THE USE OF HUMAN *albumin* SOLUTIONS IN ITALY

FARMINDUSTRIA

TABLE OF CONTENTS

INTRODUCTION

Pharmaceutical research is making great progress: currently there are no fewer than 7,000 innovative products at an advanced state of clinical development. This positive "tsunami" will make new and often revolutionary therapies available to patients.

It is a development that goes hand-in-hand with those benefits in terms of health and better living obtained from products offered by current therapeutic options, such as medicines derived from human blood.

Albumin is one such product and since the 40s it has been a fundamental instrument in fluid therapy, and still today is unique for its properties and tolerability.

In terms of therapeutic efficacy but also efficiency measured in cost/benefit terms, albumin is essential not only for the treatment of various stages of cirrhosis but also for other pathologies.
Considerable clinical evidence has led healthcare authorities and scientific societies to lay down precise rules to ensure an ever-more appropriate use.

This publication, by bringing together the latest information on the functions, structure, properties and therapeutic indications of albumin solutions, sets out to promote prescriptive appropriateness and contribute towards optimising albumin use to the advantage of patients, even where its use has not yet been standardised.

Massimo Scaccabarozzi, President of Farmindustria

Chapter 1
THE STRUCTURE, METABOLISM AND FUNCTIONS OF ALBUMIN

The structure, metabolism and functions of albumin

Structure

Albumin is the most abundant protein circulating in the human body (3.5-5 g/dl), making up about 50% of plasma's overall protein content.
It is a small globular protein (molecular weight: 66.5 kDa) made up of a single 585 amino acid sequence structured into three repeating homologous domains (I, II and III), each of which divided into two specific sub-domains (A and B). Of the 35 cysteine residues in the albumin molecule, 34 are involved in internal disulfide bonds that stabilise the molecule's spatial configuration, while the cysteine in position 34 (Cys-34) remains free, constituting the molecule's principle active site. [1-3]

Metabolism

In physiological conditions, the liver synthesises about 10-15 gm of albumin a day, which are released into the bloodstream with limited or no intracellular storage. Hormonal factors such as insulin, cortisol and growth hormones (GH) stimulate the production of albumin while pro-inflammatory mediators, including cytokines such as interleukin 6 (IL-6) and the tumour necrosis factor α (TNF-α), have an inhibitory effect. About 30-40% of the albumin produced remains within the vascular compartment, while the remaining part is distributed in the interstices and tissues. Protein leaves the vascular compartment by transcapillary migration and returns through the lymphatic system with a circulatory half-life equivalent to about 16-18 hours, which is much less than its total half life of between 12 and 19 days in a healthy young adult. Its catabolism is a widespread process that involves many tissues but its principal sites are muscles, liver and kidneys, while a small amount is lost in the gastrointestinal tract. [1-3]

Functions

The scientific findings of recent years have clearly shown that albumin has a long list of clinically important functions. Besides its well-known oncotic power, albumin performs many activities grouped under the definition of non-oncotic properties (Figure 1).

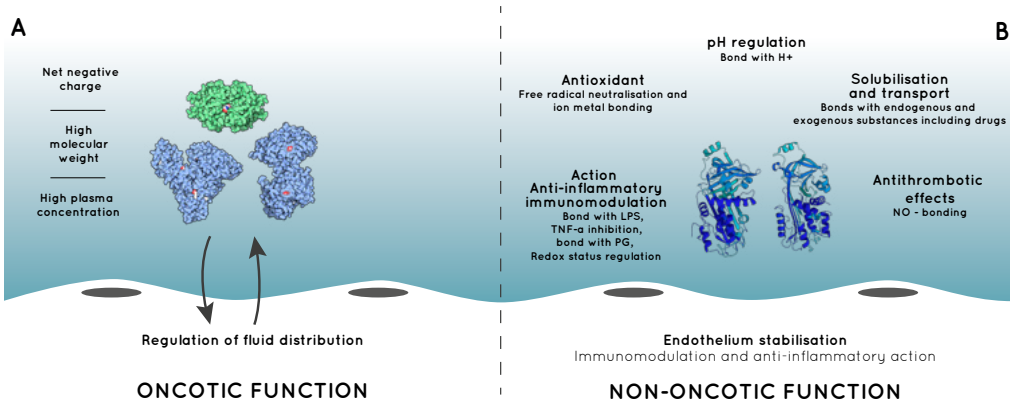

Figure 1
Oncotic (A) and non-oncotic (B) properties of the albumin molecule.

ONCOTIC POWER

Albumin is the principal fluid distribution modulator in the various compartment of the human body accounting for 70-80% of plasma's oncotic pressure. Two-thirds of its oncotic power derives from the direct osmotic effect of its molecular mass, while one-third is due to the Gibbs-Donnan effect, which, due to the net negative charge of the pH physiological molecule, allows protein to attract and retain positively charged molecules (especially sodium) and thus water in the intravascular compartment.

These features, together with its long circulatory half-life and total half-life (see above) make albumin an excellent plasma expander and at present constitute the main reason for its use in clinical practice. [3]

NON-ONCOTIC PROPERTIES

Albumin is endowed with a series of biological properties that are independent of its oncotic power and closely related to the molecule's dynamic and flexible structure. [1-3] The main non-oncotic properties are briefly set out below.

Binding, transport and detoxification
The albumin molecule contains a large number of binding and transport sites. The main domains are able to fold into hydrophobic pockets that open and close and host large insoluble anions, while cationic groups situated on the molecule's surface allow the formation of ionic bindings with many substances. Consequently, albumin binds and transports a large variety of hydrophobic molecules, including endogenous substances (such as cholesterol, fatty acids, bilirubin and thyroxine) or exogenous (such as medicinal products and toxic molecules, for example a-toxin G), metallic transition ions and gases (such as nitric oxide) with clear implications in terms of their solubilisation, transport and metabolism.

Given the close correlation between structure and function, the limited total concentration of circulatory albumin and molecular variations that occur in many acute and chronic pathologies have an important and negative impact upon these functions, for example, by altering the pharmacokinetics and pharmacodynamics of a number of medicines, including antibiotics, with obvious consequences upon their efficacy and safety. [3]

RECENT SCIENTIFIC EVIDENCE CLEARLY DEMONSTRATES THAT ***albumin*** PERFORMS A LONG SERIES OF CLINICALLY IMPORTANT FUNCTIONS: BESIDES ITS WELL-KNOWN ONCOTIC POWER, IT PERFORMS MANY OTHER ACTIVITIES THAT COME WITHIN THE DEFINITION OF NON-ONCOTIC PROPERTIES.

Antioxidant action
The albumin molecule is the main extracellular source of reduced sulfhydryl groups (-SH), which play a strong scavenger role of the reactive oxygen and nitric oxide species, respectively ROS and RNS (free radicals), making protein the body's main circulatory antioxidant.

Cysteine residue in position 34 (Cys-34) is the largest extracellular reservoir of reduced sulfhydryl groups, thereby constituting the main circulatory antioxidant system.
Under physiological conditions, and according to the reduced status of the sulfhydryl group in position Cys-34, three albumin isoforms can be identified:

- 70-80% circulates as *mercaptalbumin (HMA)*, characterised by a reduced Cys-34 with a preserved functional activity;
- 20-30% circulates as *non-mercaptalbumin-1 (HNA1)*, with the reversibly oxidised Cys-34 residue and linked to small thiol molecules, with impaired functionality;
- 5% circulates as *non-mercaptalbumin-2 (HNA2)*, with a not reversibly oxidised Cys-34 residue, with a consequent and definitive loss of functionality.

In chronic and acute pathological states characterised by pro-oxidant and pro-inflammatory circulatory micro environment the share of oxidised albumin is significantly higher and represents an independent predictor of mortality. [4]
Albumin's antioxidant function also depends on the capacity of the N-terminal part of the molecule to bind various metallic ions, including copper, cobalt, nickel, zinc and iron, thus preventing from catalysing chemical reactions that generate them free radicals. In this manner, not only does albumin neutralise free radicals, but also reduces their formation.

The modulation of the inflammatory and immunological response
Albumin can modulate the secretion and activation of various mediators of inflammatory and immunological response, including pro-inflammatory cytokines (TNF-alfa) and factors of complement (C5a). Alongside direct mechanisms, this action of albumin seems to be mediated by the capacity to antagonize the effects of oxidative stress.

Moreover, albumin is capable of binding the prostaglandin E_2 (PGE_2), that have an immuno-suppressive effect by reducing its bioavailability. It has recently been demonstrated that in patients with hepatic insufficiency, the administration of exogenous albumin can contribute towards the re-establishment of a condition of immuno-competence throught a reduction in PGE_2, in such patients that are also at great risk of developing bacterial infections and sepsis. [5]

Antithrombotic action
Albumin is able to bind nitric oxide mainly at the level of the Cys-34 site with the consequent formation of nitroso-albumin. This compound appears to prevent the rapid inactivation of nitric oxide and prolong its anti-aggregating effect on platelets. In addition to the foregoing activity, albumin also seems to perform a heparin-like anticoagulant function.

Capillary permeability and endothelial stabilisation
Albumin contributes to the vascular integrity by binding to interstitial matrix (glycocalyx) in the sub-endothelial space, thereby contributing towards the maintenance of normal capillary permeability. This function may derive not only from the high negative charge with its consequent electrostatic repulsion of negatively charged molecules but also from a mechanical action explained by the phenomenon of spatial occupation.

Moreover, albumin plays an active role in stabilising endothelial functionality during bacterial infection by reducing the activation of endotethial cells, preserving capillary permeability and preventing neutrophil adhesion to the endothelium.

Regulation of acid-base equilibrium
Albumin's molecular structure comprises 16 imidazole residues of histidine that provide the molecule with its intra and extra-buffer functionality, which can provide positive charges in the case of alkalosis and negative charges in the case of acidosis.

Concept of an efficacious albumin concentration
In recent years the concept of an efficacious albumin concentration has emerged. This derives from the sum of a quantitative factor corresponding to the circulatory albumin concentration and a qualitative factor corresponding to the amount of albumin with a normal molecular structure. In brief, the molecule's global functions deriving from its oncotic and non-oncotic properties depend not only on the circulatory quantity of albumin but also upon its structural integrity.

Patients with acute and chronic illnesses often exhibit hypoalbuminaemia which represents one of the main prognostic factors for predicting morbidity and mortality. Alongside a reduction in the quantity of circulatory albumin, such pathological conditions lead to structural alterations that can negatively impact numerous molecular functions

This means that in these patients the *efficacious albumin concentration* is certainly below the circulatory serum albumin concentration routinely measured with standard laboratory methods. Consequently, the exogenous administration of albumin should serve the twin purpose of increasing both the total quantity of circulatory albumin and the proportion of functionally integrated albumin. [3,6]

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Chapter 2
FLUID THERAPY: USE OF CRYSTALLOIDS AND COLLOIDS

Fluid therapy: the use of crystalloids and colloids

Fluid therapy is usually used to replenish good volume losses and restore an effective circulation as well as correcting electrolytic disorders and reinstating an acid-base equilibrium.
Fluid replacement is carried out by the use of different solutions belonging to two large and distinct categories of substances: crystalloids and colloids. This classification, despite dating back to the second half of the nineteenth century, is still in force. It was invented by Thomas Graham, a Scottish chemist, who divided substances on the basis of their capacity to pass through a parchment membrane. Crystalloids refer to substances that can pass through such a membrane while colloids refer to those that cannot.

Crystalloids

Crystalloids are electrolytic solutions made up of small molecules that can pass through most semi-permeable biological membranes and very easily spread into extracellular space. Among the most commonly used crystalloids there are 5% glucose solutions, 0.9% saline solutions, Ringer's lactate or acetate solution, electrolytic solutions and, in general, all solutions obtained by mixing various low-molecule weight molecules with water.
Crystalloids are sometimes used as solutions for restoring or maintaining normovolaemia and as a vehicle for administering medicinal products. The choice of the individual crystalloid will be based upon the pathology to be dealt with. The "ideal" solution would be one that reflects the composition and concentration of the liquid lost by the body. [1,2]

Fluid therapy IS USUALLY USED TO REPLENISH GOOD VOLUMETRIC LOSSES AND *restore* AN EFFECTIVE CIRCULATION AS WELL AS FOR *correcting* ELECTROLYTIC DISORDERS AND REINSTATING AN ACID-BASE EQUILIBRIUM.

VOLUMIC REPLACEMENT IS CONDUCTED BY THE USE OF DIFFERENT SOLUTIONS BELONGING TO TWO LARGE AND DISTINCT CATEGORIES OF SUBSTANCES: ***crystalloids e colloids.***

Colloids

Colloids are intermediate solutions halfway between solution and diffusion in which larger and heavier molecules being unable to pass through most semi-permeable biological membranes remain in a finely dispersed or "micro-heterogeneous" state. These preparations are able to produce an increase in oncotic pressure and increase plasma volume by attracting water from extra-cellular space. [1,2]

The colloids available for clinical use are of two types:

- artificial or synthetic colloids (non-protein colloids)
- natural colloids (plasma and human albumin)

ARTIFICIAL OR SYNTHETIC COLLOIDS

Synthetic, colloid solutions are all mixtures containing dextrans, gelatins and starches. Individual colloids differ from one another by their capacity to expand plasma volume according to each fluid's colloid-osmotic pressure (COP). The use of synthetic colloids varies considerably on account of the large variety of evaluations as to the clinical indications and contraindications due to adverse reactions and taking into account the regulatory and prescriptive indications in force in various nations. [3]

Dextrans
Dextrans are polysaccharides with a high molecular weight composed by glucose residues able to exercise a COP of 40 mmHg. Dextrans can cause infrequent but potentially very serious adverse reactions: anaphylactic/ anaphylactoid shock, fluid overload with pulmonary edema, a platelet dysfunction leading to spontaneous bleeding and acute kidney failure. Therefore, they are contraindicated for patients with diabetes or renal impairment. In practice, dextrans are rarely used in Italy.

Gelatins
Gelatins, purified polypeptide solutions obtained from the hydrolysis of animal collagen (usually bovine), produce a limited plasma expansion of short duration on account of the rapid renal elimination and deterioration by the reticuloendothelial system's protease. They entail the risk of triggering allergic reactions and inducing bleeding and kidney failure.

Starches
Starches are complex polysaccharides of which various types exist. They can be distinguished by their origin (whether from corn or potatoes) and structure (molecular weight, C2/C6 ratio or the number of replacements). Although representing a theoretical alternative to crystalloids for the expansion or maintenance of blood volume, they are substances extraneous to the body, and if administered intravenously they are not metabolised and they accumulate in cells. It can be reasonably supposed that this characteristic provides the theoretical base for the long known and severe adverse reactions associated with the use of such compounds (kidney failure, bleeding, hepatic damage, allergic reactions and pruritus).

A number of products with modified formulations have been developed in recent years to reduce the risk of adverse reactions (molecular size, number of replacements or C2/C6 ratio). Among such products, hydroxyethyl starch (HES) is the most investigated and used synthetic colloid. It is a branched chain polysaccharide similar to glycogen and mainly comprising amidopectins (98%) and exercises an oncotic pressure (COP) of about 30 mmHg (6% solution).
These products, announced as "innovative and possessing a high safety profile", may, however, cause serious adverse reactions, thus retaining important contraindications in some clinical conditions. In addition big concernes arised about the validity of the critical studies done by dr. Boldt, the so mentioned "Boldt case".

The "Boldt case" and the recent recommendations of regulatory agencies on the clinical use of starch

The new synthetic starches witnessed a first phase of distribution spurred on by numerous studies published by Joachim Boldt, a former professor and Head of the Department of Anaesthesiology and Intensive Care at Giessen University, Germany, and author of a large number of publications on starches and their therapeutic benefits.

However, the findings of these publications became the subject of serious questioning after the discovery of widespread and repeated infringements of the principle of Good Clinical Practice (GCP) and the absence of any approval by the Ethical Committee for most of the trials conducted by Boldt. Moreover, the editors of 18 scientific reviews in the field of anaesthesiology and other fields, jointly and publicly confuted the reliability of the findings of these studies. Furthermore, besides infringing GCP principles, it was also discovered that many data had been blatantly modified and falsified. Joachim Boldt was, therefore, suspended from his clinical positions and teaching post. [4] The case, having received widespread attention in the scientific world and the media, led the regulatory authorities, especially the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA), to review the indications and modify specific marketing authorisations (MA) of synthetic starches containing HES, and especially in view of the latest recent randomised clinical trials.

Three important randomised clinical trials (VISEP, 6S and CHEST) [5,6,7] on the treatment of hypovolaemia and hypovolemic shock in critical patients in intensive care, with severe sepsis or burns, have not only shown the non-therapeutic superiority of HES with respect to crystalloids (saline), but that there is also a greater overall risk of hepatic and renal toxicity (up until the need for dialysis) and mortality in this category of patients.

Following a systematic revision of the available studies, conducted at the European level in the recommendations of the Pharmacovigilance Risk Assessment Committee (PRAC), EMA, therefore, issued strongly restrictive indications in 2013 on the use of synthetic starches in specific populations and imposed modifications to the data sheet of the products involved. [8,9] As regards Italy, AIFA (Italian Medicines Agency) took steps to adopt EMA's indications. Moreover, the Coordination Group for Mutual Recognition and Devolved Procedures for human use (DMDh) approved PRAC's recommendations. [10]

The summary of AIFA's recommendations is as follows:

- *Products containing HES must only be used for the treatment of hypovolaemia caused by acute haemorrhage whenever crystalloids are deemed insufficient.*
- *Products containing HES must be used at the lowest effective dose for the shortest duration. Treatment must be guided by continual haemodynamic monitoring so that as soon as appropriate haemodynamic values are reached the infusion can be interrupted.*
- *Products containing HES are now contraindicated in the following conditions:*
  - *sepsis*
  - *burns*
  - *renal failure or renal replacement therapy*
  - *intracranial or cerebral haemorrhage*
  - *critical patients (typically undergoing intensive care)*
  - *hyperhydrated patients including patients with pulmonary edema*
  - *dehydrated patients*
  - *hyperkalaemia (only applicable to products containing potassium)*
  - *severe hyponatraemia or severe hyperchloraemia*
  - *severe coagulopathy*
  - *severely compromised hepatic function*
  - *congestive heart failure*
  - *patients with organ transplants*

NATURAL COLLOIDS

Human albumin is the principal natural colloid. Human albumin solutions are available both at low concentrations (5%) that can produce a COP of 20 mmHg and at high concentrations (20-25%), with a COP of 70 mmHg. It should be noted that the latter is the highest COP obtainable from colloidal solutions. As concerns its clinical use, we can anticipate that the therapeutic indications of albumin constitute a subject that, on the one hand, encounters areas of considerable agreement and, on the other, widespread national and international questioning. In the discussion of the clinical indications for the use of albumin, both the consensual and the critical positions will be the subject of the next chapter.

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HUMAN *albumin*
IS THE PRINCIPAL
NATURAL COLLOID

Chapter 3
THERAPEUTIC USE OF ALBUMIN IN LIVER CIRRHOSIS

Therapeutic use of albumin in liver cirrhosis

Physiopathological background

Hypoalbuminaemia is a typical characteristic of cirrhosis. It is the result of a reduction in hepatic synthesis, the dilution of protein content in extracellular fluid following an expansion of the total plasma volume, an increase in catabolism of the molecule and a higher rate of transcapillary passage towards extra-vascular space, at least in patients with refractory ascites. [1,2]
Besides quantitative change, albumin undergoes structural and functional changes that are probably facilitated by the pro-inflammatory and pro-oxidant state of the advanced cirrhosis. [1,2]
A cirrhotic patient's albumin is characterised by extensive post-transcriptional modifications that involve a number of sites on the molecule, thus compromising normal physiological functions. [3]

In physiological terms decompensated cirrhosis is characterised by two major systemic events: circulatory dysfunction and chronic inflammation.
These alterations are closely correlated to one another and contribute towards multi-organ dysfunction and failure. [4]
Predominant haemodynamic alteration is a progressive reduction in effective volaemia as a result of the decline in peripheral vascular resistance, mainly at the splanchnic level due to the production of vasoactive substances (e.g. nitrogen oxide, carbon monoxide, endocannabinoids) that induces vasodilation and limits vasoconstrictor response. The activation of neurohumoral compensation systems, including the renin-angiotensin-aldosterone system (RAA), the sympathetic nervous

Patients WITH DECOMPENSATED CIRRHOSIS ARE HYPOVOLEMIC AND EXHIBIT CARDIOVASCULAR.

system (SNS) and vasopressin (ADH), in its turn, produces vasoconstriction and the retention of sodium and water in the kidney. Thus, in functional terms, patients with decompensated cirrhosis are hypovolemic and exhibit cardiovascular hypoactivity, although their cardiac flow may be normal or high. Nevertheless, a fall in cardiac output, with the consequent worsening of effective hypovolaemia is found in more advanced stages of the illness due to the development of a clinically observed cardiac dysfunction, the so-called "cirrhotic cardiomyopathy". At the terminal stage, the extreme decline in effective volaemia directly produces a further decline in perfusion in the kidneys and other organs, thus generating ischemic tissue injury leading to the development of multi-organ failure. In this physiopathological scenario, the conservation of effective blood volume is the primary objective in treating these patients. [4]

Patients with decompensated cirrhosis also exhibit a chronic condition of systemic inflammation, due to the stimulation of immune system cells by the translocation of bacteria and their fragments from the intestinal lumen to the blood stream as a result of the quantitative and qualitative changes taking place in the intestine. The cytotoxic agents released during the inflammatory process contribute towards the creation of a vicious circle by producing splanchnic vasodilation and suppressing cardiac contractility, thus aggravating circulatory dysfunction. They can also contribute directly to organ dysfunction by inducing microvascular coagulation and cell damage. [4]
The level of inflammation and oxidative stress increases rapidly in patients with acute-on-chronic liver failure; a clinical syndrome characterised by the development of hepatic and extrahepatic organ failure (kidneys, brain, lungs, coagulation and circulation) and by a high risk of immediate mortality and often precipitated by an identifiable clinical event such as bacterial infection or acute alcoholic hepatitis. [5]

On the basis of the foregoing physiopathological evidence, albumin administration can exercise - through the molecule's oncotic and non-oncotic properties - a beneficial effect in various phases of the foregoing vicious cycle that combines circulatory dysfunction, inflammatory response and oxidative stress in patients with decompensated cirrhosis. (Figure 1).

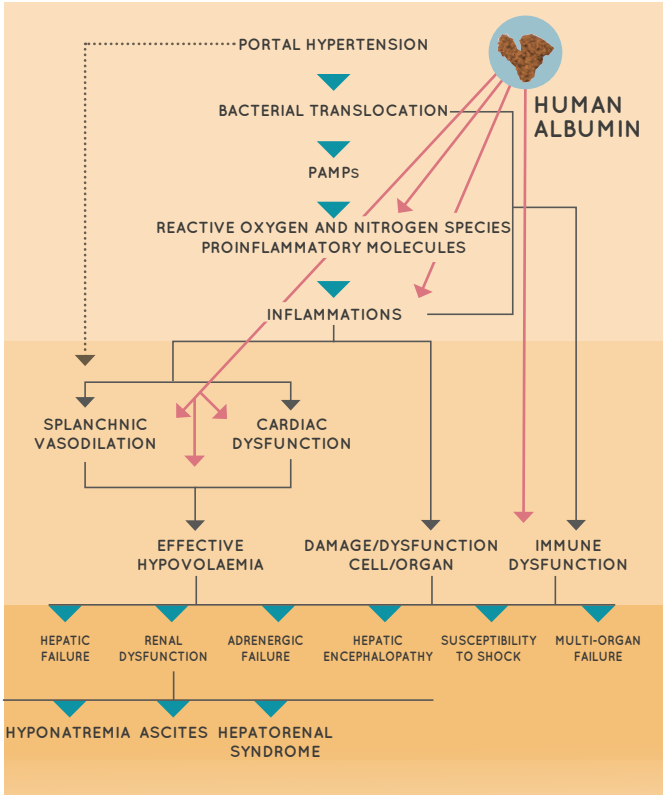


Figure 1. Principal physiopathological and clinical events in decompensated cirrhosis. The arrows indicate the possible sites of albumin's beneficial action through its oncotic and non-oncotic properties. PAMP: pathogen associated molecular pattern.

Current use of albumin in hepatology

The therapeutic use of human albumin in hepatology is a common practice, sustained by numerous scientific findings and by the guidelines of leading national and international scientific associations. [6.7]

The principal indications on the use of albumin are currently represented by some clinical complications associated with the most advanced stages of cirrhosis, all characterised by a marked condition of effective hypovolaemia: the prevention of post-paracentesis circulatory dysfunction (PPCD), kidney failure induced

by spontaneous bacterial peritonitis (SBP) and the diagnosis and treatment of the hepatorenal syndrome (HRS) in association with vasoconstrictors.

The recent publication of the findings of the trial 'ANSWER' has revealed significant benefits from the long-term albumin treatment on patients with cirrhosis and uncomplicated ascites who do not respond to diuretic treatment. [8]

However, other pathological conditions related to hepatic cirrhosis such as severe hyponatraemia and septic shock, can also benefit from the administration of albumin, but currently they lack the backing of equally solid scientific evidence.

In this context, it is important to underline the strange situation as regards obtaining marketing authorisations in Italy. The reimbursement and prescription of albumin through the National Health Service (NHS) are governed by Note 15, issued in 2005 by the Italian Medicines Agency (AIFA), which limits its use to:

- *after large-volume evacuative paracentesis in cirrhosis of the liver;*
- *serious hydrosaline retention in ascitic cirrhosis, in the nephrotic syndrome or in malabsorption syndromes (e.g. due to post-surgery short intestine or protein dispersion) that does not respond to appropriate diuretic treatment, often when associated with hypoalbuminaemia and particularly with clinical signs of hypovolaemia.*

While Note 15 does not, on the one hand, include all the indications found in the technical sheets approved in non-EC countries, on the other it does allow the chronic use of albumin in ascites therapy. The existence of different guidelines, often not updated, due to differences in procedures as also in prescriptive practice, not only nationally but also within the same region, means that universality and equity in healthcare treatment - virtues of the Italian health system - cannot be guaranteed.

AISF-SIMTI recommendations for the appropriate use of albumin in cirrhosis of the liver

For the foregoing reasons the Associazione Italiana per lo Studio del Fegato (AISF) (the Italian Association for the Liver Research) and the Società Italiana di Medicina Trasfusionale e Immunoematologica (SIMTI) (the Italian Society of Transfusion Medicine and Immunohaematology) appointed a joint committee of experts to review the literature available and set out practical clinical recommendations for the use of human albumin on patients with cirrhosis of the liver in order to furnish a shared instrument for prescribing this blood product in an appropriate manner so as to prevent its use in ways not based on scientific evidence and harmonise its prescription at a national level (Tables 1 and 2). [9]

Table 1. Grading efficacy tests and recommendations (adopted from the GRADE system)

QUALITY OF EFFICACY TESTS
A - HIGH It is very unlikely that further research can change our ideas on the reliability of the estimate of effects. • Various high quality studies with constant results • In special cases: a large, high quality, multi-centre study
B - MODERATE It is likely that additional research will make an important impact on our view about the reliability of the estimate of effect and modify it. • A high quality study • Various studies with some limitations
C - LOW It is very likely that additional research will make an important impact on our view about the reliability of the estimate of effect and will probably modify it. • One or more studies with serious limitations
D - VERY LOW Any estimate of effect remains very uncertain. • Expert opinion • No direct proof of experimental efficacy • One or more studies with very serious limitations
STRENGHT OF THE RECOMMENDATIONS
1 - Strong Factors that influence the strength of the recommendations include the quality of the efficacy tests, presumably important results for both patient and cost.
2 - Weak Variability in the choices and values or greater uncertainty: it is more likely that a weak recommendation is justified. The recommendation is given with less certainty: high cost or excess consumption of resources.

Source: http://www.simti.it/pdf/volume_albumina.pdf

Table 2. Summary of the recommendations for the use of albumin in patients with cirrhosis of the liver

CLINICAL CONDITION		DOSE AND TIMES OF ADMINISTRATION	INDICATIONS FOR ALBUMIN USE	QUALITY OF THE EFFICACY TESTS AND RECOMMENDATION'S STRENGTH
DCPP prevention	Paracentesis ≥ 5 litres	6-8 g per litre of ascitic liquid removed	Mandatory in all patients	A1
	Paracentesis < 5 litres		Preferred in the event that there are contraindications for the use of synthetic colloids or crystalloids	B1
Prevention of renal failure after PBS	High-risk patients	1,5 g/kg at diagnosis+ 1 g/kg on the third day	Mandatory in all patients	A1
	Low-risk* patients		To be considered for single patients	B1
SER diagnosis		1 g/kg/die for 2 consecutive days	To be used on a regular basis	D1
Treatment of type 1 SER (in association with vasoconstrictor)		1 g/kg at diagnosis + 20-40 g/die until the suspension of the vasoconstrictors	Mandatory in all patients	A1
Long-term treatment of ascites		To be defined	To be considered for ascites that are difficult to treat	C1
Treatment of serious hyponatraemia		To be defined	To be considered if standard therapy is without response	D1
Prevention of renal failure after bacterial infection other than PBS		–	Currently not indicated	B1
Treatment for septic shock		To be defined	To be considered for all patients	C1
Treatment of hepatic encephalopathy		–	Currently not indicated	B1

*Low-risk patients: serum bilirubin <4 mg/dl and serum creatinine <1 mg/dl.
PPCD: post-paracentesis circulatory dysfunction; HPS: hepatorenal syndrome; SBP: spontaneous bacterial peritonitis.

Source: http://www.simti.it/pdf/volume_albumina.pdf

The AISF-SIMTI recommendations were officially presented during a conference organised by the Centro Nazionale Sangue (CNS) (National Blood Centre) in March 2016 at the Istituto Superiore di Sanità (National Institute of Health) in Rome.

PREVENTION OF POST-PARACENTESIS CIRCULATORY DYSFUNCTION (PPCD)

Evacuative paracentesis is the primary treatment for patients with tense or refractory ascites. Removal of a large volume of ascites (> 5 litres) may cause the so-called post-paracentesis circulatory dysfunction characterised by a brusque and lasting deterioration of the condition of effective hypovolaemia in association with a significant increase in patient mortality. [10]

This complication is overcome by the use of plasma expanders during and/or at the conclusion of paracentesis. Albumin was found to be superior to crystalloids and synthetic colloids in cases of paracentesis of over 5 litres of ascites, while no significant differences were found with the removal of smaller volumes. [11, 12]

AISF-SIMTI RECOMMENDATIONS

- **Albumin must be administered after paracentesis higher than 5 L at a dose of 6-8 g/L of ascites removed as it lowers the incidence of PPCD and improves the clinical outcome of the patient (A1).**
- **When the quantity of ascites removed exceeds 5 L, the use of plasma expanders is not recommended as they are less effective in PPCD prevention (A1). Moreover, the combination of albumin and other plasma expanders is not recommended in order to reduce the albumin dose (D1).**
- **When the quantity of ascites removed is less than 5 L, albumin can be used in the case of possible risks associated with the administration of crystalloids and synthetic colloids (volume overload, renal failure, coagulopathy) (B1).**
- **The use of vasoconstrictors in place of albumin or the use of low doses of albumin should be limited to controlled clinical trials (C1).**

The recommended dose (6-8 g per litre of ascites removed) should not be reduced arbitrarily.

PREVENTION OF RENAL FAILURE AFTER SPONTANEOUS BACTERIAL PERITONITIS

Spontaneous bacterial peritonitis (SBP) represents the most frequent bacterial infection found with cirrhosis of the liver and is an important cause of in-hospital mortality (about 20% of all cases). The development of renal failure, independently of the resolution of the infection, is an independent predictor of mortality, [13] The administration of albumin, together with antibiotic therapy, significantly reduces the incidence of renal failure after SBP and also improves in-hospital and 3-month survival. This positive result is clearly exhibited in patients in more advanced stages of illness defined by serum bilirubin >4 mg/dL and serum creatinine >1 mg/dL, while it appears even more controversial with low-risk patients (with serum bilirubin <4 mg/dL and serum creatinine <1 mg/dL). [14]

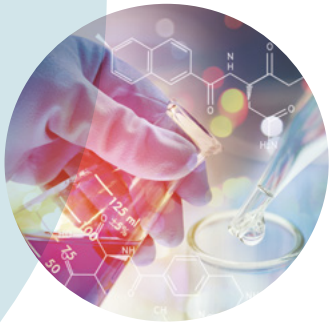
AISF-SIMTI RECOMMENDATIONS

- **Albumin (1.5 g/kg body weight at diagnosis and 1 g/kg body weight at day 3) must be administered in association with antibiotic therapy in cirrhotic patients with SBP given that this approach reduces the incidence of renal failure and improves survival (A1).**
- **Patients with serum bilirubin <4 mg/dL and serum creatinine <1 mg/dL are at low risk of developing renal failure after SBP. In this group of patients, the benefit of albumin is not clear and the decision to administer it should be tailored to the individual (B1).**
- **The use of crystalloids and colloids instead of albumin or in association with it is not recommended (D1).**
- **The use of low doses of albumin should be limited to controlled clinical trials (level C1).**

DIAGNOSIS AND TREATMENT OF THE HEPATORENAL SYNDROME

The hepatorenal syndrome (HRS) is a form of "functional" renal failure which in the absence of therapy has an ominous short-term prognosis. A HRS diagnosis, besides excluding organic causes of nephropathy, is based upon failure to respond to plasma expansion, to be performed according to the opinion of the experts of the *International Club of Ascites* (ICA) with an albumin dose of 1 g/kg body

THE ***hepatorenal syndrome*** IS A FORM OF RENAL FAILURE. WHICH IN THE ABSENCE OF THERAPY IS "FUNCTIONAL" FOR AN OMINOUS SHORT-TERM PROGNOSIS.



weight for two consecutive days, even if no specific studies on the question exist. [15]
As concerns treatment, the combined administration of albumin and vasoconstrictors (the most used is terlipressin, but also noradrenaline and the association of octreotide and midodrine) was found to be significantly better than a placebo or albumin alone, for curing renal failure and improving 3-month survival. [16]

AISF-SIMTI RECOMMENDATIONS

- **Albumin administered (1 g/kg body weight for two consecutive days) should be used to expand plasma volume for differential HRS diagnosis (D1).**
- **Albumin must be administered with terlipressin to patients with type I HRS at a dose of 1 g/kg body weight on day 1 followed by 20-40 g die until the suspension of terlipressin (A1). When possible, the albumin dose should be calibrated according to the level of central venous pressure. Alternatively, albumin should be reduced or interrupted in the presence of clinical signs of volume overload and/or pulmonary edema (A1).**
- **Albumin should be administered along with other vasoconstrictors (noradrenaline or midodrine plus octreotide) in patients with type 1 HRS in the same doses used for terlipressin (A1).**
- **If patients with type 2 HRS are treated with vasoconstrictors, albumin should be added in the dosages used for type 1 HRS (B1).**

LONG-TERM TREATMENT OF ASCITES

The long-term administration of albumin for the treatment of ascites, although based on theoretical physiopathological premises (effective hypovolaemia is the root cause of the renal retention of sodium and water) still remains a matter of controversy in the field of hepatology, on account of the lack of definitive scientific evidence to substantiate its clinical benefit.

However, this use is permitted by the Italian National Health Service but the reimbursement for non-hospital prescriptions is limited to patients with ascites non-responsive to standard diuretic therapy (Note 15 of the Italian Medicines Agency).

Only two randomised clinical trials, whose experimental design cannot, in one case, be easily transferred to current clinical practice and whose results, in the other, are limited by the low number of patients involved, have shown a benefit from the chronic administration of albumin in ascitic decompensation management. [17,18]

The lack of successive confirmatory trials, together with the high cost of this therapeutic strategy, explains why the long-term infusion of albumin is not included among the recommendations of international guidelines.

A reply to this controversial clinical problem was provided by the findings of the Italian, non-profit, multi-centre randomised trial promoted by the Italian Medicines Agency (ANSWER study, Clinical Trials.gov: NCT 01288794) which evaluated long-term albumin treatment in patients with hepatic cirrhosis and ascites non responsive to diuretic treatment. [8]
This study compared two groups of cirrhotic patients with non-complicated ascites. One was treated with conventional (antimineralocorticoids + furosemide) and the other with conventional therapy + albumin (40 grams two times a week for two weeks and successively 40 grams once a week, with patients monitored for 18 months). The end points of the trial were survival (primary end point), the need to recur to paracentesis, the appearance of cirrhosis complications, the quality of life, and admission to hospital (secondary end points). The trial findings were very positive. There was a significant increase in the survival rate and statistically significant benefits for the following parameters: paracentesis, refractory ascites, spontaneous bacterial peritonitis, episodes of renal failure, type 1 hepatorenal syndrome and grade III-IV hepatic encephalopathy. A reduction in hospital admission and an improvement in life quality were also observed. [8]*

*The description of the findings of the Answer trial does not form part of the AISF – SIMTI document.

AISF-SIMTI RECOMMENDATIONS
- **Long-term albumin administration can be considered efficacious in the treatment of ascites in association with diuretics (C1).**
- **The efficacy, dosage and timing of albumin administration must be defined by controlled, randomized trials with an adequate sample size.***

***This recommendation precedes the publication of the findings of the Answer trial.**

TREATMENT OF SERIOUS HYPONATRAEMIA

The serum concentration of sodium is an important negative prognostic factor in cirrhosis: hyponatraemia, especially when serious (<125 mmol/L), can by itself induce neurological complications or degenerate into hepatic encephalopathy and can promote the emergence of pontine myelinolysis after liver transplant. [19]

Basing themselves upon strong physiopathological reasoning - in other words the reduction of the non-osmotic hypersecretion of ADH through an improvement of effective hypovolaemia - many hepatologists consider albumin infusion an effective treatment for hyponatraemia although no clinical studies exist on the question.

AISF-SIMTI RECOMMENDATIONS
- **On the basis of physiopathological premises, albumin could be efficacious for correcting serious hyponatraemia (<125 mmol/L), non-responsive to standard therapy, especially as regards patients with hyponatraemia correlated symptoms or awaiting liver transplants (D1).**

TREATMENT OF SEPTIC SHOCK

Patients with septic shock exhibit an improvement in survival when a therapeutic response is immediate and based upon a combination of broad-spectrum empirical antibiotic therapy, vasoconstrictors and volume replacement.
Although a only few patients with cirrhosis were enrolled in the available trials, (two in particular: SAFE and ALBIOS) and the findings cannot, therefore, be automatically applied to the condition of cirrhosis with septic shock, some considerations do favour the use of albumin. [20,21]

In the first place, expansion with saline solution or Ringer solution requires the infusion of large volumes of liquids which may worsen the patient's existing ascites and edema. Moreover, the use of HES solutions, as mentioned, raises fears on account of the increased risk of renal and hepatic damage and coagulopathy. In conclusion, one specific benefit of albumin could also derive from the molecule's non-oncotic properties as they could antagonise some of the physiopathological mechanisms linked to septic shock.

AISF-SIMTI RECOMMENDATIONS
- **Albumin could be efficacious and safe in cirrhotic patients affected by septic shock (C1).**

PREVENTION OF RENAL FAILURE DURING BACTERIAL INFECTIONS OTHER THAN SBP

Bacterial infections are a frequent complication in patients with hepatic cirrhosis and an important direct and indirect cause of death. As in the case of SBP, other bacterial infections can lead to complications with the emergence of renal failure, which will determine a significant decline in the survival rate.

The efficacy of albumin administration for bacterial infections other than SBP is still being studied. Two randomised clinical trials failed to find significant benefits from albumin administration either in terms of the incidence of renal failure or survival. [22,23]

However, post-hoc analyses have suggested a possible positive effect for clinically more serious patients and with more advanced hepatic illnesses.
In order to reply to this question, a large, European multi-centre trial is currently in course (INFE- CIR-2, ClinicalTrials.gov: NCT 02034279), promoted by the *Chronic Liver Failure Consortium* (CLIF), whose purpose is to evaluate the effect of the albumin administration in high-risk patients, as defined by the presence of hepatic and renal insufficiency as also by the positive parameters of the systemic inflammatory response syndrome (SIRS) and the kind of infection.

AISF-SIMTI RECOMMENDATIONS
- **The administration of human albumin in association with antibiotics is currently not indicated in cirrhotic patients with bacterial infections other than SBP (B1).**

TREATMENT OF HEPATIC ENCEPHALOPATHY

Hepatic encephalopathy (EE), an alteration in mental state often induced by a precipitating event (bacterial infection, gastrointestinal bleeding, renal failure

In patients WITH ADVANCED HEPATIC CIRRHOSIS, ***albumin*** ADMINISTRATION IS INDICATED FOR CLINICAL CONDITIONS IN WHICH TREATMENT OR PREVENTION IS ABSOLUTELY INDEPENDENT OF THE PATIENT'S ***plasma albumin*** CONCENTRATION.

or hyponatraemia) is one of the most important complications of cirrhosis, and associated with a high mortality rate, poor quality of life and high risk of relapse. [24]

A small randomised clinical trial has found albumin administration, which in theory could reduce the damage occasioned by the oxidative stress associated with the development of EE, to be inefficacious in resolving acute episodes of the illness. [25]

AISF-SIMTI RECOMMENDATIONS
- **Albumin administration is currently not indicated for the treatment of hepatic encephalopathy (B1).**

HYPOALBUMINAEMIA

In patients with advanced hepatic cirrhosis, the administration of albumin is indicated for clinical conditions in which treatment or prevention is absolutely independent of the concentration of plasma albumin in the patient. It is no coincidence that none of the foregoing recommendations makes reference to threshold of albuminaemia values above which its use is advised against. In order to underline the concept that the prescription of albumin must not be correlated with laboratory findings on its plasma concentration, the committee of experts made the following recommendations.

AISF-SIMTI RECOMMENDATIONS
- **In the specific context of patients with advanced cirrhosis, the presence of hypalbuminaemia must not be a necessary requisite for prescribing albumin.**
- **As in other clinical contexts, in patients with advanced cirrhosis, hypalbuminaemia is not, by itself, an indication for prescribing albumin (B1).**

COMPARISON BETWEEN INTERNATIONAL GUIDELINES

As already stated, the guidelines of the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) [6] makes provision for the use of albumin for the prevention of PPCD and renal failure induced

THE PRESCRIPTION OF *albumin* FOR THE LONG-TERM TREATMENT OF ASCITES IS POSSIBLE IN ITALY THANKS TO NOTE 15 OF THE ITALIAN MEDICINES AGENCY (AIFA).

by SBP and for the diagnosis and treatment of HRS in association with vasoconstrictors.
As regards these three indications, the Italian AISF-SIMTI recommendations are substantially in agreement with AASLD and EASL guidelines, although more detailed in describing the scope of albumin use and the absence of indications on the use of other plasma expanders.

However, AASLD and EASL guidelines do not deal with other clinical indications such as chronic albumin use, non-SBP bacterial infections, septic shock and hepatic encephalopathy, which, instead, are the subject of AISF-SIMTI recommendations. The sole exception is represented by serious hyponatraemia for which albumin can be administered as, for that matter, in AISF-SIMTI recommendations.
This difference can, first and foremost, be explained by bearing in mind that EASL guidelines were published in 2010 and ASSLD's in 2013, and thus the findings of randomised clinical trials on non-SBP bacterial infections and hepatic encephalopathy, which albeit negative, were not available. Secondly, as already stated, albumin prescription for the long-term treatment of ascites is possible in Italy thanks to Note 15 of the Italian Medicines Agency (AIFA).

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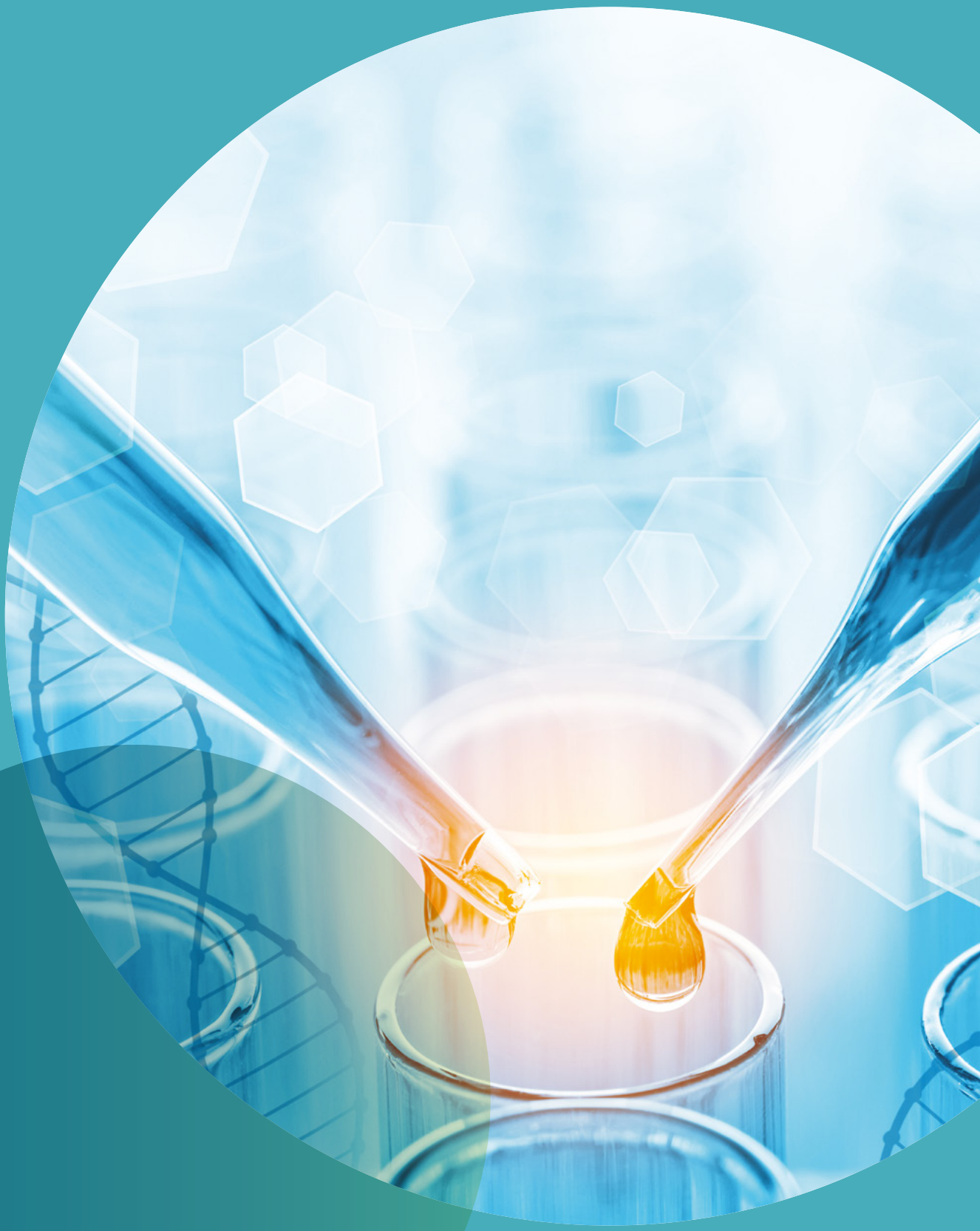

Chapter 4
THERAPEUTIC USE OF ALBUMIN IN CRITICAL PATIENTS AND OTHER PATHOLOGICAL CONDITIONS

Therapeutic use of albumin in critical patients and other pathological conditions

In addition to cirrhosis, albumin is administered for a wide range of pathological conditions and illnesses. Certainly, "critical patients in intensive care" represents a wide and heterogeneous area of use in which major randomised multi-centric trials, conducted over the past two decades, have progressively permitted better prescription appropriateness as concerns some indications that still remain controversial, while the superiority of albumin with respect to crystalloids has still not been clearly demonstrated.

Albumin in critical patients

The use of fluids for vital support and re-animation is a widely used practice in the intensive care of critical patients. Albumin has been used for decades in a wide variety of pathological situations including shock, sepsis, multiple-injuries, burns, acute respiratory distress syndrome (ARDS), cerebral haemorrhage and many others. [1]
The physiopathological rationale at the basis of albumin use is well founded and fully discussed: it is based on the combination of the molecules' oncotic properties (plasma expansion), and multiple non-oncotic properties (transport and neutralisation of endogenous and exogenous toxic substances, antioxidant and anti-inflammatory properties, the buffer function for alterations of the base-acid equilibrium and the maintenance of capillary integrity).
Non-protein crystalloids and colloids have also been proposed and used for the foregoing pathologies, but the debate on the advantages of each type of solution is still on going.
In 1998, a Cochrane meta-analysis conducted on 30 randomised clinical trials highlighted a higher mortality risk, amounting to 6%, in patients to whom albumin had been administered for treating traumatic hypovolaemia, major surgery, burns or hypoproteinaemia. [2]
However, successive meta-analysis including a larger number of randomised clinical trials failed to confirm this negative effect on mortality in these categories of patients. [3,4]
Therefore, to clarify the use and safety of albumin in patients undergoing intensive care, an extensive, double-blind, randomised clinical trial (Saline versus Albumin Fluid Evaluation study, SAFE study) recruited 6997 patients requiring volume support and administered them either crystalloids (saline solution) or albumin. [5]
The SAFE trial did not find significant differences in mortality at 28 days, and above all confirmed that albumin can be safety used in critical patients.

One of the reasons for the diversity in the findings in the different trials is due to the fact that the term "critical patient in intensive care" includes very diverse kinds of patients in both clinical and physiopathological terms. Consequently, the effect of albumin may differ according to the type of patient in question.

THE DENOMINATION *"critical patients in intensive care"* INCLUDES PATIENTS WHO DIFFER CONSIDERABLY IN CLINICAL AND PHYSIOPATHOLOGICAL TERMS.

If albumin has, on the one hand, shown to negatively impact the survival of patients with cerebral trauma, on the other hand it does appear to be beneficial in other conditions (e.g. extensive burns, ARDS) and especially cases of severe sepsis and septic shock, as these are situations in which the effects of the molecule's non-oncotic properties are found to be very useful.

SEVERE SEPSIS AND SEPTIC SHOCK

The first important evidence of albumin's favourable effect in patients with severe sepsis emerged from the SAFE study where multivariate analysis highlighted a survival advantage for this subgroup. This finding was later confirmed by the results of a meta-analysis on trials conducted on patients with severe sepsis and septic shock. [6]
In 2014 the findings of an open-label, randomized multicentre trial (Albumin Italian Outcome Sepsis; ALBIOS trial), designed to evaluate the survival benefit of volume support where albumin was compared to crystalloids in patients with serious sepsis admitted to intensive care. [7] The ALBIOS trial failed to demonstrate albumin's superiority in terms of survival, although confirming the safety of its use and its efficacy in terms of improving some haemodynamic parameters. However, a post-hoc analysis revealed a slight but statistically significant reduction in the mortality of the septic shock patient sub-group. Successive meta-analysis, albeit based on a low number of randomised studies, seems to confirm the advantage in this patient sub-group, thus indicating the need for further randomised clinical trials. [8]
The current recommendations of the "surviving sepsis campaign" group (2016) indicate crystalloids as the first line treatment for volumic support in patients with severe sepsis or septic shock. The use of albumin is recommended in crystalloid solutions in the event that a considerable volume is required by the patient, but too high to be infused with crystalloids alone. Synthetic colloids, on the basis of substantial evidence, are strongly contraindicated in the treatment of patients with serious sepsis/ septic shock. [9]

The foregoing recommendations for the infusion of liquids in severe sepsis are as follows:

- **the use of crystalloids is recommended as first-line treatment in intensive care for severe sepsis and septic shock.**
- **the use of albumin is recommended in infusion therapy for severe sepsis and septic shock when patients need large quantities of liquids.**

BURNS

The first clinical use of albumin was in the treatment of American soldiers who sustained burns during the attack on Pearl Harbour in 1941. Since then albumin

has been used to treat burn patients, even if recently its use was not recommended in the first phases of intensive care of burn patients and in accordance to the advice of some experts the treatment had to be exclusively limited to crystalloids.

Although burn therapy has had very satisfactory outcomes with respect to the past results, a recently observed liquid overload, the so-called "creep syndrome", today represents a serious complication in burn resuscitation. [10]

Excessive crystalloid administration and the withdrawal of colloids in certain phases of the burn patient's resuscitation are, today, deemed the most important factors for the appearance of "fluid creep". [11]

Some studies highlight the importance of the use of colloids and, especially, albumin including early treatment, particularly where large quantity of liquids are required. [12,13]

Early albumin treatment in resuscitating the burn patient would have the effect of reducing the total quantity of liquids to be administered in order to maintain effective volaemia through its effect on Startling forces and/or for its regenerating/protective action on endothelial glycocalyx. [14]

The results of a recently published clinical trial conducted on paediatric burn patients highlighted that early albumin administration in children with burns > 15-45% of total body surface reduces the quantity of crystalloids with a statistically significant reduction in cases of "fluid creep" and hospitalisation. [15]

Other pathological conditions

The clinical use of albumin has been proposed in many pathological conditions. In some cases this was based on sound physiological principles but occasionally proposed without the support of evidence obtained from solid clinical trials.

Some clinical situations are listed below which make provision for the use of albumin whenever special conditions exist.

HEART SURGERY

Albumin is preferred to synthetic colloids in paediatric heart surgery and in adults in extracorporeal circulation, and not only for haemodilution in priming heart-lung machine circuits but also for perioperative volume expansion. [16]
Finding hypalbuminaemia at the pre-operating phase is widely recognised as a reliable negative prognostic factor of post-operating mortality and morbidity. [17]
A recent randomised clinical trial has documented that in patients with low levels of albumin prior to an aortocoronary bypass operation, the exogenous supplement of albumin in quantities proportional to the degree of hypoalbuminaemia reduces the risk of acute post-operational renal damage with respect to untreated patients. [18]

MAJOR LIVER SURGERY (EXTENDED LIVER RESECTION, LIVER TRANSPLANT)

Given that the majority of patients undergoing these operations exhibit an underlying condition of hepatic cirrhosis, the use of albumin should be referenced to the conditions described above. In specific cases, albumin may be preferentially used to correct hypovolaemia and in cases of significant losses of ascitic liquid due to post-operating surgical drainage. [19]

PROTEIN LOSING ENTEROPATHY AND/ OR STATES OF MALNUTRITION

For nutritional purposes, albumin must be replaced by enteral nutrition or by total parenteral nutrition. Albumin administration can be evaluated in these cases only when the following conditions apply contemporaneously:

1. *serious diarrhoea with severe liquid loss, unresponsive to dietetic therapy;*
2. *severe hypoalbuminaemia (<2 g/dL);*
3. *clinical manifestation of hypovolaemia (hypotension, tachycardia, oliguria) and/or an anasarcous state.*

NEPHROTIC SYNDROME

Albumin use, whose infusion into patients with nephrotic syndrome usually causes an increase in albuminuria which defeats every expected effect upon

volaemia and albuminaemia, could, however, have a limited use in two conditions:

1. in patients with albuminaemia < 2 g/dL and severe clinical manifestations of hypovolaemia and pulmonary edema;
2. in an acute nephrotic syndrome at the commencement of steroidal therapy.

PLASMAPHERESIS

The use of albumin is appropriate in the case of plasma volume replacement higher than 20 mL/Kg in a single or repeated sessions within the space of one week.
Crystalloids or of albumin-crystalloid solutions can be considered in small plasma volume replacements. [20]

SERIOUS NEONATAL JAUNDICE

In the specific case of serious neonatal jaundice with the risk of severe neurological impairment or death, albumin can be used in order to bind circulating (indirect) bilirubin. [21]

EXTRACORPOREAL PURIFICATION SYSTEMS

Among the extracorporeal purification systems, the "Molecular Adsorbent Recirculating System" (MARS), based on the use of exogenous albumin on account of its binding and detoxification properties, finds specialist clinical application in the treatment of some cases of hepatic failure and irrepressible cholestatic pruritus. [22]

THE EARLY ADMINISTRATION OF ***albumin*** IN PAEDIATRIC PATIENTS WITH TOTAL SURFACE BODY BURNS > *15-45%* REDUCES THE QUANTITY OF CRYSTALLOID INFUSION.

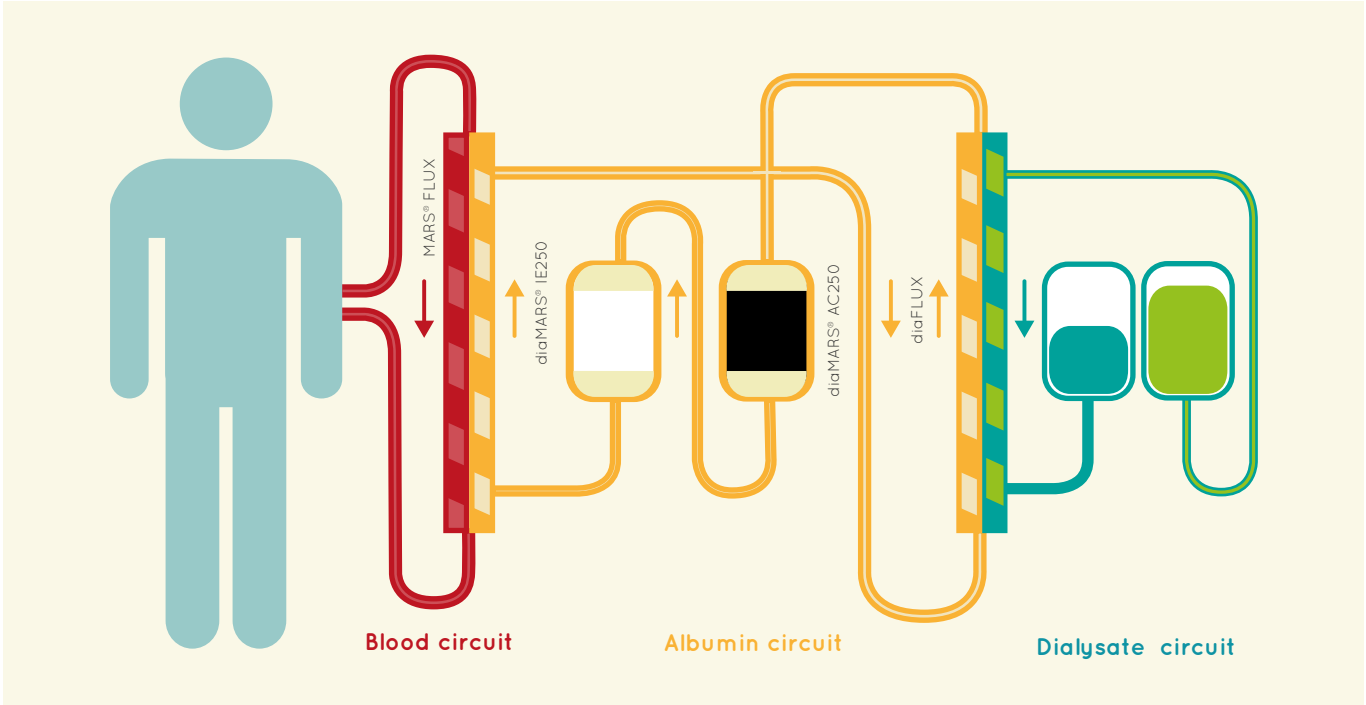

Figure 1. *Molecular Adsorbent Recirculating System (MARS).*

Albumin IS RECOMMENDED IN INFUSION THERAPY OF SEVERE SEPSIS AND SEPTIC SHOCK WHEN PATIENTS REQUIRE *considerable quantities of liquids.*

OVARIAN HYPERSTIMULATION SYNDROME

A recent revision of the literature has demonstrated possible benefits from albumin administration in the prevention of the ovarian hyperstimulation syndrome in high-risk subjects. [23]
In conclusion, it should be noted that at times albumin administration is based more upon direct clinical experience than upon scientific findings, thus leading to a situation of enormous variance in the prescription of this precious resource, in Italy as in the rest of the world.

Most inappropriate prescriptions refer to albumin use for nutritional measures or for the correction of hypoalbuminaemia per se (not associated with hypovolaemia) which still today is found in many medical fields (e.g. general surgery, internal medicine, geriatrics, and oncology).

A series of conditions are listed below in which the use of albumin is not corroborated by scientific evidence:

- *chronic hypoalbuminaemia*
- *malnutrition*
  (or otherwise for nutritional purposes)
- *general surgical operations (post-operational)*
- *cicatrisation of wounds*
- *nephrotic syndrome (chronic)*
- *protein losing enteropathy and malabsorption (uncomplicated)*
- *acute or chronic pancreatitis*
- *cerebral ischaemia.*

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THE THERAPEUTIC USE OF HUMAN *albumin* IN HEPATOLOGY IS CORROBORATED BY NUMEROUS *scientific findings* AND BY THE GUIDELINES OF THE PRINCIPAL NATIONAL AND INTERNATIONAL SCIENTIFIC ASSOCIATIONS.

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