the process of UFH anticoagulation. The ideal state is ACT/APTT collected from the venous end of the blood purification line during treatment is maintained at 1.5–2.5 times the pre-treatment level, and ACT/APTT collected from the arterial end of the blood purification line on treatment completion basically restore to pre-treatment levels. Anticoagulant Factor Xa activity may be monitored with the use of LMWH anticoagulation.

When UFH anticoagulation is employed, no matter which anticoagulation regimen is used, the UFH dose must be adjusted in a timely manner according to the changes in each pressure (including transmembrane pressure, venous pressure, arterial pressure, secondary membrane

inlet pressure, etc.), extracorporeal circulation line and filter coagulation as well as equipment alarms during the treatment process, and individualized anticoagulation should be performed.

Regional citrate anticoagulation (RCA)

Principle

A soluble calcium citrate complex is formed when sodium citrate is pumped at the arterial end of the extracorporeal circulation, which is difficult to dissociate once combined with ionized calcium (Ca_{ion}). And the level of Ca_{ion} in the extracorporeal circulation reduces to achieve the anticoagulation in the extracorporeal circulation. By pumping calcium gluconate or calcium chloride at the venous end of the extracorporeal circulation, the Ca_{ion} level in the body is restored, enhancing coagulation. Compared to heparin anticoagulation, RCA can significantly reduce the risk of bleeding and avoid heparin-related thrombocytopenia, making it the preference for patients treated with continuous renal replacement therapy (CRRT).

Considering the relative susceptibility of patients with hepatic insufficiency to citrate accumulation previously, RCA has been rarely chosen for artificial liver anticoagulation protocols. However, several studies in recent years have shown promising feasibility and safety of RCA in the treatment of liver failure with artificial liver [39–41].

Indications and contraindications

In patients with liver failure already with significant coagulation abnormalities, especially in the presence of clear active bleeding, or where UFH and LMWH use is contraindicated, RCA serves as an important optional anticoagulation model for artificial liver.

As citrate is mainly metabolized by the tricarboxylic acid cycle, diseases or pathophysiological states resulting in dysfunction of this cycle are relative contraindications to RCA, and mainly include severe hypoxemia (arterial partial pressure of oxygen < 60 mmHg) and poor tissue perfusion (blood pressure < 90/60 mmHg). In general, RCA is not recommended if the above two items are involved.

Application solutions

At the initial stage, 4% sodium citrate of 100–110 mL/h is pumped at the arterial end, and 10% calcium gluconate of 8–10 mL/h (DPMAS treatment) or 50–70 mL/h (PE treatment) is pumped at the venous end. The pumping rate of sodium citrate and calcium is adjusted during the treatment period in accordance with the presence or absence of hypocalcemia symptoms and in vitro/in vivo Ca_{ion} levels.

Monitoring and adjustment

RCA implementation requires additional infusion pumps, micropumps, as well as t connections, and extracorporeal circulation line connections are relatively complicated. Therefore, efforts should be made to formulate strict operating procedures, equipment alarms, and complication handling plans, as also strengthen personnel training. During the treatment period, various alarms should be dealt with in a timely manner to reduce the number and duration of pump stoppages. The Ca_{ion} levels in vitro and in vivo should be closely monitored by the bedside blood gas analyzer to correct any anticoagulation deficiency or excess in a timely manner, so as to improve the effectiveness and safety of anticoagulation. We should ensure patient safety by continually monitoring the patient's vital signs and promptly deal with hypocalcemia and acid–base metabolic disorders.

During the treatment, it is important to guarantee that the extracorporeal circulating Ca_{ion} concentration is maintained at 0.2–0.4 mmol/L, while the in vivo Ca_{ion} concentration is not less than 0.8 mmol/L. As the ratio of total calcium (Ca_{tot}) to Ca_{ion} correlates well with blood citrate concentration, $Ca_{tot}/Ca_{ion} \geq 2.5$ is commonly applied clinically to assess the presence of citrate accumulation in patients. Factors such as gender (especially females), high international normalized ratio, high serum creatinine level, and low serum chloride level are more prone to citrate accumulation.

Process and management of artificial liver treatment

Standardized management and application of the overall process of artificial liver treatment technology constitutes important factors affecting the efficacy. Before, during, and after the artificial liver treatment, effective communication between physicians and patients, efficient collaboration of medical staff, identification and implementation of individualized treatment modalities, and excellent quality of nursing are important aspects of the artificial liver treatment [42].

Before artificial liver treatment

The treating physician must evaluate the patient's indications and contraindications for artificial liver treatment in detail. Plans should be formulated in accordance with the requirements of the disease and the characteristics of different modalities for patients eligible for artificial liver therapy. Individualized treatment modalities should be recommended, while complications should be evaluated and prevented, contingency plans should be formulated, and possible resuscitation drugs and items should be prepared.

It is necessary to fully communicate with the patient and/or family members about the condition and treatment plan and sign an informed consent form, while paying attention to reducing patient stress and anxiety. Establish appropriate artificial hepatic vascular access and prepare the treatment site and devices for sterilization, and routine drugs and items used for treatment. The treating physician should communicate in detail with the physician responsible for the patient about the preparations to be completed in the ward prior to the implementation of the artificial liver treatment. This includes but is not limited to the pre-treatment dietary requirements, adjustments to the timing of medication administration in the ward orders, and special medications to be used in the treatment.

During artificial liver treatment

Strict implementation of aseptic procedures must be carried out to avoid cross-infection. The required medications should be prepared in the treatment preparation area. The extracorporeal circulation line must be installed according to the treatment mode and the line must be heparinized to ensure no air exists in the line after flushing. Prior to operating the device, the supplies needed for treatment should be re-checked and patient reassessment done. The IV access of the patient must be done, cardiac status monitored, as also the vital signs of the patient. This is to monitor adverse reactions and/or complications. Appropriate treatment should be given in a timely manner and related records maintained. The machine must be monitored closely for changes in pressure in response to machine alarms that occur during treatment. Effective treatment measures must be taken in a timely manner and relevant records should be maintained.

After artificial liver treatment

Once the device is discontinued, the vascular access of the patient must be properly secured and vital signs and blood leakage observed. The patient should then be transferred to the ward nurse in a stable condition. Medical waste must be disposed in accordance with the requirements of medical waste management methods of medical health institutions. Rooms and devices should be cleaned and disinfected, and ventilation should be properly maintained.

Vital signs must be monitored as well as vascular access once the patient returns to the ward. Any occurrences like blood leakage should be treated promptly. Post-treatment complications must be monitored, and care intensified for the patient. In case complications occur, effective measures must be taken for timely disposal. Central vein cannulation must be regularly maintained to avoid catheter-related infections and line coagulation. Patients should be instructed on diet post artificial liver treatment, to avoid hepatic encephalopathy, upper gastrointestinal bleeding, etc.

Efficacy of artificial liver must be assessed, including immediate post-treatment efficacy and rebound. Protocols for follow-up treatment patterns and treatment intervals should be planned based on changes in the patient's condition after treatment. When it is time to remove the central vein catheter after a course of artificial liver therapy, attention should be paid to the presence of thrombus in the catheter and in the vessels at the place of placement.

Settings and layout of artificial liver treatment room

The settings and layout of the artificial liver treatment room must comply with the requirements of the hospital infection control and other systems. It should be established according to the actual situation to satisfy all the demands of implementing the treatment. Medical units with available conditions may set up artificial liver treatment rooms in accordance with the principle of "Three Zones and Two Channels". The "Three Zones" include the Clean Zone (medical staff dressing room, clean storage room), Semi-Polluted Zone (treatment preparation zone, medical and nursing workstation), Polluted Zone (artificial liver treatment zone, soiled articles disposal room); "Two Channels" include medical staff channel and patient channel. The clean storage room, treatment preparation zone, and artificial liver treatment zone must comply with the Class III environmental standards stipulated in the *Hospital Disinfection Hygiene Standards* (GB 15982-2012). Items from polluted zones must not be re-entered into semi-polluted or clean zones.

The treatment preparation zone should be used by medical staff to prepare for treatment, and should be equipped with water baths, treatment carts (containing necessary items and drugs for artificial liver treatment), resuscitation carts (containing necessary resuscitation items and drugs), basic resuscitation devices (such as defibrillators, simple ventilators, and sputum absorbers), operating tables, item cabinets, hand hygiene devices, medical waste bins, sharps containers, etc.

The artificial liver treatment zone must be used for the respective procedures and a sufficient number of treatment units must be provided (including movable treatment beds, bedsides cabinets, artificial liver machines, electrocardiographic monitors, oxygen saturation monitors, oxygen inhalation devices, negative pressure suction devices, partition curtains, etc.) The floor area of each treatment unit should be ≥ 4 m^2, and treatment supplies for multiple patients should not be placed in a single treatment unit at the same time. Supplies such as hand hygiene devices, air conditioning, and other temperature-controlled ventilation

facilities, air disinfection devices, medical waste bins, and sharps containers should be provided.

The soiled articles disposal room should be used for temporary storage of medical waste and should be equipped with hand hygiene devices, mopping pools, medical waste bins, cleaning utensils, etc. Cleaning utensils in different zones should be clearly marked for differentiation and should not be mixed during use.

Conclusions

Artificial liver is an effective method to treat liver failure [43–46]. To conduct artificial liver therapy smoothly and effectively, medical staff need to follow a standard process: evaluate the indications and contraindications in detail, select the proper treatment time, establish useful vascular access, choose the most appropriate mode, give proper anticoagulation, handle the device alarm in time and correctly, and assess treatment efficacy.

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Declarations

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