

AISF-SIMTI position paper: the appropriate use of albumin in patients with liver cirrhosis

Paolo Caraceni¹, Paolo Angeli², Daniele Prati³, Mauro Bernardi¹, on behalf of the Italian Association for the Study of the Liver (AISF); Giancarlo M. Liumbruno⁴, Francesco Bennardello⁵, Pierluigi Piccoli⁶, Claudio Velati⁷, on behalf of the Italian Society of Transfusion Medicine and Immunohaematology (SIMTI)

¹Department of Medical and Surgical Sciences, University of Bologna, Bologna; ²Department of Medicine, University of Padua, Padua; ³Department of Transfusion Medicine and Hematology, "Alessandro Manzoni" Hospital, Lecco; ⁴Italian National Blood Centre, National Institute of Health, Rome; ⁵Immunohaematology and Transfusion Medicine Centre, Provincial Health Authority n. 7, Ragusa - "R. Guzzardi" Hospital, Vittoria; ⁶Transfusion Medicine Unit, University Hospital of Verona, Verona; ⁷Transfusion Medicine and Immunohaematology Department of Bologna Metropolitan Area, Bologna, Italy

Abstract

The use of human albumin is common in hepatology since international scientific societies support its administration to treat or prevent severe complications of cirrhosis, such as the prevention of post-paracentesis circulatory dysfunction after large-volume paracentesis and renal failure induced by spontaneous bacterial peritonitis, and the treatment of hepatorenal syndrome in association with vasoconstrictors. However, these indications are often disregarded, mainly because the high cost of human albumin leads health authorities and hospital administrations to restrict its use. On the other hand, physicians often prescribe human albumin in patients with advanced cirrhosis for indications that are not supported by solid scientific evidence and/or are still under investigation in clinical trials.

In order to implement appropriate prescription of human albumin and to avoid its futile use, the Italian Association for the Study of the Liver (AISF) and the Italian Society of Transfusion Medicine and Immunohaematology (SIMTI) nominated a panel of experts, who reviewed the available clinical literature and produced practical clinical recommendations for the use of human albumin in patients with cirrhosis.

1. Introduction

The clinical use of human albumin (HA) dates back to World War II when it was administered for fluid resuscitation. Since then, its administration has been extended to many other diseases since physicians commonly believe in its efficacy. However, apart from some clinical indications for which its use is supported by solid scientific evidence, in many other settings the efficacy of HA has been disproven by evidence-based medicine or is still under debate.

Hepatology is an area in which the use of HA is particularly common, since this treatment is currently

employed to treat or prevent severe complications of cirrhosis. Randomised clinical trials and meta-analyses have demonstrated its efficacy in the prevention of post-paracentesis circulatory dysfunction (PPCD) after large-volume paracentesis and renal failure induced by spontaneous bacterial peritonitis (SBP), and in the treatment of hepatorenal syndrome (HRS) in association with vasoconstrictors. Although endorsed by international scientific societies^{1,2}, these indications are often disregarded, even in specialised centres, mainly because the high cost of HA leads health authorities and hospital administrations to restrict its use. On the other hand, physicians often prescribe HA in patients with advanced cirrhosis for indications that are not supported by solid scientific evidence and/or are still under investigation in clinical trials. This inappropriate use may limit the availability for the patients in whom HA administration is supported by solid scientific evidence.

In order to implement appropriate prescription of HA and to avoid its futile use, the Italian Association for the Study of the Liver (AISF) and the Italian Society of Transfusion Medicine and Immunohaematology (SIMTI) nominated a panel of experts, who reviewed the available clinical literature and produced practical clinical recommendations for the use of HA in patients with liver cirrhosis. The initial draft was revised by a second panel of experts identified by the two scientific societies, so that the final version resulted from the consensus of the two working groups.

The level of evidence and strength of recommendation were judged according to the Grading of Recommendations Assessment Development and Evaluation (GRADE) system³. The strength of the evidence has been classified into four levels: high (A), moderate (B), low (C), and very low (D) quality evidence,

This article is being published jointly in "Digestive and Liver Disease".

while that of the recommendation has been divided into two: strong (1) and weak (2) (Table I). Where no clear evidence exists, the recommendations are based on the consensus advice of the writing committee and the expert opinion(s) reported in the literature.

2. The albumin molecule

2.1 Structure

HA is the main circulating protein in healthy individuals (3.5-5 g/dL), accounting for about 50% of the plasma proteins. It is a small protein (molecular weight: 66.5 kDa), consisting of a single chain of 585 amino acids organised in three repeated homologues domains (I, II, and III), each of which comprises two separate sub-domains (A and B). Of the 35 cysteine residues of the molecule, 34 are involved in internal disulphide bonds which stabilise the spatial conformation of the molecule, while the cysteine at position 34 (Cys-34) remains free in the reduced form, thus representing the major functional site of HA⁴.

2.2 Metabolism

HA is synthesised by hepatocytes and released into the circulation (about 10-15 grams every day). Its synthesis is stimulated by hormonal factors, such as insulin, cortisol and growth hormone, while pro-inflammatory mediators exert an inhibitory effect. Once produced, approximately 30-40% circulates in the blood stream, while the remaining leaves the vascular compartment at a rate of 5% per hour (transcapillary escape rate) and returns to it via the lymphatic system; the amount that returns to the vascular compartment is the same as the amount that leaves it. The circulatory half-life of HA is approximately 16-18 hours, while its total half-life varies from about 12 to 19 days in healthy young adults. HA is mainly degraded by the muscles,

liver and kidneys, although many other tissues can participate in its catabolism⁴⁻⁶.

2.3 Properties

HA is the main modulator of fluid distribution in the various compartments of the body accounting for about 70-80% of the plasma oncotic pressure. Two-thirds of the oncotic capacity derives from the direct osmotic effect related to its molecular mass and high plasma concentration while one-third is the results of the Gibbs-Donnan effect, due to the negative net charge of the molecule that is consequently able to attract positively charged molecules (i.e. sodium and, therefore, water) into the bloodstream⁴⁻⁶.

HA has many other biological properties that are unrelated to the regulation of fluid compartmentalisation (Figure 1). Some of these non-oncotic properties assume particular importance, such as scavenging and detoxification of reactive oxygen and nitrogen species, binding and transport of many hydrophobic endogenous molecules (e.g., cholesterol, fatty acids, bilirubin, thyroxine) and exogenous ones (e.g., drugs, including many antibiotics), preservation of the functional integrity of the microcirculation (e.g., endothelial stabilisation and platelet anti-aggregation), and modulation of the immune and inflammatory responses (e.g., binding of endotoxins, prostaglandins, and pro-inflammatory cytokines)^{4,5}.

3. Rationale for the use of human albumin in liver cirrhosis

Hypoalbuminaemia is a typical feature of cirrhosis and is an independent adverse prognostic factor. Beside decreased hepatocyte synthesis, it results from dilution of the extracellular fluid protein content due to the total plasma volume expansion consequent to renal sodium and water retention, from increased catabolism probably

Table I - Grading evidences and recommendations (adapted from the GRADE system).

Quality of evidence	
A - High	Further research is very unlikely to change our confidence in the estimate of effect. <ul style="list-style-type: none"> • Several high-quality studies with consistent results • In special cases: one large, high-quality multicentre trial
B - Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. <ul style="list-style-type: none"> • One high-quality study • Several studies with some limitations
C - Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. <ul style="list-style-type: none"> • One or more studies with severe limitations
D - Very low	Any estimate of effect is very uncertain. <ul style="list-style-type: none"> • Expert opinion • No direct research evidence • One or more studies with very severe limitations
Strenght of recommendation	
1 - Strong	Factors influencing the strength of the recommendation included the quality of evidence, presumed patient-important outcomes, and cost.
2 - Weak	Variability in preferences and values, or more uncertainty: more likely a weak recommendation is warranted. Recommendation is made with less certainty: high cost or resource consumption

accelerated by the damage of the molecule, and from the increased trans-capillary escape rate towards the extravascular space, at least in patients with refractory ascites^{4,5}.

In addition to quantitative changes, HA undergoes structural and functional alterations that are probably favoured by the pro-inflammatory and pro-oxidant state of advanced cirrhosis^{6,7}. Extensive post-transcriptional changes, involving several sites of the molecule, develop and increase in parallel with the disease severity⁷. Physiological functions of HA appear to be impaired, including the ability to chelate cobalt and binding and transport capacities⁸.

It can, therefore, be hypothesised that, in patients with cirrhosis, the global function of HA, resulting from both oncotic and non-oncotic properties, is not only related to its absolute concentration in the circulation, but also to the degree of preservation of its structural and functional integrity⁵⁻⁸.

Advanced cirrhosis is characterised by two major systemic features: circulatory dysfunction and chronic inflammation. These alterations are strictly inter-related and cooperate to cause the multi-organ dysfunction and failure occurring in end-stage cirrhosis (Figure 2)⁵.

The cardiovascular alterations involve both the circulation and the heart⁹. The dominant haemodynamic change is a progressive reduction of effective arterial volaemia. Effective hypovolaemia mainly results from the fall of systemic vascular resistance, mostly in the splanchnic area, due to the increased production of vasoactive substances (e.g. nitric oxide, carbon monoxide, endocannabinoids), inducing vasodilation and hampering the response to vasoconstrictors. This evokes the compensatory activation of neuro-humoral systems able to promote vasoconstriction and renal retention of sodium and water, including the renin-angiotensin-aldosterone axis (RAA), sympathetic nervous system (SNS), and arginine-vasopressin (ADH). As a result, from a functional point of view, patients with decompensated cirrhosis are hypovolaemic and exhibit cardiovascular hyporeactivity, even though their cardiac output can be normal or elevated. However, a fall in cardiac output, leading to an exacerbation of effective hypovolaemia, is observed in the more advanced stages of the disease, indicating the occurrence of clinically relevant cardiac dysfunction. In the end-stage of the disease, the extreme effective hypovolaemia directly induces a further reduction in the perfusion of kidneys and other organs, thus generating ischaemic tissue damage until multi-organ failure develops. In this pathophysiological scenario, preservation of the effective blood volume is a primary goal in the management of these patients.

Patients with decompensated cirrhosis also have a chronic state of moderate systemic inflammation, which is related to the sustained stimulation of the immune system cells activated by the translocation of bacterial products (e.g., lipopolysaccharide, bacterial DNA) from the intestinal lumen to the circulation due to quantitative and qualitative changes in gut microbiota, impairment in the intestinal mucosal barrier, increased epithelial permeability, and impaired intestinal immunity¹⁰. In a vicious circle, the cytotoxic agents released during the inflammatory process contribute to produce splanchnic vasodilation and depress cardiac contractility, thus exacerbating circulatory dysfunction¹⁰. They can also contribute directly to organ dysfunction by inducing microvascular coagulation and cell damage¹⁰.

While systemic inflammation and oxidative stress are steadily moderate in patients with decompensated cirrhosis, they become rapidly severe in patients with acute-on-chronic liver failure⁶. Acute-on-chronic liver failure is a clinical syndrome characterised by acute development of organ failure (of liver, kidneys, brain, lungs, coagulation, and circulation) and a short-term, high risk of mortality, usually precipitated by bacterial infection, acute alcoholic hepatitis or other clinical events, even if a specific cause cannot be identified in a considerable number of cases¹¹.

Due to its oncotic and non-oncotic properties, HA can exert a beneficial effect at different steps of the vicious circle that links circulatory dysfunction, inflammatory response, and oxidative stress in patients with decompensated cirrhosis.

4. Clinical use of albumin in cirrhosis

HA is given to patients with advanced cirrhosis with the purpose of antagonising the effective hypovolaemia, mainly because of its capacity to act as a potent plasma-expander by increasing cardiac output and refilling the dilated arterial vascular compartment, although some positive effects on circulatory function and cardiac contractility also appear to be mediated by its non-oncotic properties^{12,13}.

International guidelines currently endorse the use of HA to manage clinical complications of cirrhosis characterised by extreme effective hypovolaemia: (i) prevention of PPCD; (ii) prevention of renal failure induced by SBP; and (iii) diagnosis and treatment of HRS, in association with vasoconstrictor drugs^{1,2}. A consequent assumption is that the presence of hypoalbuminaemia should not be a pre-requisite for the administration of exogenous HA in these conditions.

Beside these universally accepted and evidence-based indications, the administration of HA has been proposed for other clinical conditions in patients

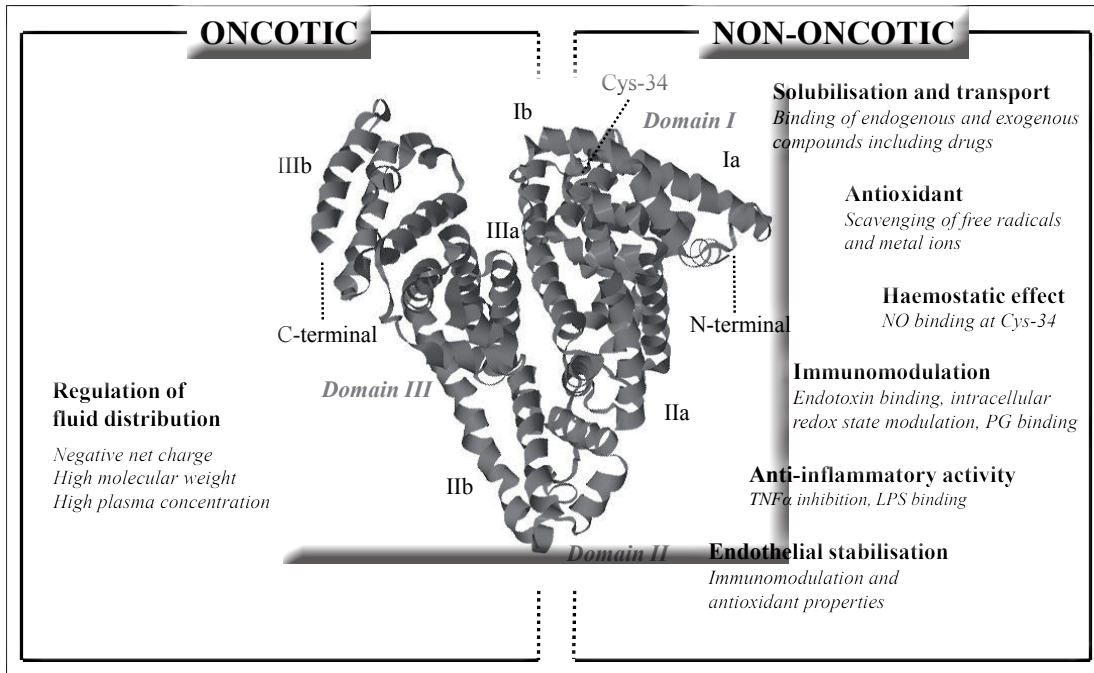


Figure 1 - Oncotic and non-oncotic properties of human albumin.
Cys-34: cysteine-34; LPS: lipopolysaccharides; NO: nitric oxide; PG: prostaglandins; TNF α : tumour necrosis factor-alpha.

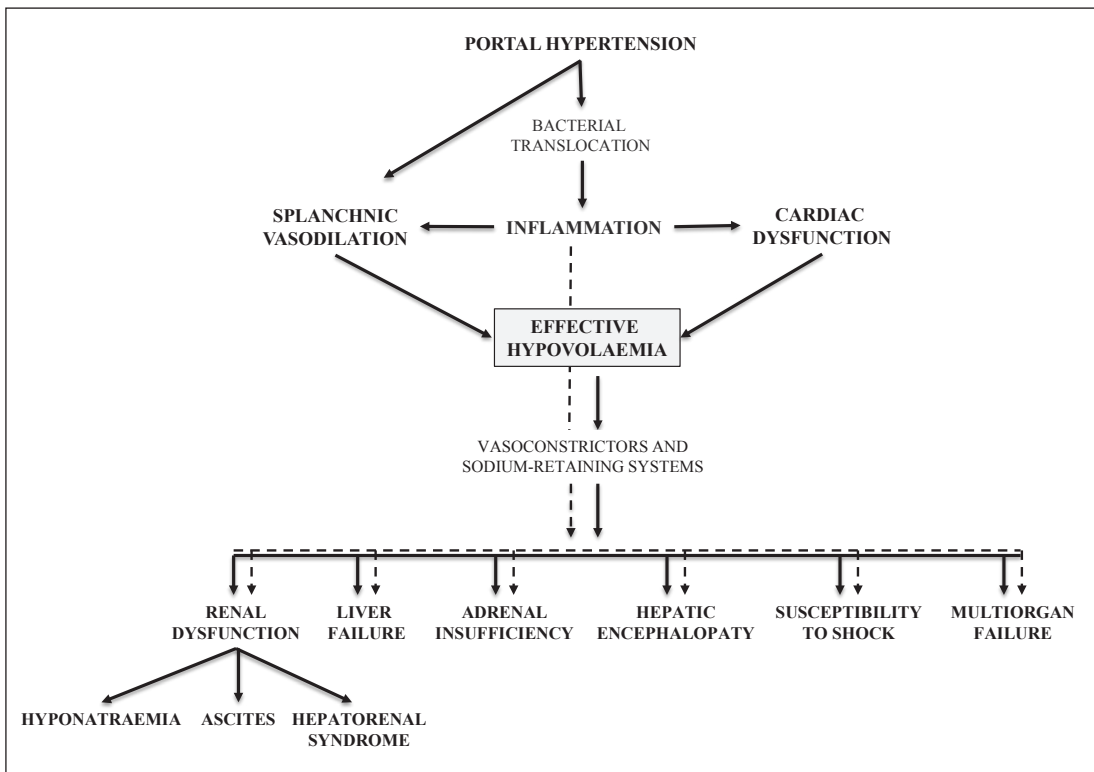


Figure 2 - Major pathophysiological events in advanced liver cirrhosis.

with cirrhosis. Long-term treatment of ascites not responding to diuretic treatment is allowed in Italy by the Italian Medicines Agency (AIFA), even if solid scientific evidence supporting its use in this context has not been published as yet. Treatment of hyponatraemia is another example of HA use not based on evidence. Other clinical indications currently under investigation in patients with cirrhosis are treatment of bacterial infections other than SBP, hepatic encephalopathy, and septic shock (Table II).

AISF-SIMTI recommendations

- *In the specific setting of patients with advanced cirrhosis, the presence of hypoalbuminaemia should not be the guide to the prescription of HA (B1).*
- *As in other clinical settings, in patients with advanced cirrhosis, hypoalbuminaemia per se is not an indication for the prescription of HA (B1).*

5. Evidence-based clinical indications

5.1 Prevention of post-paracentesis circulatory dysfunction

5.1.1 Clinical and pathophysiological background

Paracentesis is the current first-line treatment for patients with tense and refractory ascites^{1,2}. In the majority of patients not receiving plasma expansion, the removal of large volumes of ascites induces the development of PPCD, which is diagnosed by a significant increase (>50%) in plasma renin activity 4-6 days after paracentesis¹⁴. PPCD is associated with a higher rate of recurrence of the ascites, dilutional hyponatraemia, renal impairment, re-hospitalisation, and poorer survival¹⁴⁻¹⁶.

By reducing intra-abdominal pressure, large-volume paracentesis boosts venous return to the heart. As a result, right atrial pressure decreases, while cardiac output and stroke volume increase. However, because of a paradoxically excessive drop of systemic vascular resistance, effective circulating volume declines further, leading to a reduction in arterial pressure. In the days after paracentesis, there is marked activation of the RAA axis and SNS, which persists in some cases for months^{14,15,17-19}.

5.1.2 Albumin for preventing post-paracentesis circulatory dysfunction

The most effective method to prevent PPCD is to counteract effective hypovolaemia by using plasma-expanders. It was first demonstrated in the 1980s that infusion of HA after paracentesis improves circulatory dysfunction and prevents the occurrence of PPCD¹⁴.

Since the early 1990s, less costly alternatives, such as crystalloids and artificial colloid volume expanders, have been compared to HA^{15,20-26}. When more than 5 L of

ascites are removed, HA (6-8 g/L of ascites removed) has been found to be more effective at preventing PPCD than the other plasma expanders in several studies^{15,20,25,26}, although other investigations - all including very low numbers of patients - did not confirm this positive result²¹⁻²⁴.

In contrast, when less than 5 L of ascites are removed, the incidence of PPCD is low and dextran-70 (8 g/L of ascites removed), polygeline (150 mL/L of ascites removed) or saline (150 mL/L of ascites removed) show an efficacy similar to that of HA^{15,25}. However, polygeline is no longer used in many countries because of the potential risk of transmission of prions¹, while there are concerns about the possibility that dextrans and starches may induce renal failure²⁷ and accumulate in the liver²⁸. Furthermore, infusion of large volumes of saline should be avoided in fluid-overloaded patients with ascites and/or peripheral oedema.

More recently, the use of vasoconstrictors, including vasopressin, terlipressin, and midodrine, has been compared to the administration of HA after paracentesis²⁹⁻³³. However, the results of the few randomised clinical trials are variable, probably because of their very limited sample size, so that the clinical utility of vasopressors after paracentesis cannot be ascertained.

Despite this greater efficacy in preventing PPCD, randomised trials have not shown differences in the survival of patients receiving HA compared with that of patients given alternative treatments^{15,25,34}. However, a recent meta-analysis indicates that HA after large-volume paracentesis is significantly more effective than other treatments at reducing not only PPCD and hyponatraemia, but also mortality³⁵. Effect sizes were substantial, with HA lowering the odds of PPCD by 66%, hyponatraemia by 42%, and death by 36%. In all eligible trials included, the average volume of ascites removed was greater than 5 L and no major differences were apparent according to whether volumes of ascites removed were 5.5-8.0 L or more than 8 L. In the majority of studies included, the dose of HA administered per litre of ascites removed was 8 g, although 5 or 6 g were also infused in a minority of trials.

Only one randomised trial considering HA infusion after large-volume paracentesis compared standard (8 g/L of ascites removed) versus reduced (4 g/L of ascites removed) doses. The incidence of PPCD, hyponatraemia, and renal failure were low, but similar in the two groups. Although, if confirmed, these results could support a reduction of the costs related to paracentesis, the small sample size again precludes definitive conclusions³⁶.

Finally, a recent health economic analysis suggested that HA is more cost-effective than alternative but cheaper plasma volume expanders since its

Table II - Summary of the panel's indications for the use of HA in patients with cirrhosis.

Clinical condition		Doses and schedules of administration	Indications for the use of HA	Quality of evidence and strength of recommendation
Prevention of PPCD	Paracentesis \geq 5 litres	6-8 g per litre of removed ascites	Mandatory in all patients	A1
	Paracentesis <5 litres		Preferred if concerns regarding use of synthetic colloids or crystalloids	B1
Prevention of renal failure after SBP	High-risk patients	1.5 g/kg at diagnosis + 1 g/kg on the 3 rd day	Mandatory in all patients	A1
	Low-risk patients*		Consider in individual patients	B1
Diagnosis of HRS		1 g/kg/die for 2 consecutive days	To be used regularly	D1
Treatment of type I HRS (in association with vasoconstrictors)		1 g/kg at diagnosis + 20-40 g/die until vasoconstrictors are stopped	Mandatory in all patients	A1
Long-term treatment of ascites		To be defined	Consider in difficult-to-treat ascites	C1
Treatment of severe hyponatraemia		To be defined	Consider if no response to standard measures	D1
Prevention of renal failure after non-SBP bacterial infections		-	Not indicated at present	B1
Treatment of septic shock		To be defined	Consider in all patients	C1
Treatment of hepatic encephalopathy		-	Not indicated at present	B1

* Low-risk patients: serum albumin <4 mg/dL and serum creatinine <1 mg/dL.

HA: human albumin; PPCD: post-paracentesis circulatory dysfunction; HRS: hepatorenal syndrome; SBP: spontaneous bacterial peritonitis.

administration is associated with a lower number of liver-related complications within the first 30 days³⁴.

AISF-SIMTI recommendations on the use of albumin to prevent post-paracentesis circulatory dysfunction

- HA should be administered after large-volume paracentesis exceeding 5 L at the dose of 6-8 g/L of ascites removed, since it reduces the incidence of PPCD and improves patients' clinical outcome (A1).
- When the amount of ascites removed exceeds 5 L, the use of alternative plasma expanders is not recommended because they are less effective in the prevention of PPCD (A1). The combined use of HA and other plasma expanders in order to reduce the dose of HA is also not recommended (D1).
- When the amount of ascites removed is less than 5 L, HA can be used if there are concerns regarding the administration of crystalloids or synthetic colloids (volume overload, renal failure, coagulopathy) (B1).
- The use of vasoconstrictors instead of HA or the use of reduced doses of HA should be limited to controlled clinical trials (C1).
- Although there are no studies on the modalities of albumin administration, it seems advisable to infuse HA relatively slowly to avoid possible cardiac overload due to the existence of a latent cirrhotic cardiomyopathy, starting during the presumed final part of the paracentesis or at the end of paracentesis

when the volume of ascites removed is known and the paracentesis-induced increase in cardiac output begins to return to baseline (D2).

5.2 Prevention of renal failure after spontaneous bacterial peritonitis

5.2.1 Clinical and pathophysiological background

SBP is a life-threatening infection of ascitic fluid that occurs frequently in patients with advanced cirrhosis and requires prompt recognition and treatment. The diagnosis is based on the presence of >250 polymorphonuclear cells/mm³ of ascites, in the absence of an intra-abdominal source of infection or malignancy³⁷. About one-third of patients with SBP develop renal impairment, which is often progressive irrespectively of resolution of the infection and is an independent predictor of in-hospital mortality^{38,39}, as 42% of patients with this complication will die, while the mortality of those who do not develop renal impairment is only 7%³⁸.

The high incidence of renal failure after SBP is caused by the abrupt deterioration of circulatory function, involving both vascular tone and cardiac function, and is mediated by the marked activation of the pro-inflammatory and vasoactive systems. While systemic vascular resistance remains substantially unchanged, possibly as a result of a striking compensatory activation of vasoconstrictor systems, cardiac output declines significantly as a consequence of chronotropic

incompetence and reduced myocardial contractility. These events ultimately lead to a marked reduction of effective volemia and arterial pressure, thus impairing renal and, more in general, organ perfusion⁴⁰.

5.2.2 Albumin for preventing renal failure after spontaneous bacterial peritonitis

Administration of HA, but not hydroxyethyl starch, improves circulatory dysfunction in patients with SBP¹². Along with parameters reflecting plasma volume expansion, other haemodynamic effects can be explained only recalling the non-oncotic properties of the molecule. In fact, the striking rise in systemic vascular resistance seen after HA, but not after hydroxyethyl starch infusion, and the concomitant significant reduction of the circulating levels of von Willebrand-related antigen, factor VIII, and nitric oxide metabolites, indicate that HA counteracts endothelial activation¹². Furthermore, the improvement of stroke index supports a direct effect of HA on cardiac function¹², as also suggested by the experimental finding in rats with cirrhosis and ascites that plasma volume expansion with HA, but not with hydroxyethyl starch, ameliorates left ventricular function *ex vivo*¹³.

The first controlled clinical trial assessing the effect of HA administration in patients with cirrhosis and SBP showed that such treatment, associated with antibiotic therapy, significantly reduced the incidence of renal failure and the in-hospital and 3-month mortality rates⁴¹. In more detail, 126 patients were randomised to receive either HA 1.5 g/kg/body weight (b.w.) at diagnosis and 1 g/kg b.w. on day 3 in addition to cefotaxime or cefotaxime alone. Although infection resolution rates were similar in the two groups, the incidence of renal impairment dropped from 33% in patients receiving only cefotaxime to 10% in those treated with cefotaxime plus HA. Baseline independent predictors of the development of renal impairment included serum bilirubin and creatinine, and treatment with cefotaxime alone. Confirming that the occurrence of renal failure in the setting of SBP carries a highly adverse prognostic factor, 29% of patients in the cefotaxime group died in hospital and 41% within 3 months. These figures were strikingly reduced by HA administration, as in-hospital and 3-months mortality rates were 10% and 22%, respectively.

Post-hoc analysis showed that the incidence of renal impairment was higher among those with a baseline serum bilirubin ≥ 4 mg/dL (48% in the cefotaxime group and 12% in cefotaxime plus HA group) or serum creatinine ≥ 1 mg/dL (32% and 14%, respectively) than in patients with serum bilirubin < 4 mg/dL and serum creatinine < 1 mg/dL (7% and 0%, respectively).

This observation raises the question of whether all patients with SBP need HA administration. In a preliminary, small study, patients with SBP at low-risk of renal impairment (defined as bilirubin < 4 mg/dL and serum creatinine < 1 mg/dL) received only antibiotic treatment and none developed renal impairment or died⁴². In a more recent retrospective study⁴³, episodes of "low-risk" SBP were associated with a much lower incidence of renal failure as well as lower in-hospital and 3-month mortality rates compared with "high-risk" episodes (4.7%, 3.1% and 7% vs 25.6%, 38.2% and 47%, respectively). Among the latter, those treated with HA had a lower in-hospital mortality than those treated only with antibiotics (28.8% vs 46.8%) and a higher probability of survival at 3 months (62% vs 45%). Thus, HA administration clearly improves the survival of patients with high-risk SBP, but it does not seem to be necessary for patients with low-risk SBP. However, this conclusion awaits confirmation in a randomised, prospective study.

Similarly, confirmation is also needed for the results of a pilot study that assessed whether a lower dose of HA could be used⁴⁴. In the pilot study, a reduced dose regimen (1.0 g/kg b.w. at diagnosis and 0.5 g/kg b.w. on day 3) appeared to be as effective as the standard regimen in preventing renal failure in a group of cirrhotic patients with SBP including 77% at "high-risk". In-hospital (27% vs 21%) and 3-month mortality (36% vs 37%) rates also did not differ between patients receiving the reduced or the standard HA dose, respectively.

Finally, a recent meta-analysis of randomised trials substantially confirmed that HA infusion prevents renal impairment and reduces mortality among patients with SBP⁴⁵. However, there is still limited evidence available on the outcomes of patients with low-risk SBP who do not receive HA as well as on the responsiveness of low-risk patients to HA infusion.

AISF-SIMTI recommendations on the use of albumin to prevent renal failure after spontaneous bacterial peritonitis

- HA (1.5 g/kg/b.w. at diagnosis and 1 g/kg/b.w. on day 3) should be administered, in association with antibiotic therapy, in cirrhotic patients with SBP since this approach reduces the incidence of renal failure and improves survival (A1).
- Patients with baseline serum bilirubin < 4 mg/dL and serum creatinine < 1 mg/dL have a low risk of developing renal failure after SBP. In this group of patients the benefit of HA is unclear and the decision to administer HA should be individualised (B1).
- The use of crystalloids and synthetic colloids instead of HA or in association to HA is not recommended (D1).

- The use of reduced doses of HA should be limited to controlled clinical trials (Level C1).

5.3 Diagnosis and treatment of hepatorenal syndrome

5.3.1 Clinical and pathophysiological background

HRS is defined as the occurrence of renal failure in patients with advanced liver disease without another, identifiable cause⁴⁶⁻⁴⁸. Type 1 HRS is a rapidly progressive acute renal failure that frequently develops in temporal relationship with a precipitating factor, such as a bacterial infection. Its prognosis is dismal since the median survival without treatment is approximately 2 weeks. Type 2 HRS occurs in patients with refractory ascites and is characterised by a moderate, slowly progressive degree of functional renal failure, often with avid sodium retention. Patients with type 2 HRS may eventually develop type 1 HRS either spontaneously or following a precipitating event, such as SBP^{46,47}.

Marked renal arterial vasoconstriction is the main pathophysiological feature of type 1 HRS. It develops in the context of a severe reduction of the effective circulating volume, which is related both to splanchnic arterial vasodilation and to an inadequate cardiac output, leading to extreme over-activation of the endogenous vasoconstrictor and sodium-retaining systems (RAA, SNS, and ADH)^{47,49}.

5.3.2 Albumin for the diagnosis

The diagnosis of HRS is one of exclusion. Besides excluding organic causes, the diagnosis is based on the lack of response to volume expansion in order to differentiate HRS from other forms of functional renal failure⁴⁶⁻⁴⁸. No studies have been performed to establish whether plasma volume expansion should be performed with HA rather than saline. Members of the panel of the International Club of Ascites have agreed that HA causes a greater and more sustained expansion than saline^{47,48}, as it can be assumed by the studies on PPCD showing the superiority of HA over saline or synthetic colloids.

5.3.3 Albumin for the treatment of type 1 hepatorenal syndrome

Most of the existing information on treatment of HRS is related to patients with type 1 HRS. Therefore, all the following comments refer to type 1 HRS unless otherwise specified. Once diagnosed, treatment should be started early in order to prevent the progression of renal failure.

The most effective treatment of HRS currently available is the administration of vasoconstrictor drugs together with HA. Terlipressin, a vasoconstrictor analogue acting on V₁ receptors, mainly located in the splanchnic area, is the most studied vasoconstrictor. It improves the markedly impaired circulatory function by causing

vasoconstriction of the extremely dilated splanchnic vascular bed, thus increasing mean arterial pressure and renal perfusion⁵⁰. In most studies, terlipressin was given in combination with HA in order to further improve the effective circulating volume. Interestingly, when terlipressin has been used without HA, treatment was considerably less effective⁵¹.

Several randomised⁵²⁻⁵⁶ and non-randomised^{51,57,58} clinical trials have shown that terlipressin and HA improve renal function and that full reversal of type 1 HRS is obtained in up to 40-50% of patients. Although responders survive longer than non-responders, the overall survival was not significantly superior in patients receiving terlipressin plus HA than in those treated with HA alone or placebo^{52,53,57}. Nevertheless, a recent meta-analysis showed that the combined treatment is also able to improve short-term survival⁵⁹.

HA is given at the initial dose of 1 g/kg.b.w. on day 1, followed by 20-40 g/day according to the central venous pressure and/or evidence of volume overload until terlipressin is stopped^{52,53}.

A few studies have evaluated other vasoconstrictors for the management of type 1 HRS, such as noradrenaline, which showed a similar efficacy as terlipressin^{60,61}, and midodrine plus octreotide, a combination that was less effective than terlipressin⁶². With both treatment approaches, HA is given at the doses described for use with terlipressin⁶⁰⁻⁶².

Information on the use of vasoconstrictors plus HA in patients with type 2 HRS is really limited. Although the combined treatment improves renal function^{63,64}, the rate of HRS recurrence after treatment withdrawal appears to be very high.

AISF-SIMTI recommendations on the use of albumin in the diagnosis and treatment of hepatorenal syndrome

- HA administration (1 g/kg/b.w. for two consecutive days) should be used to expand plasma volume for the differential diagnosis of HRS (D1).
- HA should be given with terlipressin in patients with type 1 HRS at the dose of 1 g/kg/b.w. on day 1 followed by 20-40 g per day until terlipressin is withdrawn (A1). When possible, the HA dose should be titrated according to the level of the central venous pressure. Alternatively, HA should be reduced or stopped in the presence of clinical evidence of volume overload and/or pulmonary oedema (A1).
- HA should be given with other vasoconstrictors (noradrenaline or midodrine plus octreotide) in patients with type 1 HRS at the same doses as used with terlipressin (A1).
- If patients with type 2 HRS are treated with vasoconstrictors, HA should be added according to the dosages used in type 1 HRS (B1).

6. Non-evidence-based clinical indications

6.1 Long-term treatment of cirrhotic ascites

6.1.1 Clinical and pathophysiological background

Ascites is the most frequent complication of liver cirrhosis, occurring in more than 50% of patients within 10 years of the diagnosis, and is associated with a significant worsening of the prognosis^{65,66}. Medical treatment of uncomplicated ascites is based on diuretics associated to a mild reduction of dietary sodium intake^{65,66}. Approximately 10% of patients per year develop refractory ascites, as defined by the International Club of Ascites, either because of a lack of response to medical treatment or because of the onset of diuretic-induced complications that preclude the use of an effective dosage of these drugs^{65,67}. Refractory ascites is associated with an increased incidence of severe complications of cirrhosis, such as HRS, hyponatraemia, SBP, and umbilical hernia rupture and strangulation. Thus, the overall probability of survival of patients with refractory ascites is very poor, being approximately 30% at 2 years⁶⁵⁻⁶⁷.

Renal sodium retention and ascites formation are consequences of effective hypovolaemia, resulting from arteriolar vasodilation mainly in the splanchnic area, which promotes vasoconstriction and renal retention of sodium and water through the compensatory activation of neuro-humoral systems (RAA, SNS, ADH) and, in the more advanced stage of cirrhosis, through reduced renal perfusion⁶⁶.

Thus, preservation of the central blood volume represents a potential target in the management of ascites.

6.1.2 Albumin for the long-term treatment of ascites

The use of HA for the treatment of ascites is allowed within the Italian National Health Service, but reimbursement for out-of-hospital prescriptions is limited to patients with ascites not responding to standard diuretic therapy (Note 15 of the Italian Medicines Agency). However, the long-term administration of HA to treat ascites is still debated, because of the lack of definitive scientific evidence supporting its clinical benefit.

Apart from a few reports of uncontrolled small studies and sporadic cases from more than a half century ago, only two randomised clinical trials from an Italian group have been published so far^{68,69}. In 1999, two groups of hospitalized patients with cirrhosis and ascites were randomised to receive diuretics, given in a stepwise response-guided schedule, with or without daily infusion of 12.5 g HA during hospitalisation (median duration >20 days) followed by 25 g/week after discharge (median follow-up >20 months)⁶⁸. The treatment with diuretics plus HA was overall more effective than diuretics alone in resolving

ascites during hospitalisation and reducing the time the patients stayed in hospital. However, these results were achieved only in the subset of patients receiving low-dose diuretics (25 mg/day furosemide and 200 mg/day potassium canrenoate), while the advantage was lost when the anti-aldosteronic drug was used alone or when higher doses of diuretics were needed. No effect on survival after discharge was seen⁶⁸. Despite the positive results, it is hard to transfer these regimens into current clinical practice in which these patients are managed as outpatients.

In a subsequent study⁶⁹, a cohort of 100 patients was randomised to receive chronic treatment with either diuretics alone or diuretics plus HA (25 g/week for the first year, then 25 g every 2 weeks) (median follow >84 months). The recurrence rate of moderate to severe ascites and mortality were significantly lower in patients who received the supplemental HA. However, the relatively small sample size prevents firm conclusions from being reached.

No other controlled clinical trials have been performed so far to evaluate the effectiveness of prolonged HA administration in the treatment of cirrhosis and ascites. The lack of confirmatory randomised studies, together with the high cost of this therapeutic strategy, explain why long-term chronic HA infusion is not endorsed by international guidelines^{1,2} and it is, therefore, not usually included among therapeutic options for difficult-to-treat ascites in countries other than Italy.

A definite solution to this controversial issue will be provided by an open-label, multicentre, randomised, no-profit clinical trial, currently underway in Italy. This trial, supported by the Italian Medicines Agency, is comparing the effectiveness of long-term weekly administration of HA (40 g twice a week for the first 2 weeks and 40 g once a week for a maximum of 18 months independently of the serum albumin level) in 420 patients with cirrhosis and uncomplicated ascites receiving at least 200 mg per day of an anti-aldosteronic drug and 25 furosemide per day (ANSWER study, NCT 01288794, www.clinicaltrials.gov). The preliminary results from 386 patients were recently presented in abstract form⁷⁰, showing that patients treated with diuretics plus HA required significantly fewer paracenteses and had lower incidences of refractory ascites as well as SBP, renal impairment, and hepatic encephalopathy.

Thus, although increasing evidence supports the benefit of HA in improving the management of ascites and the clinical outcome of patients with decompensated cirrhosis, the final results of the ANSWER study are eagerly awaited to confirm the efficacy of long-term administration of HA for this indication.

AISF-SIMTI recommendations on the long-term use of albumin to treat ascites

- Long-term HA can be effective in the treatment of ascites in association with diuretics (C1). The efficacy, dosage and timing of HA administration need to be defined by adequately-powered randomised controlled trials.

6.2 Treatment of hyponatraemia

6.2.1 Clinical and pathophysiological background

Hyponatraemia is a common finding in patients with cirrhosis and is characterised by low serum sodium levels (<135 mmol/L) usually associated with the presence of ascites, often refractory, and peripheral oedema. It is caused mainly by impaired solute-free water excretion secondary to hypersecretion of ADH, which is stimulated by effective hypovolaemia and results in a disproportionate retention of water relative to sodium retention^{71,72}.

Besides the fact that serum sodium concentration is an important marker of prognosis in cirrhosis^{71,73}, hyponatremia, mostly when severe (<125 mmol/L), can induce neurological complications *per se* or precipitate hepatic encephalopathy and is associated with reduced survival after liver transplantation^{74,75}.

6.2.2 Albumin for the treatment of hyponatraemia

It is generally considered that management of hyponatremia should be started when the serum sodium concentration is lower than 130 mmol/L and includes fluid restriction, withdrawal of diuretics, and infusion of hypertonic saline solution although this latter approach is still controversial¹.

Based on a strong pathophysiological rationale to use HA, that is blunting the non-osmotic hypersecretion of ADH through the improvement of effective hypovolaemia, many hepatologists consider HA an effective treatment for hyponatraemia. However, no randomised trials directly assessing the efficacy of HA have been published *in extenso*. Apart from a positive report on a few isolated cases⁷⁶, the results of a small randomised trial, published in 2007 only in abstract form, showed that the administration of HA improves serum sodium concentration⁷⁷.

AISF-SIMTI recommendations on the use of albumin to treat hyponatraemia

- Based on the pathophysiological background, HA might be effective to correct severe hyponatraemia not responding to standard measures, particularly in patients with symptoms related to hyponatraemia or waiting for liver transplantation (D1).

7. Clinical indications under investigations

7.1 Prevention of renal failure after bacterial infections other than spontaneous bacterial peritonitis

7.1.1 Clinical and pathophysiological background

Renal failure also frequently occurs in patients with bacterial infections other than SBP. In one study that enrolled 106 consecutive patients with cirrhosis and sepsis unrelated to SBP⁷⁸, renal impairment developed in 27% of cases compared with only 8% in those without sepsis. The infections that most often led to renal failure were culture-negative sepsis (66%) and spontaneous bacteraemia (45%), followed by cellulitis, pneumonia and urinary tract infections. Unlike the situation with SBP, however, reversible renal impairment prevailed (76%), with the proportion not being substantially different from that found in patients without sepsis (62%).

As in SBP, the development of renal impairment strongly influences the outcome of patients with non-SBP bacterial infections, as 43% of these patients who developed renal impairment died in hospital⁷⁹ and 66% within 3 months⁷⁸, which are far higher percentages than those in patients who did not develop renal impairment (7% and 13%, respectively).

7.1.2 Albumin for the treatment of bacterial infections other than spontaneous bacterial peritonitis

Whether HA administration can be beneficial for non-SBP bacterial infections is still under investigation. The first published randomised trial on this issue⁸⁰ enrolled 110 patients affected by pneumonia, urinary tract or skin infections, or culture-positive bacteraemia; however, in 20% of patients, infection was only suspected. The patients were randomised to receive appropriate antibiotic treatment alone or antibiotic treatment plus HA at the "standard" dose regimen used for SBP. Although both renal function (evaluated by serum creatinine and estimated glomerular filtration rate) and circulatory function (assessed by plasma renin activity, plasma aldosterone concentration, noradrenaline level, and mean arterial pressure) improved in patients receiving HA, the occurrence of type 1 HRS and the 3-month mortality rate did not differ between the two groups. However, multivariate analysis showed that treatment with HA was an independent predictive factor of survival when groups were adjusted according to the other predictors of survival, with a 3.4 relative risk of death for patients receiving only antibiotics.

A more recent French multicentre, randomised trial⁸¹ enrolled 193 cirrhotic patients with a Child-Pugh score greater than 8 and sepsis unrelated to SBP to receive antibiotics plus HA (1.5 g/kg on day 1 and 1 g/kg on day 3) or antibiotics alone. HA infusion delayed the occurrence of renal failure (mean time to onset: 29±22

vs 12±9 days, $p=0.018$), but the 3-month survival and renal failure rate were similar (70.2 vs 78.3% and 14.3 vs 13.5%, respectively). Post-hoc analysis showed a trend toward a better survival in patients with ascites and severe circulatory dysfunction. Interestingly, pulmonary oedema developed in about 8% of patients receiving HA.

Thus, HA administration appears to produce some benefit only in selected patients with bacterial infections, i.e. those patients at high risk of renal failure and death, but further studies are needed to confirm this conclusion. An ongoing large, multicentre European randomised trial (INFECIR-2 study, ClinicalTrials.gov, Identifier: NTC02034279) has been started by the EASL Chronic Liver Failure Consortium with the aim of assessing the effect of HA administration in high-risk patients with non-SBP bacterial infections, as defined by the presence of liver and kidney impairment, parameters of systemic inflammatory response syndrome (SIRS), and type of infection.

AISF-SIMTI recommendations on the use of albumin for the prevention of renal failure after bacterial infections other than spontaneous bacterial peritonitis

- HA administration, in association with antibiotics, is not currently indicated in patients with cirrhosis and bacterial infections other than SBP (B1).

7.2 Treatment of septic shock

Patients with septic shock have shown improved survival with early goal-directed therapy, based on the combination of empirical antibiotics, vasoconstrictors, and volume replacement⁸². Regarding this last, there are not specific studies evaluating the administration of HA in cirrhotic patients with septic shock. However, some data can be extrapolated from large randomised trials comparing crystalloids with HA in the general population. In a subgroup of 1,218 patients with severe sepsis enrolled in the SAFE study, multivariate analysis revealed that those receiving HA had a lower risk of death at day 28 as compared to those receiving saline (adjusted odd ratio: 0.71)⁸³. Furthermore, a meta-analysis comparing HA and crystalloids in septic patients showed a survival benefit with HA⁸⁴. This positive result was very recently challenged by a randomised trial (the ALBIOS study), including nearly 2,000 patients with severe sepsis enrolled in about 100 Italian Intensive Care Units, showing that HA administration did not improve 28-day and 90-day survival rates compared to those achieved with administration of crystalloids. However, according to a subgroup post-hoc analysis, a benefit of HA was found in patients with septic shock⁸⁵.

Although only a few patients with cirrhosis were enrolled in these trials and the results should not, therefore, be transferred automatically to the setting

of cirrhosis, some considerations favour the use of HA in patients with cirrhosis and septic shock. First, expansion with saline or Ringer's lactate solution requires infusion of high volumes of fluids, which can be detrimental because they can worsen ascites and oedema. Moreover, the use of low-molecular-weight hydroxyethyl starch solutions raises concerns because of an increased risk of kidney and liver injury^{27,28}. Finally, a specific benefit of HA may also derive from the non-oncotic properties of the molecule since these can antagonise some of the pathophysiological mechanisms related to septic shock⁶.

AISF-SIMTI recommendations on the use of albumin in the treatment of septic shock in patients with cirrhosis

- HA solutions might be effective and safe in cirrhotic patients with septic shock (C1).

7.3 Treatment of hepatic encephalopathy

7.3.1 Clinical and pathophysiological background

Hepatic encephalopathy is characterised by an acute change in mental status, frequently induced by a precipitating event, such as constipation, severe infection, gastrointestinal bleeding, renal failure or acute liver injury. It is a major complication of cirrhosis, being associated with high mortality, poor quality of life, and a high risk of recurrence⁸⁵. The underlying pathophysiological mechanisms include over-exposure of the brain to plasma ammonia and other toxins escaping from the splanchnic circulation and the activation of inflammatory mediators, including oxidative stress, which induce swelling of astrocytes and disturb neurotransmission⁸⁵. The treatment of hepatic encephalopathy is based mainly on correcting precipitating factors and reducing ammonia absorption⁸⁶.

7.3.2 Albumin for the treatment of hepatic encephalopathy

Administration of HA may reduce oxidative stress-mediated injury and improve hepatic encephalopathy. However, so far, only one randomised clinical trial on this issue has been published: in this trial, the efficacy of HA was assessed in 56 patients with episodic grade II-IV hepatic encephalopathy, stratified according to the severity of the encephalopathy⁸⁷. The addition of HA (1.5 g/kg on the first day and 1 g/kg after 48 h) to the current standard management did not improve the resolution of the encephalopathy during hospitalisation, although treatment with HA was found to be an independent predictor of 90-day transplant-free survival.

Very recently, a small study found no differences in the incidence of overt hepatic encephalopathy after placement of a transjugular intrahepatic porto-systemic

shunt (TIPS) between a group of patients treated with HA and historical controls during the first month (34 vs 31 %) or during the follow-up (39 vs 48 %) ⁸⁸.

AISF-SIMTI recommendations on the use of albumin in the treatment of hepatic encephalopathy

- Administration of HA is not currently indicated for the treatment of hepatic encephalopathy (B1).

8. The prescription of albumin in Italy

Studies and surveys in different countries have consistently reported that many HA prescriptions, ranging from 40% up to 90%, are not supported by clinical evidence, guidelines or practical recommendations ⁸⁹⁻⁹². Most of the inappropriate prescriptions derive from the use for nutritional interventions or for correcting hypoalbuminaemia *per se* (without hypovolaemia), which still occurs in many clinical areas (e.g. surgery, internal medicine, geriatrics, oncology), despite the existence of solid data against a real benefit. Other clinical uses for HA administration not supported by solid scientific evidence are nephrotic syndrome, pancreatitis, abdominal surgery, acute respiratory distress syndrome, cerebral ischaemia, and enteric disease ⁸⁹⁻⁹².

The Italian consumption of HA from 2007 to 2011 was analysed in the first Italian report on the prescription of plasma-derived medicinal product ^{93,94}.

The total demand for HA remained substantially stable in the above 5-year period, decreasing only minimally (-1%) from 36,652,396 g in 2007 to 36,442,660 g in 2011. A similar trend (-3%) was maintained when HA consumption was standardised per population, going from 620 g per 1,000 residents in 2007 to 601 g per 1,000 residents in 2011 ⁹⁵. This trend was evident in all the Italian regions, with the exception of Valle d'Aosta, Umbria, and Lombardy, where the standardised consumption increased considerably (+57%, +54%, and +25%, respectively).

The differences in the amount of prescribed HA among the Italian regions are quite remarkable. The five regions with the highest HA standardised consumption were Sardinia, Puglia, Campania, Calabria, and Lazio, with levels of 103%, 53%, 23%, 21%, and 17% above the Italian mean, respectively. It is important to note that these five regions account for 28% of the total Italian consumption although their combined population is 19.1% of the total Italian population. On the other hand, the five-lowest standardised HA demands were recorded in Bolzano, Trento, Friuli-Venezia Giulia, Marche, and Piedmont, being 62%, 61%, 54%, 39%, and 38% lower than the national mean level, respectively ⁹⁶.

HA consumption also appears to be greatly influenced by the channel of HA distribution (pharmacies open to

the public, public healthcare system, private healthcare facilities) ⁹⁴.

Most HA was distributed through the public healthcare system with a mean national amount of 422 g per 1,000 residents. This channel of distribution was particularly predominant in Sardinia and Tuscany (157% and 49% above the mean national level, respectively).

The mean national level of HA distributed by pharmacies open to the public was 83 g per 1,000 residents in 2011. However, this channel of distribution was much more substantial in Campania, Puglia and Calabria, accounting for 270, 262, and 231 g per 1,000 residents, respectively. These three regions showed really remarkable deviations above the national mean level of 324%, 314%, and 277%, respectively. Furthermore, these are among the Italian regions with the highest standardised HA consumption.

As far as the distribution by private healthcare facilities is concerned, the mean national value in 2011 was 67 g per 1,000 residents. Conspicuous use was reported in Lazio, Molise and Lombardy, where private hospitals account for a significant part of the healthcare organisation; in these three regions the deviation above the national mean value was 153%, 128%, and 68%, respectively.

Finally, benchmarking national data shows that the 2011 standardised HA consumption per 1000 residents was several times higher in Italy (601 g) than in other European countries of comparable socio-economic level, such as France (238 g), Germany (148 g), and the United Kingdom (82 g) ⁹⁶.

Unfortunately, this report lacks data regarding the clinical indications for the HA prescriptions, thus precluding an analysis of appropriateness. However, although the very high prevalence of cirrhosis, particularly in the Southern regions, may at least in part explain the above described differences, all these data together suggest that there is substantial room for improving the appropriate use of HA.

Besides the large proportion of inappropriate use, the high cost, theoretical risk of disease transmission and existence of more economic alternatives of comparable efficacy have prompted interventions aiming at rationalising and rendering more appropriate the use of HA ⁸⁹⁻⁹¹. In this regard, a recent report from an Italian academic hospital showed that the enforcement of in-hospital guidelines produced two major consequences: first, the increasing trend observed before implementation of the recommendations was interrupted and HA consumption dropped about 15% remaining stable in the following years; second, a more liberal use of HA was guaranteed for indications supported by solid scientific data, while its futile administration in settings in which there is a lack of

clinical evidence of efficacy was avoided. This more appropriate prescription of HA was achieved while maintaining health care expenditure under control⁹⁷.

Acknowledgements

The Writing Committee would like to express its deep gratitude to the Colleagues who reviewed the manuscript: Carlo Alessandria (Division of Gastroenterology and Hepatology, AOU Città della Salute e della Scienza, University of Turin), Oliviero Riggio (Department of Clinical Medicine, "Sapienza" University of Rome), and Francesco Salerno (Department of Internal Medicine, Policlinico IRCCS San Donato, University of Milan) as AISF experts; Pierluigi Berti (Immunohaematology and Transfusion Service, Aosta), Giuseppina Facco (Italian National Blood Centre, National Institute of Health, Rome and Immunohaematology and Transfusion Medicine Unit, AOU "Città della Salute e della Scienza", Turin), and Francesco Fiorin (Transfusion Service, San Donà di Piave) as SIMTI experts.

Disclosure of conflicts of interest

PC has been a speaker for Grifol and Baxalta and a scientific consultant for Kedrion; PA has been a speaker for Baxalta; DP has been a speaker for Grifols; MB has been a speaker for Baxalta and PPTA Europe, and consultant for CLS Behring GmbH. GML, FB, PP, and CV declare no conflict of interest.

References

- 1) European Association for the Study of the Liver. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. *J Hepatol* 2010; **53**: 397-417.
- 2) Runyon BA. Introduction to the revised American Association for the Study of Liver Diseases. Practice Guideline management of adult patients with ascites due to cirrhosis 2012. *Hepatology* 2013; **57**: 1651-3.
- 3) The GRADE system. Available at: www.gradeworkinggroup.org/. Accessed on 05/09/2015.
- 4) Fanali G, di Masi A, Trezza V, et al. Human serum albumin: from bench to bedside. *Mol Aspects Med* 2012; **33**: 209-90.
- 5) Garcia-Martinez R, Caraceni P, Bernardi M, et al. Albumin: pathophysiologic basis of its role in the treatment of cirrhosis and its complications. *Hepatology* 2013; **58**: 1836-46.
- 6) Arroyo V, Garcia-Martinez R, Salvatella X. Human serum albumin, systemic inflammation, and cirrhosis. *J Hepatol* 2014; **61**: 396-407.
- 7) Domenicali M, Baldassarre M, Giannone FA, et al. Post-transcriptional changes of serum albumin: clinical and prognostic significance in hospitalized patients with cirrhosis. *Hepatology* 2014; **60**: 1851-60.
- 8) Jalan R, Schnurr K, Mookerjee RP, et al. Alteration in the functional capacity of albumin in patients with decompensated cirrhosis is associated with increased mortality. *Hepatology* 2009; **50**: 555-64.
- 9) Møller S, Henriksen JH. Cardiovascular complications of cirrhosis. *Postgrad Med J* 2009; **85**: 44-54.
- 10) Bernardi M, Moreau R, Angeli P, et al. Mechanisms of decompensation and organ failure in cirrhosis: from peripheral arterial vasodilation to systemic inflammation hypothesis. *J Hepatol* 2015; **63**: 1272-84.
- 11) Moreau R, Jalan R, Gines P, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology* 2013; **144**: 1426-37.
- 12) Fernández J, Monteagudo J, Bargallo X, et al. A randomized unblinded pilot study comparing albumin vs. hydroxyethyl starch in spontaneous bacterial peritonitis. *Hepatology* 2005; **42**: 627-34.
- 13) Bortoluzzi A, Ceolotto G, Gola E, et al. Positive cardiac inotropic effect of albumin infusion in rodents with cirrhosis and ascites: molecular mechanisms. *Hepatology* 2013; **57**: 266-76.
- 14) Ginès P, Tito LV, Arroyo V, et al. Randomized comparative study of therapeutic paracentesis with and without intravenous albumin in cirrhosis. *Gastroenterology* 1988; **94**: 1493-502.
- 15) Ginès A, Fernandez-Esparrach G, Monescillo A, et al. Randomized controlled trial comparing albumin, dextran-70 and polygelin in cirrhotic patients with ascites treated by paracentesis. *Gastroenterology* 1996; **111**: 1002-10.
- 16) Solà R, Vila MC, Andreu M, et al. Total paracentesis with dextran 40 vs. diuretics in the treatment of ascites in cirrhosis: a randomized controlled study. *J Hepatol* 1994; **20**: 282-8.
- 17) Panos MZ, Moore K, Vlavianos P, et al. Single, total paracentesis for tense ascites: sequential hemodynamic changes and right atrial size. *Hepatology* 1990; **11**: 662-7.
- 18) Pozzi M, Osculati G, Boari G, et al. Time course of circulatory and humoral effects of rapid total paracentesis in cirrhotic patients with tense, refractory ascites. *Gastroenterology* 1994; **106**: 709-19.
- 19) Ruiz del Arbol L, Monescillo A, Jimenez W, et al. Paracentesis-induced circulatory dysfunction: mechanism and effect on hepatic hemodynamics in cirrhosis. *Gastroenterology* 1997; **113**: 579-86.
- 20) Planas R, Ginès P, Arroyo V, et al. Dextran-70 versus albumin as plasma expanders in cirrhotic patients with tense ascites treated with total paracentesis. Results of a randomized study. *Gastroenterology* 1990; **99**: 1736-44.
- 21) Salerno F, Badalamenti S, Lorenzano E, et al. Randomized comparative study of hemaccel vs. albumin infusion after total paracentesis in cirrhotic patients with refractory ascites. *Hepatology* 1991; **13**: 707-13.
- 22) Fassio E, Terg R, Landeira G, et al. Paracentesis with dextran 70 vs. paracentesis with albumin in cirrhosis with tense ascites. Results of a randomized study. *J Hepatol* 1992; **14**: 310-6.
- 23) Altman C, Bernard B, Roulot D, et al. Randomized comparative multicenter study of hydroxyethyl starch versus albumin as a plasma expander in cirrhotic patients with tense ascites treated with paracentesis. *Eur J Gastroenterol Hepatol* 1998; **10**: 5-10.
- 24) Garcia-Compeán D, Blanc P, Larrey D, et al. Treatment of cirrhotic tense ascites with dextran-40 versus albumin associated with large volume paracentesis: a randomized controlled trial. *Ann Hepatol* 2002; **1**: 29-35.
- 25) Sola-Vera J, Miñana J, Ricart E, et al. Randomized trial comparing albumin and saline in the prevention of paracentesis-induced circulatory dysfunction in cirrhotic patients with ascites. *Hepatology* 2003; **37**: 1147-53.
- 26) Abdel-Khalek EE, Arif SE. Randomized trial comparing human albumin and hydroxyethyl starch 6% as plasma expanders for treatment of patients with liver cirrhosis and tense ascites following large volume paracentesis. *Arab J Gastroenterol* 2010; **11**: 24-9.
- 27) Brunkhorst FM, Angel C, Bloos F, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med* 2008; **358**: 125-39.
- 28) Christidis C, Mal F, Ramos J, et al. Worsening of hepatic dysfunction as a consequence of repeated hydroxyethylstarch infusions. *J Hepatol* 2001; **35**: 726-32.

- 29) Moreau R, Asselah T, Condat B, et al. Comparison of the effect of terlipressin and albumin on arterial blood volume in patients with cirrhosis and tense ascites treated by paracentesis: a randomised pilot study. *Gut* 2002; **50**: 90-4.
- 30) Singh V, Kumar B, Nain CK, et al. Noradrenaline and albumin in paracentesis-induced circulatory dysfunction in cirrhosis: a randomized pilot study. *J Intern Med* 2006; **260**: 62-8.
- 31) Singh V, Kumar R, Nain CK, et al. Terlipressin versus albumin in paracentesis-induced circulatory dysfunction in cirrhosis: a randomized study. *J Gastroenterol Hepatol* 2006; **21**: 303-7.
- 32) Appenrodt B, Wolf A, Grunhage F, et al. Prevention of paracentesis-induced circulatory dysfunction: midodrine vs albumin. A randomized pilot study. *Liver Int* 2008; **28**: 1019-25.
- 33) Singh V, Dheerendra PC, Singh B, et al. Midodrine versus albumin in the prevention of paracentesis-induced circulatory dysfunction in cirrhotics: a randomized pilot study. *Am J Gastroenterol* 2008; **103**: 1399-405.
- 34) Moreau R, Valla DC, Durand-Zaleski I, et al. Comparison of outcome in patients with cirrhosis and ascites following treatment with albumin or a synthetic colloid: a randomised controlled pilot trial. *Liver Int* 2006; **26**: 46-54.
- 35) Bernardi M, Caraceni P, Navickis RJ, Wilkes MM. Albumin infusion in patients undergoing large-volume paracentesis: a meta-analysis of randomized trials. *Hepatology* 2012; **55**: 1172-81.
- 36) Alessandria C, Elia C, Mezzabotta, et al. Prevention of paracentesis-induced circulatory dysfunction in cirrhosis: standard vs half albumin doses. A prospective, randomized, unblinded pilot study. *Dig Liver Dis* 2011; **43**: 881-6.
- 37) Rimola A, García-Tsao G, Navasa M, et al. Diagnosis, treatment and prophylaxis of spontaneous bacterial peritonitis: a consensus document. *International Ascites Club. J Hepatol* 2000; **32**: 142-53.
- 38) Follo A, Llovet JM, Navasa M, et al. Renal impairment after spontaneous bacterial peritonitis in cirrhosis: incidence, clinical course, predictive factors and prognosis. *Hepatology* 1994; **20**: 1495-501.
- 39) Tandon P and Garcia-Tsao G. Renal dysfunction is the most important independent predictor of mortality in cirrhotic patients with spontaneous bacterial peritonitis. *Clin Gastroenterol Hepatol* 2011; **9**: 260-5.
- 40) Ruiz-del-Arbol L, Urman J, Fernández J, et al. Systemic, renal, and hepatic hemodynamic derangement in cirrhotic patients with spontaneous bacterial peritonitis. *Hepatology* 2003; **38**: 1210-8.
- 41) Sort P, Navasa M, Arroyo V, et al. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. *N Engl J Med* 1999; **341**: 403-9.
- 42) Sigal SH, Stanca CM, Fernandez J, et al. Restricted use of albumin for spontaneous bacterial peritonitis. *Gut* 2007; **56**: 597-9.
- 43) Poca M, Concepción M, Casas M, et al. Role of albumin treatment in patients with spontaneous bacterial peritonitis. *Clin Gastroenterol Hepatol* 2012; **10**: 309-15.
- 44) De Araujo A, De Barros Lopes A, Rossi G, et al. Low-dose albumin in the treatment of spontaneous bacterial peritonitis: should we change the standard treatment? *Gut* 2012; **61**: 1371-2.
- 45) Salerno F, Navickis RJ, Wilkes MM. Albumin infusion improves outcomes of patients with spontaneous bacterial peritonitis: a meta-analysis of randomized trials. *Clin Gastroenterol Hepatol* 2013; **11**: 123-30.
- 46) Arroyo V, Ginès P, Gerbes AL, et al. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. *International Ascites Club. Hepatology*. 1996; **23**: 164-76.
- 47) Salerno F, Gerbes A, Ginès P, et al. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. *Gut* 2007; **56**: 1310-8.
- 48) Angeli P, Gines P, Wong F, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. *Gut* 2015; **64**: 531-7.
- 49) Ginès P, Schrier RW. Renal failure in cirrhosis. *N Engl J Med* 2009; **361**: 1279-90.
- 50) Moreau R, Lebrec D. The use of vasoconstrictors in patients with cirrhosis: type 1 HRS and beyond. *Hepatology* 2006; **43**: 385-94.
- 51) Ortega R, Ginès P, Uriz J, et al. Terlipressin therapy with and without albumin for patients with hepatorenal syndrome: results of a prospective, nonrandomized study. *Hepatology* 2002; **36**: 941-8.
- 52) Martín-Llahí M, Pépin M-N, Guevara M, et al. Terlipressin and albumin vs albumin in patients with cirrhosis and hepatorenal syndrome: a randomized study. *Gastroenterology* 2008; **134**: 1352-9.
- 53) Sanyal AJ, Boyer T, Garcia-Tsao G, et al. A randomized, prospective, double-blind, placebo-controlled trial of terlipressin for type 1 hepatorenal syndrome. *Gastroenterology* 2008; **134**: 1360-8.
- 54) Neri S, Pulvirenti D, Malaguarnera M, et al. Terlipressin and albumin in patients with cirrhosis and type I hepatorenal syndrome. *Dig Dis Sci* 2008; **53**: 830-5.
- 55) Solanki P, Chawla A, Garg R, et al. Beneficial effects of terlipressin in hepatorenal syndrome: a prospective randomized placebo-controlled clinical trial. *J Gastroenterol Hepatol* 2003; **18**: 152-6.
- 56) Yang YZ, Dan ZL, Liu NZ, et al. Efficacy of terlipressin in treatment of liver cirrhosis with hepatorenal syndrome. *J Intern Intens Med* 2001; **7**: 123-5.
- 57) Salerno F, Cazzaniga M, Merli M, et al. Diagnosis, treatment and survival of patients with hepatorenal syndrome: a survey on daily medical practice. *J Hepatol* 2011; **55**: 1241-8.
- 58) Rodriguez E, Elia C, Solà E, et al. Terlipressin and albumin for type-1 hepatorenal syndrome associated with sepsis. *J Hepatol* 2014; **60**: 955-61.
- 59) Gluud LL, Christensen K, Christensen E, Krag A. Terlipressin for hepatorenal syndrome. *Cochrane Database Syst Rev* 2012; **9**: CD005162.
- 60) Alessandria C, Ottobreilli A, Debernardi-Venon W, Todros L, Cerenzia MT, Martini S, et al. Noradrenalin vs terlipressin in patients with hepatorenal syndrome: a prospective, randomized, unblinded, pilot study. *J Hepatol* 2007; **47**: 499-505.
- 61) Singh V, Ghosh S, Singh B, et al. Noradrenaline vs. terlipressin in the treatment of hepatorenal syndrome: a randomized study. *J Hepatol* 2012; **56**: 1293-8.
- 62) Cavallin M, Kamath PS, Merli M, et al. Terlipressin plus albumin versus midodrine and octreotide plus albumin in the treatment of hepatorenal syndrome: a randomized trial. *Hepatology* 2015; **62**: 567-74.
- 63) Alessandria C, Venon WD, Marzano A, et al. Renal failure in cirrhotic patients: role of terlipressin in clinical approach to hepatorenal syndrome type 2. *Eur J Gastroenterol Hepatol* 2002; **14**: 1363-8.
- 64) Ghosh S, Choudhary NS, Sharma AK, et al. Noradrenaline vs terlipressin in the treatment of type 2 hepatorenal syndrome: a randomized pilot study. *Liver Int* 2013; **33**: 1187-93.
- 65) Moore KP, Wong F, Gines P, et al. The management of ascites in cirrhosis: report on the Consensus Conference of the International Ascites Club. *Hepatology* 2003; **38**: 258-66.
- 66) Gines P, Cardenas A, Arroyo V, Rodes J. Management of cirrhosis and ascites. *N Eng J Med* 2004; **350**: 1646-54.
- 67) Arroyo V, Gines P, Gerbes AL, et al. Definition and diagnostic

- criteria of refractory ascites and hepatorenal syndrome in cirrhosis. *Hepatology* 1996; **23**: 164-76
- 68) Gentilini P, Casini-Raggi V, Di Fiore G, et al. Albumin improves the response to diuretics in patients with cirrhosis and ascites: results of a randomized, controlled trial. *J Hepatol* 1999; **30**: 639-45.
 - 69) Romanelli RG, La Villa G, Barletta G, et al. Long-term albumin infusion improves survival in patients with cirrhosis and ascites: an unblinded randomized trial. *World J Gastroenterol* 2006; **12**: 1403-7.
 - 70) Bernardi M, Riggio O, Angeli P, et al. Long-term use of human albumin for the treatment of ascites in patients with hepatic cirrhosis: the interim analysis of the ANSWER study. *Dig Liv Dis* 2015; **47** (Suppl 1): e6.
 - 71) Ginès P, Berl T, Bernardi M, et al. Hyponatremia in cirrhosis: from pathogenesis to treatment. *Hepatology* 1998; **28**: 851-64.
 - 72) Angeli P, Wong F, Watson H, Gines P. Hyponatremia in cirrhosis: results of a patient population survey. *Hepatology* 2006; **44**: 1535-42.
 - 73) Kim WR, Biggins SW, Krmers WK, et al. Hyponatremia and mortality among patients on the liver transplant waiting list. *N Engl J Med* 2008; **359**: 1018-26.
 - 74) Guevara M, Baccaro ME, Rios J, et al. Risk factors for hepatic encephalopathy in patients with cirrhosis and refractory ascites: relevance of serum sodium concentration. *Liver Int* 2010; **30**: 1137-42.
 - 75) Yun BC, Kim WR, Benson JT, et al. Impact of pretransplant hyponatremia on outcome following liver transplantation. *Hepatology* 2009; **49**: 1610-5.
 - 76) McCormick PA, Mistry P, Kaye G, et al. Intravenous albumin infusion is an effective therapy for hyponatraemia in cirrhotic patients with ascites. *Gut* 1990; **31**: 204-7.
 - 77) Jalan R, Mookerjee R, Cheshire L, et al. Albumin infusion for severe hyponatremia in patients with refractory ascites: a randomized clinical trial. *J Hepatol* 2007; **46**: 232A [Abstract].
 - 78) Terra C, Guevara M, Torre A, et al. Renal failure in patients with cirrhosis and sepsis unrelated to spontaneous bacterial peritonitis: value of MELD score. *Gastroenterology* 2005; **129**: 1944-53.
 - 79) Fasolato S, Angeli P, Dallagnese L, et al. Renal failure and bacterial infections in patients with cirrhosis: epidemiology and clinical features. *Hepatology* 2007; **45**: 223-9.
 - 80) Guevara M, Terra C, Nazar A, et al. Albumin for bacterial infections other than spontaneous bacterial peritonitis in cirrhosis. A randomized, controlled study. *J Hepatol* 2013; **57**: 759-65.
 - 81) Thévenot T, Bureau C, Oberti F, et al. Effect of albumin in cirrhotic patients with infection other than spontaneous bacterial peritonitis. A randomized trial. *J Hepatol* 2015; **62**: 822-30.
 - 82) Jones AE, Puskarich MA. The Surviving Sepsis Campaign guidelines 2012: update for emergency physicians. *Ann Emerg Med*. 2014; **63**: 35-47.
 - 83) SAFE Study Investigators, Finfer S, McEvoy S, et al. Impact of albumin compared to saline on organ function and mortality of patients with severe sepsis. *Intensive Care Med* 2011; **37**: 86-96.
 - 84) Delaney A, Dan A, McCaffrey J, Finfer S. The role of albumin as a resuscitation fluid for patients with sepsis: A systematic review and meta-analysis. *Crit Care Med* 2011; **39**: 386-91.
 - 85) Caironi P, Tognoni G, Masson S, et al. Albumin replacement in patients with severe sepsis or septic shock. *N Engl J Med* 2014; **370**: 1412-21.
 - 86) Vilstrup H, Amodio P, Bajaj J, et al. Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. *Hepatology* 2014; **60**: 715-35.
 - 87) Simón-Talero M, García-Martínez R, et al. Effects of intravenous albumin in patients with cirrhosis and episodic hepatic encephalopathy: a randomized double-blind study. *J Hepatol* 2013; **59**: 1184-92.
 - 88) Riggio O, Nardelli S, Pasquale C, et al. No effect of albumin infusion on the prevention of hepatic encephalopathy after transjugular intrahepatic portosystemic shunt. *Metab Brain* 2015; DOI 10.1007/s11011-015-9713-x.
 - 89) Vargas E, De Miguel V, Portolés A, et al. Use of albumin in two Spanish university hospitals. *Eur J Clin Pharmacol* 1997; **52**: 465-70.
 - 90) Debrix I, Combeau D, Stephan F, Benomar A, Becker A. Clinical practice guidelines for the use of albumin: results of a drug use evaluation in a Paris hospital. *Tenon Hospital Paris. Pharm World Sci* 1999; **21**: 11-6.
 - 91) Tarín Remohí MJ, Sánchez Arcos A, Santos Ramos B, et al. Costs related to inappropriate use of albumin in Spain. *Ann Pharmacother* 2000; **34**: 1198-205.
 - 92) Tanzi M, Gardner M, Megellas M, et al. Evaluation of the appropriate use of albumin in adult and pediatric patients. *Am J Health Syst Pharm* 2003; **60**: 1330-5.
 - 93) Calizzani G, Lanzoni M, Candura F, et al. Analisi della domanda dei principali medicinali plasmaderivati in Italia. Anni 2007-2011. Roma: Istituto Superiore di Sanità; 2012. Rapporti ISTISAN 12/53. Available at: <http://www.iss.it/binary/publ/cont/dodici53web.pdf>. Accessed on 31/10/2013.
 - 94) Lanzoni M, Biffoli C, Candura F, et al. Plasma-derived medicinal products in Italy: information sources and flows. *Blood Transfus* 2013; **11** (Suppl 4): 3-7.
 - 95) Vaglio S, Calizzani G, Lanzoni M, et al. The demand for human albumin in Italy. *Blood Transfus* 2013; **11** (Suppl 4): 26-32.
 - 96) Vaglio S, Calizzani G, Grazzini G, et al. Italian albumin usage (or misuse?). *Eur J Intern Med* 2014; **25**: e31-2.
 - 97) Mirici-Cappa F, Caraceni P, Domenicali M, et al. How albumin administration for cirrhosis impacts on hospital albumin consumption and expenditure. *World J Gastroenterol* 2011; **17**: 3479-86.

Correspondence: Giancarlo M. Liembruno
 Centro Nazionale Sangue
 Istituto Superiore di Sanità
 Via Giano della Bella 27
 00162 Roma, Italy
 e-mail: giancarlo.liembruno@iss.it
