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## **Emergencies in Hematology**

**Milan, Italy**  
**April 11-12, 2003**

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**ENRICA MORRA AND FRANCESCO BAUDO**

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# Emergencies in Hematology

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ENRICA MORRA AND FRANCESCO BAUDO

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# Emergencies in Hematology

## *Foreword*

Why have we chosen *Emergencies in Hematology* as subjects of education and debate?

Patients with acute or emergency problems related to hematology are either already in medical wards or attend the emergency-service. Doctors, who see first these patients and are involved in the diagnosis and medical interventions, are often internists, surgeons and experts in other areas of medicine. Hematologists have acquired experience attending their patients in the wards and acting as consultants. The purpose of this meeting is to convey this particular experience to doctors involved in family practice, general medicine and surgery and in other specialties. We have selected speakers who have acquired their clinical expertise by daily care of patients with these difficult problems. They will tell us how they diagnose and treat these patients and discuss the limits that we encounter in our daily practice. A free debate with the audience will focus on any problems that might be raised.

*Enrica Morra, Francesco Baudo*

## Tumor lysis syndrome in hematologic malignancies: prediction and management

MARCO MONTILLO, SARA MIQUELEIZ, FRANCESCA RICCI, ALESSANDRA TEDESCHI, ENRICA MORRA

**T**umor lysis syndrome (TLS) is an oncologic emergency including a group of metabolic complications that can occur spontaneously, during chemotherapy or radiation of certain hematologic malignancies.<sup>1-5</sup> The syndrome has been observed, although rarely, after treatment of solid tumors.<sup>6-8</sup> It is characterized by the biochemical disturbances consequent to a rapid destruction of tumor cells with subsequent synchronized massive release of cellular breakdown products that overwhelm normal renal excretory mechanisms and the cellular buffering mechanisms leading to elevation of the serum concentration of nuclear metabolites and acute renal failure.

### **Incidence and etiology**

The overall incidence of TLS cannot be accurately estimated. TLS has typically been detected in the setting of tumors with high growth fractions, approaching 100% in some instances. Among hematologic malignancies, Burkitt's lymphoma is a paradigm for tumor lysis syndrome (Table 1). In one series of 37 patients with Burkitt's lymphoma, evidence of tumor lysis syndrome was found in 15 patients after chemotherapy.<sup>2</sup> Tumor lysis causes renal failure in 10% of patients receiving induction chemotherapy for acute lymphoblastic leukemia.<sup>9</sup> Patients with other types of high-grade non-Hodgkin's lymphoma or acute leukemia undergoing induction chemotherapy are also at relatively high risk. More effective treatment has led to more indolent hematologic disorders, such as chronic lymphocytic leukemia, manifesting TLS.<sup>10</sup> It has been described not only after intensive chemotherapy for high-grade non-Hodgkin's lymphoma or acute leukaemia but also during the treatment of metastatic breast carcinoma,<sup>11-12</sup> small cell lung carcinoma,<sup>13</sup> seminoma,<sup>12</sup> metastatic medulloblastoma<sup>14</sup> and Merkel's cell carcinoma.<sup>15</sup> It is rare in solid tumors that are typically unresponsive to therapy, such as pancreatic, colorectal, and non-small cell lung cancer. It has been reported after a single dose of intrathecal methotrexate<sup>16</sup> in untreated systemic lymphoma. While it is clearly documented that cytotoxic therapy of highly proliferative tumors is the primary cause, some particular chemotherapeutic agents have been more

closely associated with TLS, e.g. cisplatin, cytosine arabinoside, etoposide and taxanes.<sup>17-19</sup>

In addition TLS has occurred in patients treated by non-chemotherapy regimens such as steroid therapy,<sup>20</sup> hormonal therapy,<sup>11</sup> and cytokine therapy.<sup>9</sup> With non-chemotherapy treatment, the time course of TLS may be extended.

With highly specific targeted therapies TLS may be becoming increasingly common. It has been reported as a complication of treatment with anti CD-20 monoclonal antibody.<sup>21</sup> TLS has been observed in conjunction with biological modifiers and a tyrosine kinase inhibitor.<sup>22</sup> Furthermore the syndrome has even been seen in cases of highly refractory malignancies treated with hematopoietic stem cell transplantation.

Irradiation of bulk disease in leukemia patients brings about a marked rise in serum uric acid associated with a decrease in leukemic tissue mass.<sup>23</sup>

With the advent of effective support for renal failure, including extracorporeal dialysis, it has become possible to treat sensitive tumors, even in the presence of impaired renal failure.<sup>24</sup>

### **Prediction**

For a given condition, the likelihood of developing tumor lysis syndrome is related to the sensitivity of the tumour to the particular treatment modality, the disease bulk and clinical stage, and the patient's renal function. Patients with bulky tumor burden are at higher risk than are patients with a smaller tumor load.<sup>2</sup> Areas of ischemia within a large tumor may favor rapid cell breakdown during treatment. The serum lactate level may be predictive and serum lactate dehydrogenase has also been found to be a useful indicator of the risk of TLS in both hematopoietic and non-hematopoietic malignancies. Pre-treatment values of >600 IU are associated with significant post-treatment metabolic disturbances. An elevated serum urate level independent of impaired renal function also indicates an increased likelihood of TLS.

Renal excretion is the main homeostatic mechanism for dealing with cellular breakdown products. Pre-treatment renal impairment, as a result of parenchymal infiltration, outflow tract obstruction or an unrelated medical condition, significantly increases the chances of a post-treatment metabolic disturbance. Indeed, a reduced urinary flow rate resistant to therapeutic maneuvers is a pretreatment indicator of those cases destined to develop frank renal failure.<sup>25</sup> Difficulty in

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**Table 1. Tumor lysis syndrome: risk by tumor type data, in part, from Chasty *et al.*<sup>27</sup>**

<i>Degree of risk</i>	<i>Tumor type</i>	<i>Supporting data</i>
Highest	Burkitt's lymphoma	Frequent cases
	Lymphoblastic lymphoma	
	T-cell acute lymphoblastic leukemia	
	Other acute leukemias	
Moderate	Low-grade lymphoma treated with chemotherapy, radiotherapy, or corticosteroids	Recognized complications, but few occurrences
	Multiple myeloma	
	Breast carcinoma treated with chemotherapy or hormonal therapy	
	Small-cell lung carcinoma	
Lowest	Germ cell (seminoma, ovarian)	Case reports only
	Low-grade lymphoma treated with interferon	
	Merkel's cell carcinoma	
	Medulloblastoma	
	Adenocarcinoma of the gastrointestinal tract	

maintaining an adequate fluid output and fluid balance is most often seen where there is a predisposition to fluid collection in extravascular third spaces, e.g. serous effusions or limb edema from venous or lymphatic obstruction.<sup>26</sup>

A risk factor scoring system in order to assess the chances of TLS developing and to select an appropriate management strategy has been proposed<sup>27</sup> (Table 2).

## Pathophysiology

### Hyperkalemia

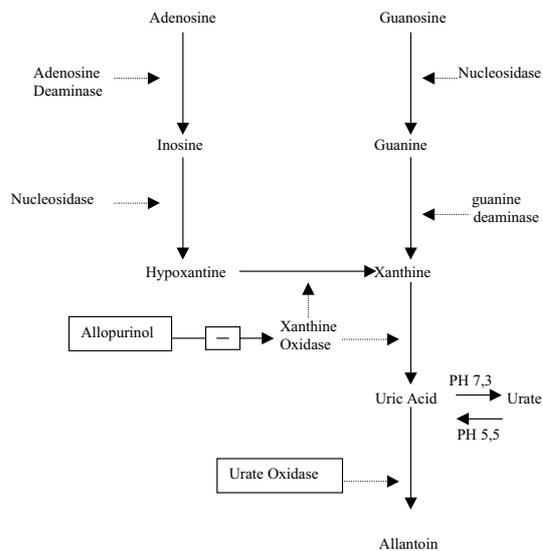
Hyperkalemia is a life-threatening abnormality that develops during acute TLS. A rise in serum potassium levels occurs characteristically 12-24 hours after chemotherapy. Potassium is a predominantly intracellular ion, the gradient across cell membranes being maintained by an energy-dependent sodium/potassium ATPase. Cellular metabolism may be stressed by exposure to chemotherapy or radiotherapy and reduced ATP levels may allow leakage of potassium out of the tumor cells before complete lysis, resulting in this early peak in serum potassium concentration. At plasma potassium levels above 6.5 mmol/L cardiac arrhythmias may occur leading to sudden death; this predisposition is exacerbated by a low serum calcium and acidosis.

**Table 2. Proposed risk score for assessing the likelihood of developing acute tumour lysis syndrome (from Chasty *et al.*)**

	<i>Score</i>
Bulk disease	2
Marked sensitivity to the treatment modality	2
Renal impairment	1
Raised lactate dehydrogenase	1
Raised serum uric acid	1

Score 4-7 = high risk; 3 = medium risk; < 3 = low risk.

To prevent this complication, measures should be taken proportional to the predicted risk of tumor lysis syndrome. Therapy should be planned to avoid an expected peak of potassium levels occurring during the night. In the presence of a rapidly rising serum potassium levels (>5.5 mmol/L), infusion of 50 mL of 50% glucose together with 15 IU of insulin over 1 hour promotes cellular uptake of potassium and will temporarily lower serum levels while renal excretion is increased by fluids and diuretics. If urine output is unsatisfactory (<125 mL/m<sup>2</sup>/h) with a positive fluid balance and increasing serum potassium levels, dialysis is indicated.



**Figure 1. The purine metabolic pathway.**

### **Hyperphosphatemia and hypocalcemia**

The fragmentation of DNA in rapidly dividing cells caused by chemotherapeutic agents results in cell death and the release of degenerate nuclear material, including nucleotides and phosphate. The maximal levels of phosphate are reached between 48–96 hours<sup>28</sup> after chemotherapy when phosphate release from degenerating tumour cells exceeds renal phosphate excretion. Failure of phosphate reutilization by the tumour may also be significant. The excretion of phosphate is limited as phosphate is actively conserved by the kidneys under normal circumstances. However, once the renal threshold has been exceeded phosphate excretion and hyperphosphatemia usually results in renal insufficiency. As a consequence of the hyperphosphatemia there is reciprocal depression of the serum calcium level. Despite this, the calcium x phosphate solubility product may still be exceeded, resulting in precipitation of calcium phosphate crystals in the renal tubules.

### **Hyperuricemia**

Uric acid is the end product of purine metabolism in humans. Purines are metabolized through hypoxanthine and xanthine to urate which is excreted by the kidney. Pyrimidines are broken down to their constituent amino acids and re-used. (Figure 1). With cell lysis there is a rapid increase in nucleotide metabolites, swamping the salvage pathways and resulting in increased urate production. Renal handling of this urate load involves free

filtration at the glomerulus, partial proximal tubular reabsorption and distal renal tubular secretion.

Uric acid is 13 times more soluble at pH 7.0 than at pH 5.0.<sup>29</sup> This means that urate can crystallize in the distal tubule, where it may reach high concentrations as a result of active secretion in the face of ongoing tubular acidification. The rate of urate clearance is highly dependent on the rate with which the glomerular filtrate flows through the renal tubule and may fall significantly if dehydration is present.

The acute urate nephropathy seen in TLS results from pathologic urate crystal deposition in the distal renal tubules.

### **Clinical signs and symptoms**

The initial manifestations of the tumor lysis syndrome are clinical biochemical abnormalities. Typically, increases in the serum potassium and phosphorus levels are noted within 12 hours of the initiation of chemotherapy in patients with acute leukemia, high-grade lymphoma, and other highly chemosensitive cancers. Elevations of the serum uric acid level are usually evident within 24 hours of treatment of such tumors. Abnormalities in renal function follow 2 or 3 days later, corresponding to the time required for crystal deposition in the kidneys.<sup>30</sup>

Clinical signs and symptoms can arise in response to the hyperkalemia, hypocalcemia, or acute renal failure. Hyperkalemia is associated with abnormalities of cardiac conduction, especially at potassium concentrations greater than 6 mM.<sup>31</sup> The earliest electrocardiographic manifestation is peaking and narrowing of the T wave. As the hyperkalemia becomes more severe, the QRS complex is widened and prolonged with decreasing amplitude of the R wave. Yet further worsening of hyperkalemia is associated with flattening and widening of the P wave, which can ultimately disappear. If treatment is inadequate, the wide QRS complex envelops the T wave, leading to a *sign wave* cardiogram. Unstable ventricular tachyarrhythmias soon follow. In these circumstances, 10 mL of 10% calcium gluconate may be given intravenously.

The acute hypocalcemia associated with tumor lysis syndrome is not usually symptomatic but if it is sufficiently severe it can cause neuromuscular irritability, tetany and even fits. Mild cases may be detected by Chvostek's sign, performed by tapping the seventh cranial nerve anterior and inferior to the external auditory meatus or at one of the branches located between the zygomatic arch and the corner of the mouth.<sup>32</sup> Trousseau's sign is observed as tetany in the carpal muscles following the inflation of a blood pressure cuff to a pressure exceeding the patient's systolic pressure for a duration of at least 3 minutes.<sup>32</sup> More profound hypocalcemia may result in laryngospasm or lowering of

the seizure threshold. Falling serum calcium is associated with prolongation of the electrocardiogram QT interval and may be associated with dysrhythmias. Severe hypocalcemia may rarely be associated with depression of myocardial contractility and heart failure.<sup>31</sup>

The TLS can cause acute renal failure.<sup>9,30,33,34</sup> Oliguria (or, rarely, even anuria) with rising blood urea nitrogen and serum creatine levels and metabolic acidosis (in addition to the previously discussed hyperkalemia and hypocalcemia) are also present. Hypertension or congestive heart failure may result from overload during acute renal failure. Uremic pericarditis, platelet aggregation dysfunction, nausea, anorexia, asterixis, and eventually seizures and coma are other possible manifestations of acute renal failure.<sup>35</sup>

### **Pathophysiology of renal failure**

Renal failure in tumor lysis syndrome results from a combination of two major pathogenetic factors. First, varying degrees of pre-existing volume depletion are present before the onset of the renal failure in many patients; and second, precipitation of uric acid and/or calcium phosphate complexes in the renal tissue causes acute renal injury.<sup>36-40</sup>

### **Role of volume depletion**

The importance of volume depletion has been repeatedly emphasized in the literature. Volume depletion in patients with these malignancies occurs for several reasons: (i) patients may be anorexic with poor oral fluid intake or may have gastrointestinal symptoms including nausea, vomiting, and diarrhea; (ii) fever and tachypnea may be present and lead to insensible losses; (iii) staging work-up may include procedures for which the patient is unable to ingest food or water and/or receives intravenous radiocontrast. Thus it has been emphasized that establishing diuresis with a hypotonic urine is an important prophylactic and therapeutic maneuver in patients at risk of or afflicted by renal failure attributable to acute TLS.

### **Role of tumor lysis products**

Many patients with neoplastic diseases have pre-existing hyperuricemia and renal failure due to tumor necrosis, before the onset of therapy.<sup>1,36,41</sup> Indeed, histopathologic studies in humans and experimental animals with acute uric acid nephropathy indicate that intranephronal hydro-nephrosis is associated with uric acid precipitates which predominate particularly in the distal nephron and in the medullary rays.<sup>39,40,42</sup> Moreover, a granulomatous reaction to intraluminal uric acid crystals may occur, as may necrosis of distal tubular epithelium; sparing of the proximal tubule is a notable feature.<sup>42</sup> Finally, uric acid stones, occurring as a result of tumor lysis, can cause ureteral and

pelvic obstruction leading to extranepronal urinary tract obstruction and acute renal failure.

As pointed out above, profound hyperphosphatemia and hypocalcemia, in addition to renal uric acid crystallization, occur commonly. The effect of sudden hyperphosphatemia is acute hypocalcemia and metastatic calcification causing acute renal failure. The mechanism of hyperphosphatemia is the same as that of hyperuricemia, namely tumor lysis with release of inorganic phosphate from intracellular stores. Similar effects were observed in patients who received large oral, intravenous, or rectally administered exogenous phosphate loads.<sup>43-45</sup>

### **Management of tumor lysis syndrome**

The clinical manifestations of acute TLS could be prevented treating patients at risk of developing the condition in a proactive fashion. Hydration, which produces high urine flow rates, reduces uric acid reabsorption in the proximal tubules, as does alkalization, which increases urate ionization and has been recommended when the serum urate level is elevated at presentation. Intensive hydration should be initiated *prior* to cytotoxic therapy and continued throughout the duration of treatment. Diuresis promotes good urine output and may decrease urate and calcium phosphate crystals. Very close monitoring in order to assess electrolyte imbalances is mandatory in patients with tumor lysis syndrome and those at risk of developing it.<sup>46-48</sup>

### **Management of specific metabolic disturbances**

**Hyperkalemia.** Because of the severity of the clinical consequences of hyperkalemia, measures to decrease potassium levels should be instituted promptly. Many approaches have been used. Cation exchange resins bind potassium, so that this ion can be eliminated through the bowel. Calcium gluconate antagonizes the action of potassium on the heart and can be given when ECG changes are noted. Sodium bicarbonate corrects acidosis, causing a shift of potassium back into cells. Hypertonic dextrose and insulin work to shift potassium into cells. Diuretics can be used, especially for patients at risk of fluid overload, to maintain urine output and promote potassium excretion.<sup>46,47</sup> However, when hyperkalemia occurs in the setting of TLS, dialysis should be started immediately.

**Hyperphosphatemia and hypocalcemia.** Hyperphosphatemia may be prevented by increased hydration before and during treatment, together with loop diuretics which have a phosphaturic action. A rising phosphate level before or after treatment, despite such interventions, and an inability to maintain a high urine flow rate in the face of hyperphosphatemia are both indications for dialysis.

Phosphate reduction may be needed to correct the hyperphosphatemia and hypocalcemia. Medical managements of hyperphosphatemia include the use of oral phosphate binders such as aluminum hydroxide. Hypertonic dextrose and insulin are useful as well. It should be noted that alkalinization of the urine can exacerbate the tendency to nephrocalcinosis seen with hyperphosphatemia. Bicarbonate should therefore not be administered after the urate level has been normalized or if the phosphate level begins to rise following treatment. Correction of hyperphosphatemia leads to improvement in serum calcium levels.

**Hyperuricemia.** Uric acid reduction may be initiated before chemotherapy begins. Alkalinization is one method that helps to prevent urate crystals from forming in the renal tubules. Historically, allopurinol has been the most widely used agent to reduce plasma uric acid concentrations. New alternatives, such as urate oxidase, may provide greater advantages, including a more rapid onset of activity.<sup>46,48</sup>

### **Alkalinization**

Uric acid remains ionized when the urinary pH is maintained above 7.0 and this reduces urate crystal deposition in renal tubules. Administration of sodium bicarbonate increases the urinary pH. However, as reported above, urine alkalinization can have adverse consequences on renal function. It may predispose the patient to urinary calcium phosphate precipitation, leading to a decrease in glomerular filtration rate. Consequently, careful monitoring is essential when sodium bicarbonate is administered to alkalinize the urine.<sup>47</sup>

### **Allopurinol**

Allopurinol (typically administered orally as 100 mg tablets) in combination with alkaline hydration has been the mainstay of treatment for hyperuricemia for many years. Allopurinol increases the total amount of oxypurines which can be excreted by the kidney at physiologic pH by promoting excretion in 3 forms: xanthine, hypoxanthine and urate. Each of these has an independent solubility in urine. Allopurinol is metabolized by xanthine oxidase to an oxypurinol derivative, which subsequently inhibits further xanthine oxidase activity. This should normally prevent crystal nephropathy provided none of the 3 purine metabolites exceeds its solubility coefficient. Hypoxanthine has a solubility similar to that of urate but unfortunately xanthine is considerably less soluble and there are case reports of xanthine crystal nephropathy occurring after tumor lysis syndrome when allopurinol was used.<sup>49,50</sup>

The decrease in uric acid levels is observed 2 to 3 days after the initiation of allopurinol therapy. In fact allopurinol prevents the formation of addi-

tional uric acid but does not reduce the level of acid uric that is present prior to initiation of allopurinol. A standard maintenance dose for allopurinol is 300 mg daily, but in patients with renal impairment it is necessary to reduce the dose in relation to the creatinine clearance rate; for patients receiving hemodialysis, the dose of allopurinol needs to be reduced by 50%.<sup>51</sup> Because of the long half-life of allopurinol, a loading dose is advisable if immediate lysis is expected. Since allopurinol acts by competitive inhibition of xanthine oxidase, the effect may be swamped by a massive release of purine during tumor lysis unless increased doses are used. For high risk patients with normal renal function a loading dose of 500 mg/m<sup>2</sup> reduced after 2 days to 200 mg/m<sup>2</sup> has been suggested.<sup>2</sup>

Allopurinol interferes with the degradation of 6-mercaptopurine and azathioprine, such that the standard prescribed dose of those agents must be reduced to approximately one third to one fourth. Allopurinol has been reported to enhance the marrow toxicity of cyclophosphamide,<sup>51</sup> and to antagonize the antineoplastic effect of 5-fluorouracil *in vitro*.<sup>52</sup>

### **Urate oxidase**

In cases that are refractory to these measures, or in those in which severe tumour lysis is unavoidable, uricase (uric acid oxidase) has been used to catalyze the conversion of uric acid to allantoin, which is significantly more soluble in urine. Urate oxidase is an enzyme that occurs naturally in all mammals except primates. Rapid reduction in uric acid levels occurs with no precursor build-up because urate oxidase degrades existing uric acid rather than inhibiting its synthesis. However, administration of urate oxidase derived from natural sources may elicit allergic reactions. Moreover, urate oxidase is contraindicated in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency who are unable to break down hydrogen peroxide, an end product of the urate oxidase reaction.

Recent advances in genetic engineering and molecular biology have led to the development of a recombinant urate oxidase. The gene coding for a recombinant urate oxidase has been isolated as a cDNA clone for *Aspergillus flavus* and is expressed in the yeast strain *Saccharomyces cerevisiae*, which yields large quantities of the pure protein.<sup>53</sup>

Pui *et al.* administered recombinant urate oxidase to 131 children and young adults with leukemia and lymphoma. Plasma uric acid concentrations were low throughout treatment, despite cytoreductive chemotherapy. Serum creatinine levels decreased after day 1 in patients with or without hyperuricemia ( $p=0.0003$  and  $p=0.02$ , respectively). Overall, the drug was well tolerated. The

investigators concluded that recombinant urate oxidase is a safe and effective prophylaxis and treatment of hyperuricemia in patients with leukemia or lymphoma.

### **Dialysis for treatment of tumor lysis syndrome**

In some instances, either prior to or, in some cases, after implementation of the prophylactic and therapeutic options outlined above, tumor lysis syndrome induces acute renal failure. When other therapeutic options are exhausted, hemodialysis should be considered.<sup>54</sup> Dialysis may effectively and rapidly reduce the load of circulating metabolic toxins, and may help to control volume in uremic patients, hemodialysis is preferred over peritoneal dialysis, because it is more effective at rapidly removing uric acid and phosphorus. Patients with established renal failure and hyperkalemia may benefit from beginning hemodialysis even before cytotoxic therapy is initiated. Nevertheless, with enhanced awareness of the metabolic imbalances that can lead to tumor lysis syndrome and proactive attention to monitoring and prophylactically treating hyperuricemia, fewer patients will be likely to develop renal failure necessitating dialysis.

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## Metabolic emergencies in paraproteinemic syndromes

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**M**etabolic disorders are more frequent in multiple myeloma than in other hematologic malignancies, as a consequence of the high frequency of both renal and bone injury. The onset and the evolution of metabolic problems secondary to renal failure or osteolytic bone destruction are usually chronic events, but severe metabolic emergencies are not infrequent, both at the time of diagnosis and during the course of the disease.

In contrast, as a consequence of the low proliferation rate of neoplastic cells and low sensitivity to anti-neoplastic drugs, metabolic complications due to tumor lysis syndrome are less frequent events in both multiple myeloma and Waldenström's disease, than in the more aggressive and chemo-sensitive hematologic malignancies, such as acute leukaemia and aggressive lymphomas.<sup>1-4</sup> For this reason tumor lysis syndrome has been seldom reported in plasma cell dyscrasias, even if the potential association with renal function impairment could put such patients at high risk and prompt recognition and treatment are necessary. In any case the treatment strategy of tumor lysis syndrome in plasma cell dyscrasias is not different from that recommended in other hematologic neoplasias.

The present analysis is, therefore, been focused on renal failure and hypercalcemia which are the most frequent and typical emergencies in myeloma patients.

### Acute renal failure

Authors agree that renal impairment occurs in up to 50% of myeloma patients.<sup>5,6</sup> This is evidenced in about 20% at diagnosis and later on in the remaining 30%.<sup>7-9</sup> The increase in serum creatinine is usually mild and reversible and the percentage of patients requiring dialysis or other major interventions for advanced renal impairment is about 10%.<sup>9-11</sup> When the onset of renal failure is late in the course of multiple myeloma and the disease is already resistant to chemotherapy, it is difficult that the renal function will improve and urgent treatment is less useful. In contrast, the presence of acute renal failure at diagnosis always requires urgent

intervention in order to correct the renal damage early and to prevent long-term irreversible dialysis-dependence.<sup>12</sup> Up to 50% of patients with myeloma and acute renal failure are observed before the diagnosis of myeloma has been suspected.<sup>13</sup> This group of patients needs to be seen and managed as a matter of urgency. In fact it has been demonstrated from two recent retrospective studies that the reversibility of renal failure is an important favorable prognostic factor and patients in whom renal failure was reversible did not have a poorer survival rate than those with normal creatinine levels.<sup>9,14</sup> The need for prompt and appropriate treatment is underlined by the possibility of even obtaining dialysis independence when adequate treatments for renal failure, associated with high dose chemotherapy regimens, are applied.<sup>15,16</sup>

### Pathogenesis

The pathogenesis of renal failure in myeloma is multi-factorial.<sup>17,18</sup> The main etiologic factors and their mechanism of action are listed in Table 1.

Cast nephropathy, secondary to Bence Jones proteins, is the most important factor.<sup>19</sup> In healthy subjects small amounts of light chains are filtered from the glomerulus, but they are regularly reabsorbed and catabolized from proximal tubular cells. In myeloma, as a consequence of the high light chain burden, the capacity of the proximal tubules to reabsorb light chains is exceeded, and light chains reach the distal tubules, where they can combine with the Tamm-Horsfall protein and precipitate as obstructing casts.<sup>20</sup> Such obstruction results in tubular cell and subsequent interstitial damage and leads to the appearance of *myeloma kidney*. The linkage between light chains and Tamm-Horsfall protein and the formation of casts is dependent on the light chain structure and is favored by a series of independent factors, such as dehydration, hypercalcemia and low pH, which can act as precipitating factors of an acute failure.<sup>21,22</sup>

The degree of tubular damage, as a result of cast nephropathy, can be influenced by different factors such as: a) the amount of Bence Jones protein;<sup>7,23</sup> b) the previous integrity of tubular cells;<sup>24</sup> c) the chemical and physical characteristics of the light chains;<sup>25,26</sup> d) the dehydration status and consequent Bence Jones concentration in the tubules.<sup>19</sup>

Besides the Bence Jones nephropathy, in myeloma patients, plasma cell local infiltration can sometimes directly contribute to tubular and glomerular damage,<sup>18</sup> as can amyloid deposition,<sup>27</sup> or basement membrane and mesangial light chain deposition with immunoprolifer-

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**Table 1. Most important factors that can favor renal failure in multiple myeloma. (NSAID: non-steroidal anti-inflammatory drugs).**

<i>Etiologic factors</i>	<i>Sites of lesion</i>	<i>Clinical effect</i>
<b>Bence Jones</b>		
• Cast nephropathy	• Distal tubulus	• Obstructive nephropathy
• Proximal tubular damage	• Proximal tubulus	• Fanconi's syndrome
<b>Precipitating factors</b>		
• Dehydration	• Tubulus	Worsening of cast nephropathy and
• Hypercalcemia	• Tubulus and glomerulus	glomerular filtration rate
• Hyperuricemia	• Tubulus and glomerulus	
• Hyperviscosity	• Glomerulus	
• NSAID	• Tubulus	
<b>Other factors</b>		
• Plasma cell infiltration	• Glomerulus and tubulus	• Nephron disruption
• Light chain deposition	• Tubulus	• Nephrotic syndrome
• Amyloidosis	• Glomerulus and tubulus	• Nephrotic syndrome

ative disorders.<sup>28</sup>

Often, when renal failure develops so rapidly as to determine an emergency, this is not due to highly increased production of light chains, but is the result of one or more events that, with independent action, favor renal cast formation and tubular damage in the nephron, which has already been overloaded with light chains for a long time. The main factors that can favor tubular collapse and precipitate renal failure are: a) dehydration, from any cause, such as fever, diuretics and diarrhea, with a reduction of the glomerular filtration rate and an increase plasma and intratubular concentrations of light chain; b) hypercalcemia, which is associated with both direct tubular damage and glomerular filtration reduction secondary to dehydration and vasoconstriction; c) hyperuricemia, with its peculiar tubular nephropathy; d) nephrotoxic drugs, mainly some antibiotics and non-steroidal anti-inflammatory agents (NSAID); e) hyperviscosity syndrome with renal blood flow modification; f) infections.

The interactions between the most important etiological factors are summarized in Figure 1.

### **Treatment**

The best treatment strategy for acute renal failure in myeloma patients requires a preliminary evaluation of the possibility of obtaining an improvement in both renal function and bone marrow plasma cell infiltration, according to the patient's age, eligibility for an adequate chemotherapy regimen

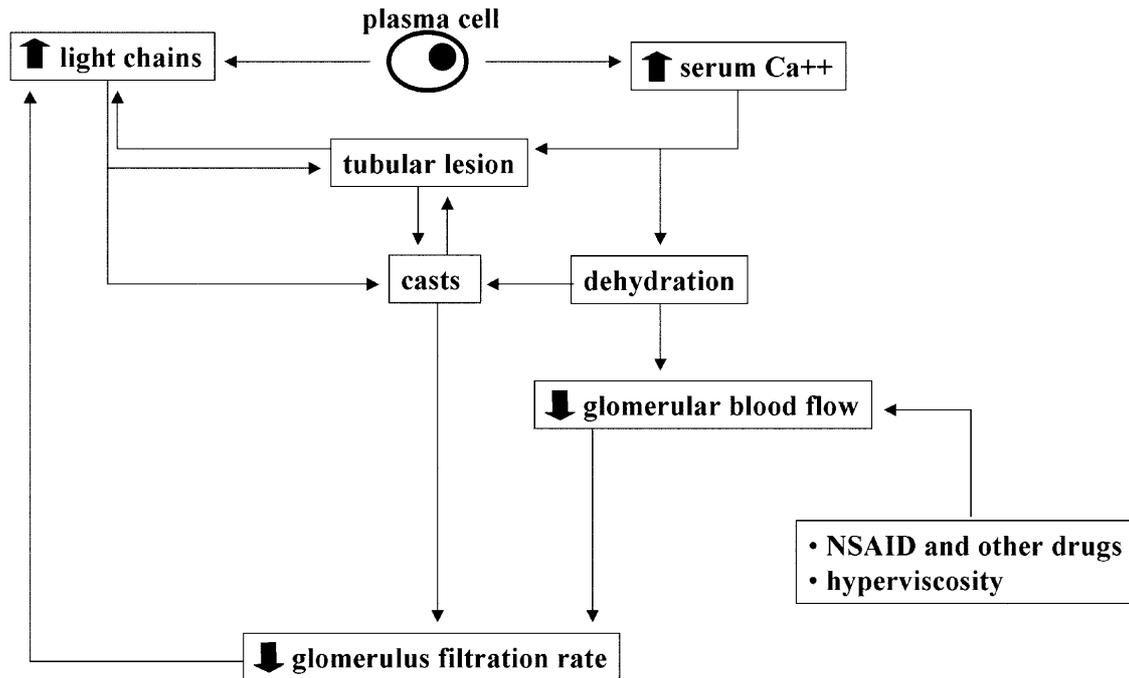
and time of renal failure onset. The need for an aggressive, urgent approach, in order to pursue renal function recovery, is greatest when renal failure is evident at diagnosis. The treatment approach needs, in any case, strict communication between hematology and renal teams and personalization according to the clinical situation, even though general guidelines have been published.<sup>29</sup>

### **Renal failure management**

The most useful procedures in order to support renal function are summarized in Table 2. In the majority of patients a moderate creatinine increase of less than 400  $\mu\text{mol/L}$  is present, and renal function will respond to simple measures such as rehydration, alkalinization, diuretics and discontinuation of nephrotoxic drugs, while more aggressive treatments, mainly dialysis, are reserved for a minority of cases with severe acute renal failure.

Intravenous rehydration should achieve the goal of a urine flow of over 3 L/day, while the introduction of bicarbonate should obtain a urinary pH of at least 7.0. Intravenous dopamine, administered at a low dosage, can be used to improve renal blood flow and glomerular filtration rate. Particular attention must be paid to correcting hypercalcemia, following the guidelines reported below, and to discontinuing nephrotoxic drugs, particularly NSAID.

Dialysis is no longer under discussion in severe renal failure in myeloma patients.<sup>30-33</sup> Most studies report the difficulty of discontinuing dialysis in this



**Figure 1. Interactions between the most important causes of myeloma cast nephropathy. (NSAID = non steroidal anti-inflammatory drugs).**

group of patients, while the survival of patients requiring dialysis is poorer than that of control patients, mainly as an effect of early complications and mortality.<sup>9,10,14,33</sup> There is, however, agreement among authors that patients with severe renal failure requiring dialysis, who survive the first 2-4 months on dialysis, may have the same good response to chemotherapy and survival as control patients.<sup>7,9,10</sup>

Therapeutic plasma exchange is theoretically useful in the acute phase, associated with chemotherapy, in order to remove large amounts of light chains rapidly and improve renal function. However, only two small randomized trials have tested this procedure and they gave conflicting results.<sup>34,35</sup> Although the apheretic procedure can be suggested from the results of other non-randomized studies,<sup>36-38</sup> so far there are no evidenced-based indications and plasma exchange should preferably be reserved to a trial setting.<sup>29</sup> More evidence is available for the use of plasma-exchange in cryoglobulinemia and Waldenström's macroglobulinemia, when associated with hyperviscosity syndrome.<sup>38</sup>

### **Chemotherapy**

The best chemotherapy regimen for myeloma patients and acute renal failure is still a matter of discussion,<sup>6,29</sup> but the theoretical benefit of aggressive chemotherapy, capable of rapidly reducing the light chain burden is evident. The major challenge,

in order to avoid the risk of excessive toxicity, is the correct choice of drugs and their dosages, which need to be appropriate for the abnormal catabolism of drugs, secondary to renal impairment.

In myeloma, alkylator-based chemotherapy regimens do not seem to offer a survival advantage over oral melphalan and prednisone alone.<sup>39</sup> Unfortunately, when renal failure is present, both melphalan-prednisone and other combination chemotherapy schedules are associated with a high early mortality rate, mainly because of toxic events.<sup>9,14</sup> Cyclophosphamide can be removed from the plasma by dialysis. However active metabolites of cyclophosphamide are eliminated by the kidney, and, even if Grochow et al failed to find any difference in hematologic toxicity according to renal function,<sup>40</sup> some severe toxic events have been reported,<sup>41</sup> thus, caution and reduction of doses are recommended.<sup>29</sup>

High dose dexamethasone alone,<sup>42</sup> or in combination with vincristine and doxorubicin in the VAD regimen,<sup>43,44</sup> is associated with a high response rate of 60-80%, a complete remission rate of about 10-20%, minimal myelotoxicity, and minimal damage to the stem cell compartment. Moreover VAD induces a rapid response, with 90% of the maximum responses reached after the first two courses. For these reasons the VAD regimen is recommended as primary chemotherapy in patients for whom it is intended to offer the chance of high dose chemotherapy with autologous stem cell rescue.<sup>29</sup>

**Table 2. Common procedures useful in treating acute renal failure. (NSAID = non-steroidal anti-inflammatory drugs).**

<i>Procedures</i>	<i>Situations in which they are indicated</i>	<i>Usefulness</i>
To rehydrate with intra-venous fluid in order to achieve a urine flow of over 3l/die	Always useful, particularly when: <ul style="list-style-type: none"> <li>• Dehydration</li> <li>• Fever</li> <li>• Hypercalcemia</li> <li>• Hyperuricemia</li> </ul>	To increase renal blood flow and diuresis
Include bicarbonate in the intravenous regimen in order to reach a urine pH > 7.0	Particularly if: <ul style="list-style-type: none"> <li>• Urine pH &lt; 6.0</li> <li>• Hyperuricemia</li> </ul>	To avoid: <ul style="list-style-type: none"> <li>• Cast formation</li> <li>• Acid uric crystals precipitation</li> </ul>
Diuretics (furosemide)	When creatinine > 200 µmol/L	To increase diuresis
Intravenous dopamine at low dosage (1-3 µg/kg)	When serum creatinine > 400 µmol/L, mainly when: <ul style="list-style-type: none"> <li>• Bence Jones burden is high</li> <li>• NSAID are associated</li> </ul>	To increase renal blood flow and diuresis
To withdraw NSAID and other nephrotoxic drugs	When nephrotoxic drugs were associated	To avoid their toxic effect
Rasburicase	When hyperuricemia is present	To avoid precipitation of uric acid crystals in the tubules
To correct hypercalcemia	When hypercalcemia is associated	To avoid dehydration and other side effect due to hypercalcemia
Dialysis	When necessary on the basis of creatinine and potassium levels	To support life
Plamapheresis	No evidence of efficacy. More indicated in Waldenström's disease	To reduce plasma hyperviscosity

Neither vincristine nor doxorubicin is subjected to kidney catabolism or excretion and their safety, without any dose reduction, has been documented in patients with severe renal failure.<sup>45</sup> For these reasons VAD and VAD-like regimens are considered the best initial option for patients with renal failure.<sup>6,29</sup>

The toxicity of oral melphalan is difficult to predict, as it is highly dependent on inter-individual intestinal absorption, mainly when renal failure is present. However intravenous administration should be considered in the presence of renal failure. Catabolism and excretion are, in fact, independent of renal function.<sup>46,47</sup> The main problem is still a high inter-individual variation, secondary in this case to a variable plasma hydrolysis rate,<sup>47,48</sup> which is difficult to predict and can cause prolonged myelotoxicity with a risk of severe septic events in some patients. However, when acute renal failure is present, an important advantage of the initial approach with intravenous melphalan should be the rapidity of response to this drug, with some chance of renal function recovery and independence from dialysis,

as first demonstrated by Pecherstorfer *et al.*<sup>49</sup> In our personal experience (*data not published*), among 112 myeloma patients observed at diagnosis from 1994 to 2002, seven had creatinine levels higher than 500 µmol/L and two of them required dialysis at the time of diagnosis. Their mean age was 73 years (range 63-80) and four patients were older than 70. All seven patients were treated with one or two courses of intravenous melphalan 25 mg/m<sup>2</sup> on day 1 followed by G-CSF 300 µg/die from day 6, until the granulocyte count exceeded 0.5×10<sup>9</sup>/L. A granulocytopenia of less 0.5×10<sup>9</sup>/L for a few days (range 3-8) was induced by the first course of melphalan, but no patient died of sepsis or of other complications. If a clinical response occurred, patients younger than 70 were candidates for collection of peripheral stem cells to support at least one course of melphalan 100 mg/m<sup>2</sup>. After the first melphalan course four patients showed a creatinine reduction of more than 50%, and one of the two patients in dialysis became dialysis-independent. Two of the three patients younger than 70 years successfully mobi-

lized stem cells and underwent subsequent autologous stem cell transplant without major problems. This strategy seems promising even in patients older than 70.

In myeloma patients under 60 years of age, the superiority of high dose melphalan and autologous stem cell support over conventional chemotherapy has been well demonstrated by both the randomized study by Attal *et al.*<sup>50</sup> and some retrospective comparisons.<sup>51,52</sup> High dose treatment is also considered for patients from 60 to 70 years old,<sup>53,54</sup> while no evidence exists so far to recommend it for over 70-years old.<sup>29</sup> Renal failure is not yet considered a major contraindication to high dose melphalan and autologous stem cell rescue, even when patients are on dialysis, and some cases are reported in whom important renal function improvement and dialysis-independence has been obtained after autologous transplantation.<sup>15,16,55,56</sup> The main problem remains the high toxicity and the transplant-related mortality, which is significantly higher than in patients with normal renal function.<sup>16,56</sup> The main predictors of transplant-related mortality, for patients with severe renal failure, are poor performance status, hemoglobin < 0.5 g/dL, and albumin levels lower than 3.5 g/dL.<sup>16,56</sup> Moreover a conventional conditioning regimen of melphalan 200 mg/m<sup>2</sup> showed excessive toxicity and no more than 140 mg/m<sup>2</sup> or even 80 mg/m<sup>2</sup> is now suggested for this set of patients.<sup>16,55</sup>

In conclusion, in patients with myeloma and severe acute renal failure, VAD or dexamethasone alone is recommended, on the basis of evidence, as primary chemotherapy treatment.<sup>29</sup> Intravenous melphalan, as primary treatment, can be considered a promising strategy, but it should be limited to the context of experimental trials. There is, so far, no evidence-based recommendation for high dose chemotherapy, but this strategy, if reduced dosages of melphalan are used, is applicable with success for selected groups of patients.

### Hypercalcemia

Hypercalcemia is the second most frequent metabolic emergency in myeloma patients. The incidence of hypercalcemic episodes has fallen during recent years, as long-term biphosphonate therapy is now recommended for all myeloma patients, in order to prevent skeletal events and improve quality of life.<sup>29,57-60</sup> The benefit of biphosphonate treatment has been well demonstrated by controlled, randomized trials with both oral clodronate,<sup>61,62</sup> intravenous pamidronate<sup>63</sup> and intravenous zoledronate.<sup>64</sup> Sufficient efficacy has not been shown for intravenous ibandronate<sup>65</sup> and oral pamidronate.<sup>66</sup> In any case, hypercalcaemia, even if less frequent than in the past, can still constitute a severe emergency at both diagnosis and late during the course of the disease.

### Pathogenesis

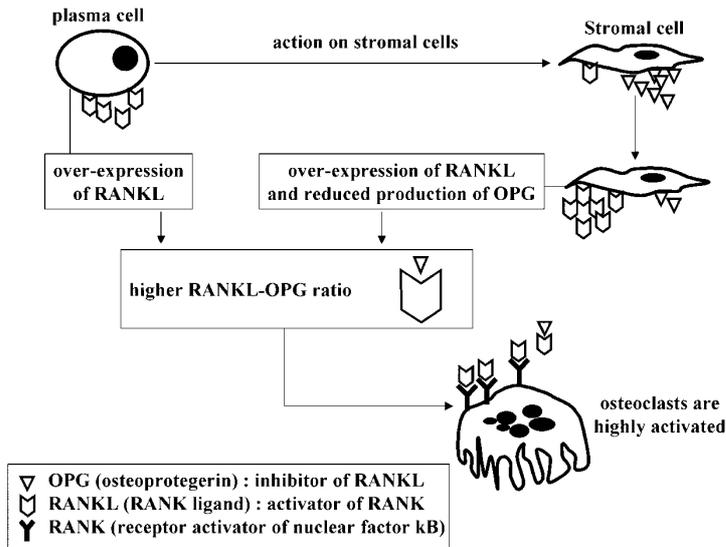
The most important molecular mechanisms that regulate the interaction between myeloma plasma cells and the bone marrow microenvironment, inducing osteoclastogenesis and hypercalcemia, have been recently identified in a disruption of the equilibrium between the receptor activator of nuclear factor- $\kappa$ B ligand (RANKL), its receptor (RANK) and osteoprotegerin (OPG).<sup>58,67-69</sup> RANK, RANKL and OPG form a cytokine system that is essential for the regulation of all aspects of osteoclast function. RANK is normally expressed in the osteoclastic lineage, while RANKL is normally produced by osteoblasts as well as immune cells. Following the activation of RANK by its ligand RANKL, osteoclasts are highly activated to proliferate and differentiate. The potent stimulatory effect of RANKL on RANK is inhibited by OPG, which is secreted by bone marrow microenvironment cells and blocks RANKL, thus preventing RANK activation. The physiologic balance of bone resorption is regulated by the local RANKL-to-OPG ratio, which is unbalanced in favor of RANKL in myeloma, as summarized in Figure 2. Myeloma cells both express RANKL themselves and stimulate stromal cells to over-express RANKL. Moreover myeloma cells inhibit contemporary OPG secretion by stromal cells. The consequent increased RANKL-to-OPG ratio, adjacent to myeloma cells, favors osteoclast activation and consequent osteolytic activity and the risk of hypercalcemia. In a vicious circle, cytokines and growth factors liberated by bone resorption can further stimulate myeloma cell proliferation.<sup>70</sup> This stresses the importance of any treatment strategy capable of reducing the RANK-to-OPG ratio.

### Symptoms

Mild hypercalcemia can be associated with only non-specific symptoms such as anorexia, nausea, fatigue, constipation and vomiting. When the hypercalcemia is more severe, it is more easily suspected, on the bases of the presence of significant polyuria, polydipsia and dehydration. As the level of hypercalcemia increases yet further, neurologic symptoms increase from muscle weakness and apathy to alteration of consciousness, seizures and coma. While mild hypercalcemia may be well tolerated and is difficult to suspect, acute and severe hypercalcemia causes marked neurologic problems and dehydration, and urgent diagnosis and therapy are needed.

### Treatment

Together with both major supportive strategies and anti-neoplastic chemotherapy, biphosphonates are at present the keystone of treatment for hypercalcemia secondary to myeloma, because of their ability to inhibit bone resorption in a number of interesting anti-osteoclastic ways.<sup>58,71</sup> New inhibitors of bone resorption, with even more direct



**Figure 2. Pathogenesis of hyperosteoclastogenesis and hypercalcemia in myeloma. See text. (RANK = receptor activator of nuclear factor- $\kappa$ B; RANKL = receptor activator of nuclear factor  $\kappa$ B ligand; OPG = osteoprotegerin).**

action on the RANKL-to-OPG ratio, are under study. In this setting, subcutaneous injection of OPG is under discussion, and the first human pilot studies are promising, inducing a rapid decrease of biochemical markers of bone turnover in both postmenopausal women<sup>72</sup> and multiple myeloma patients.<sup>73</sup> Until results of studies on OPG or other inhibitors are available, the choice is limited to one of the different bisphosphonate molecules. Intravenous pamidronate, at a dosage of at least 60-90 mg, has so far been the recommended strategy.<sup>58,71,74</sup> More recently, intravenous zoledronate has been tested in two identical, concurrent, parallel, randomized trials,<sup>75</sup> and dosages of both 4 and 8 mg of zoledronate showed better results than 90 mg of pamidronate. Moreover, zoledronate has the advantage of requiring only 10 minutes to be infused whereas at least 90 minutes are necessary for pamidronate. For these reasons, intravenous zoledronate, at a dose of 4 mg, is already recommended for treating hypercalcemia of multiple myeloma and other malignancies.<sup>29,76</sup> Even if pamidronate at conventional doses can be considered safe in patients with renal failure and hypocalcemic crisis have seldom been described,<sup>77-79</sup> caution and/or dose reduction of bisphosphonates are mentioned in guidelines on the use of this drug in the presence of moderate to severe renal failure, in order to avoid hypocalcemia.<sup>29</sup>

In case of severe acute hypercalcemia, supportive treatment is urgently needed,<sup>80</sup> and this is mainly based on the infusion of intravenous fluids, in order to correct the dehydration which is secondary to vomiting, decreased fluid intake and polyuria. Therapy is generally begun by infusing 1 or 3 liters of iso-

tonic saline over 1 to 4 hours, depending on the level of dehydration and on cardiovascular function. Intravenous hydration should increase urinary calcium excretion and improve renal function. Furosemide does not have additional benefits in enhancing calcium excretion, but it is recommended when there is the risk of volume overload, mainly for cardiac reasons. Serum potassium and magnesium levels should be checked frequently and replaced when necessary. Hypotonic fluids should be given if hyponatremia is present. However rehydration alone has a limited and temporary effect on severe hypercalcemia in myeloma patients and, as soon as proper rehydration has been obtained, bisphosphonate therapy with zoledronate 4 mg or pamidronate 60 to 90 mg should be started.

Other drugs utilized in the past, such as gallium nitrate, calcitonin and plicamycin (mithramycin) are at present less recommended than bisphosphonate, because of their higher toxicity or reduced efficacy.<sup>80</sup> Dialysis may sometimes be useful in severe situations in which profound renal failure or congestive heart failure contraindicate sufficient rehydration.

The use of corticosteroids is not based on evidence of efficacy against hypercalcemia, although they can be useful for their anti-plasma cell effect.<sup>79</sup> The association with anti-neoplastic chemotherapy is in any case indispensable to prevent rapid relapse of hypercalcemia.

In conclusion the best treatment strategy is based on the association of adequate rehydration, intravenous bisphosphonates and anti-neoplastic chemotherapy.

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## Emergencies in patients with cancer: spinal cord compression

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Spinal cord compression (SCC) occurs in 5% to 30% of the oncology population and affects the patient's function, comfort, and general quality of life. Patients with lung cancer, breast cancer, prostate cancer, cancer with an unknown primary site, or renal cancer are all at high risk of developing SCC by metastatic tumor. Spinal cord compression can also occur in sarcoma, myeloma, leukemia, thyroid cancer, lymphoma, melanoma, and gastrointestinal malignancies, i.e. in malignancies of virtually all histologies. A favorable response to treatment is directly correlated with early recognition of the signs and symptoms of SCC and rapid establishment of the presence and site of a compressive lesion by magnetic resonance imaging, which is the only accurate investigation in this clinical setting. Treatment includes administration of corticosteroids, radiation therapy, surgery, and chemotherapy, combined depending on histotype. General practitioners, oncologists, and nurses should watch for early symptoms (particularly pain), obtain a thorough history, perform a complete physical examination, and teach the patient and his or her family about signs and symptoms of SCC that need to be reported as soon as they occur.

### Introduction

Compression of the spinal cord and nerve roots is the second most frequent neurologic complication of cancer (brain metastases are the most frequent neurologic complication).<sup>1</sup> Each year in the United States, approximately 20,000 people with cancer develop SCC; this group represents 5% to 10% of the general cancer population.<sup>2,3</sup> Because of improved treatments and prolonged survival in various cancers, the incidence of SCC may be increasing.<sup>4</sup>

Cancers most likely to spread to the spine are lung, breast, and prostate cancer; kidney cancer and lymphoma tend to spread to the spinal cord as well.<sup>1,5,6</sup> Patients with melanoma, renal cell carcinoma, multiple myeloma, or certain sarcomas are also at risk of SCC.<sup>1,3</sup> Sarcomas and neuroblastoma cause more than 80% of cases of metastatic SCC in children.<sup>2</sup>

Malignant SCC is defined as a compressive indentation, displacement, or encasement of the spinal cord's thecal sac by metastatic or locally advanced cancer.<sup>1</sup> Spinal cord compression produces edema, inflammation, and mechanical compression, which causes direct neural injury to the cord, as well as vascular damage and impairment of oxygenation.<sup>6</sup>

Malignancies of the breast, prostate, lung, and kidney have a propensity to metastasize to bony structures, but any invasive cancer capable of hematogenous spread can produce SCC. Cancers that spread to the spine move to the bone marrow of the vertebral column by way of blood vessels. Spinal cord compression can also occur through direct tumor extension, which is frequently seen in non-Hodgkin's lymphoma. In such cases, there is direct extension of a paraspinal mass through the epidural foramen, and this extension produces the compression. Finally, metastasis results when tumor cells in the cerebrospinal fluid deposit tumor cells in the epidural space. This scenario most often occurs in leukemia.<sup>2</sup>

Spinal cord compression results when a metastatic tumor grows into the epidural space and impinges on the *dura mater*, thereby producing pressure on nervous tissue. As the mass grows, it destroys the bony structure of the vertebrae and weakens them to the point of collapse. The spinal column may then become weak and destabilized<sup>1,2</sup> (Figure 1).

Spinal cord compression constitutes a true emergency because the initial injury to the spinal cord will lead to permanent loss of neurologic function if the pressure of the tumor on the cord is not relieved quickly. Prognosis depends greatly on the length of time of the cord impingement, the location of the mass in the spinal column, and the tissue type of the mass.

The prognosis of SCC also depends on the functional status and duration of survival after treatment. Spinal cord compression is fatal only if it occurs in the cervical region of the spinal cord (C4 and above) and if it results in respiratory paralysis that is uncompensated by mechanical ventilation.<sup>7</sup> Tumor tissue type must be considered when the treatment plan is being determined. Some tumors, such as Hodgkin's lymphoma and small cell lung cancer, are very sensitive to chemotherapeutic agents, whereas lymphoma and myeloma are more sensitive to radiation therapy, and breast and prostate cancers may be sensitive to hormonal agents.<sup>2,4,8</sup>

General practitioners, clinical nurse specialists, and independent hospice and home care nurses are often

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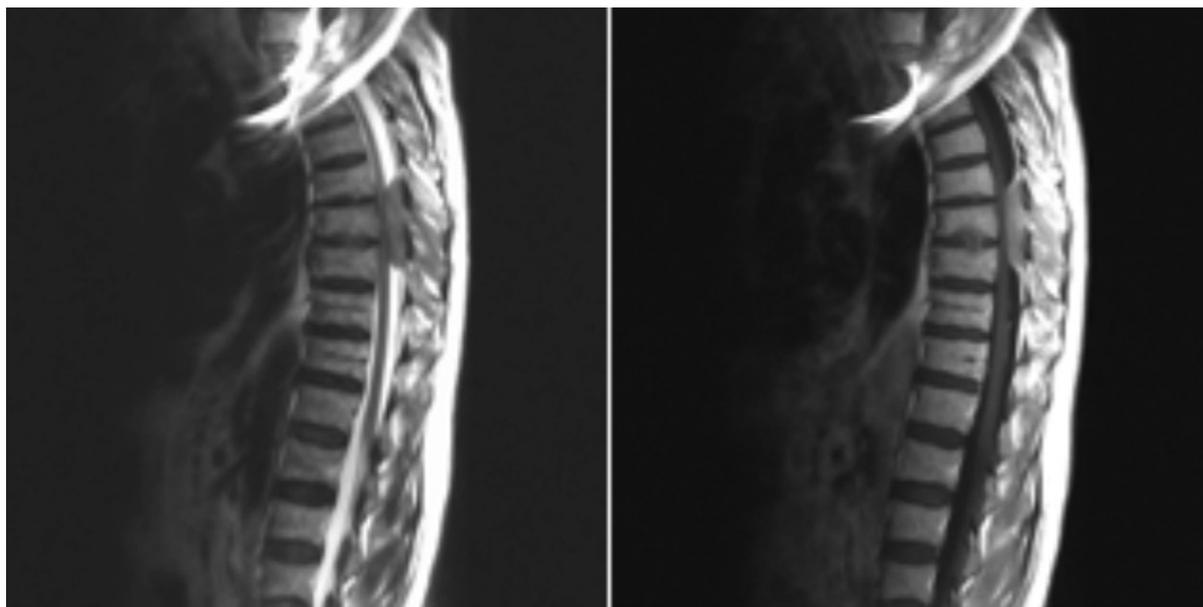


Figure 1. Magnetic resonance imaging of spinal cord compression in a patient with non-small cell lung cancer.

the first members of the health care team to see the patient and detect the signs and symptoms of SCC. These health care providers may encounter SCC in any practice serving patients with a cancer diagnosis. Any of these professionals may see patients with SCC in an outpatient clinic, the emergency department of a community or rural hospital, or the primary care setting.

#### **Clinical presentation and diagnostic work-up**

The presenting signs and symptoms depend on the location and level of the metastatic tumor.<sup>5</sup> (Table 1). The thoracic spine is the site most often involved (70% of cases), followed by the lumbosacral spine (20%) and the cervical spine (10%).<sup>9</sup> Other variables include the degree of cord impingement and the duration of tumor involvement.<sup>3</sup> The cardinal initial symptom of SCC is back pain, reported by 90% to 95% of patients. The pain can be localized, radicular, or both and usually precedes other symptoms by 2–4 months.<sup>3</sup>

Local pain occurs over the area of the tumor and is caused by vertebral destruction or stretching of the bone by an enlarging tumor mass. Radicular pain is caused by compression of nerve roots and is found in the dermatomes affected by the nerve roots.<sup>6</sup> Radicular pain may travel down the extremity associated with the area of compression and may be aggravated by the Valsalva maneuver.<sup>7,8</sup> Often the pain is described as a soreness or vague discomfort, which progresses to more severe symptoms such as weakness in one or both limbs, loss

of sensation, and then autonomic dysfunction and paralysis.<sup>2,3</sup> This pain often begins as a nonspecific soreness, which could be attributed to any number of other conditions, such as arthritis, muscle strain, or old injury to the vertebrae.

#### **History and physical examination**

A thorough history and a complete physical examination are necessary to differentiate SCC from other conditions. The health care provider must ask about the location, radiation, and duration of the pain, as well as specific characteristics (burning or stabbing), severity of pain, and whether the pain is present at night.<sup>10</sup> It is important to ask the patient whether the pain is present when he or she is lying down, because SCC, unlike strains or old injuries, causes pain that is unrelieved or even increased in the recumbent position. It is also important to ask about the time of the pain, because early morning stiffness may indicate arthritis, and evening discomfort could indicate muscle strain or an old injury. The patient must be asked about the existence of other symptoms, such as muscle stiffness, feelings of heaviness, difficulty climbing stairs, and coordination problems.<sup>2</sup> Motor weakness is the second most common symptom of SCC, occurring in 80% of cases, and it can be present at the same time as sensory loss.<sup>5</sup> Sensory dysfunction is also present in SCC. Therefore, the health care provider must question the patient about the existence, location, and onset of numbness, tingling, or coolness in the arms, hands,

fingers, legs, feet, toes, and trunk.

The patient should also be asked about constipation or urinary retention because these symptoms are early indicators of injury to the autonomic nerves. The presence of urinary and/or bowel incontinence indicates advancing autonomic involvement, and perianal numbness indicates *cauda equina* syndrome, a condition requiring immediate decompression.<sup>2,10</sup> Surgical intervention within 48 hours of the onset of symptoms generally improves sensory and motor deficits and urinary and rectal function.<sup>11</sup>

*Cauda equina* syndrome usually occurs as a result of a massive disc herniation in the lumbar region and should therefore be considered in the differential diagnosis.<sup>11</sup> Other conditions to consider include infections or epidural abscess, hematoma, or damage to the spinal cord from exposure to radiation, syrinx, and neoplastic meningitis.<sup>3,10</sup>

Physical examination findings correspond to the location of the tumor, degree of cord impingement, and duration of involvement.<sup>3</sup> The health care provider should palpate the entire spine to determine whether there is any tenderness or pain. Tenderness is an early sign of SCC and thus may indicate the start of neurologic injury, the prompt treatment of which will result in complete recovery of function. Often the patient will complain of soreness or tenderness over the vertebral body with tumor involvement.

Having the patient walk heel to toe will establish whether there are any gait problems. Checking the patient's ability to move specific muscles in response to resistance by the examiner can rule out muscle weakness and paresis.<sup>2</sup> Pain that progresses down the patient's asymptomatic (or less symptomatic) leg when the leg is raised straight may suggest SCC.<sup>3</sup>

If cord compression is left untreated, weakness often develops, preceded or accompanied by sensory loss.<sup>9</sup> In a patient with a history of cancer, bilateral leg weakness that is noted during stair climbing, paresthesias in the legs, and bowel or bladder dysfunction are all red flags for SCC. Sensory function - specifically, the ability to distinguish temperatures and feel vibration - is evaluated using hot and cold tuning forks.<sup>2</sup> Pain recognition is assessed using dull and sharp tools.

A rectal examination should be performed to assess sphincter tone. Weak rectal sphincter tone is a late sign of SCC, signaling worsening injury to the nerve roots affected by the increasing compression of the spinal cord. If the patient has urinary complaints, the bladder is catheterized for postvoiding residual urine. Urinary volumes > 200 mL may suggest a neurogenic bladder. Once such autonomic symptoms appear, SCC usually progresses rapidly, and it may result in irreversible paralysis in hours to days if untreated.<sup>9</sup>

**Table 1. Tumor location and symptoms of spinal cord compression.**

<i>Location</i>	<i>Signs and symptoms</i>
Cervical spine	Headache or neck, shoulder, or arm pain Breathing difficulties Loss of sensation in the arms Muscle weakness in the neck, trunk, arms, and hands Paralysis involving the neck, trunk, arms, and hands
Thoracic spine	Pain in the chest and/or back Loss of sensation below the level of the tumor Increased sensation above the level of the tumor Muscle weakness Paralysis Positive Babinski reflex Bladder and bowel problems Sexual dysfunction
Lumbosacral spine	Low back pain that may radiate down the legs and/or perineal area Weakness in the legs and feet Paralysis in the legs and feet Loss of sensation in the legs and feet Bladder and bowel problems Sexual dysfunction Foot drop Decreased or absent reflexes in the legs

### **Diagnostic tests**

Laboratory tests include a complete blood cell count with differential, an erythrocyte sedimentation rate determination, urinalysis, and a chemistry profile including calcium and liver function studies. The complete blood cell count and erythrocyte sedimentation rate may be useful in differentiating SCC from infection, whereas the chemistry profile may indicate the primary cancer or the patient's general condition.<sup>10</sup>

Imaging studies include plain radiography and magnetic resonance imaging (MRI) with contrast of the spine. Plain films of the spine frequently demonstrate associated vertebral blastic or lytic lesions.<sup>12</sup> However, gadolinium-enhanced MRI provides the best definition of spinal lesions. Magnetic resonance imaging not only shows cord compression caused by extradural masses but also shows paravertebral masses, intramedullary disease, and bone metastases. Magnetic resonance imaging of the entire spine should be ordered, because approximately 10% to 30% of patients with clinical symptoms of SCC have multiple lesions.<sup>4</sup> Lumbar puncture is contraindicated because removal of cerebrospinal fluid may worsen the SCC.<sup>3</sup>

### **Proposed referral guideline based on symptoms and signs of spinal cord compression**

A very important prospective observational study examined the diagnosis, management and outcome of 319 patients diagnosed with SCC at three Scottish cancer centers between January 1998–April 1999.<sup>13</sup> The aim of this study was to report details concerning symptoms (especially pain) preceding the development of malignant SCC; delays between onset/reporting of symptoms and confirmed diagnosis of malignant cord compression; and accuracy of investigations carried out. The process was considered from the perspectives of the patient, the general practitioner and the hospital doctor. At diagnosis, most patients (82%) were either unable to walk or only able to do so with help. Pain was reported by nearly all patients interviewed (94%) and had been present for approximately 3 months (median, 90 days). It was severe in 84% of cases, with the distribution and characteristics of nerve root pain in 79%. The site of pain did not correspond to the site of compression. When reported, weakness and/or sensory problems had been noticed by the patient for some time before diagnosis (median intervals 20 and 12 days, respectively). Most patients reported early symptoms to their general practitioner and diagnosis was established, following referral and investigation, approximately 2 months (median, 66 days) later. In conclusion, authors documented that patients who develop spinal metastases are at risk of irreversible spinal cord damage. Weakness and sensory abnormalities are reported late and identified even later, despite patients having reported pain for a considerable time. Patients with cancer who describe severe back or spinal nerve root pain need urgent assessment on the basis of their symptoms, as signs may occur too late. Plain films and bone scans requested for patients in this audit accurately predicted the level of compression in only 21% and 19% of cases, respectively. The only accurate investigation to establish the presence and site of a compressive lesion is magnetic resonance imaging (MRI). A referral guideline based on suspicious symptoms in addition to suspicious signs was suggested by Levack *et al.*<sup>13</sup>

## **Treatment**

### **Corticosteroid therapy**

Treatment is palliative in most cases, but goals are relief of pain and maintenance or restoration of neurologic function. Other goals include spinal column stabilization and local tumor control.<sup>2,8</sup> The choice of therapy depends on the tumor type and location, the speed of onset, and the degree of

function before onset of symptoms.<sup>14</sup>

The patient is admitted to the hospital, usually by the medical oncologist, who has typically consulted with the radiation oncologist and the neurosurgeon. A course of treatment with dexamethasone is started in order to reduce the edema and cord compression caused by the tumor mass and to thereby relieve the pain. Dexamethasone has lympholytic activity against lymphomas involving the epidural space.<sup>15</sup> Some controversy exists regarding the optimal dose of dexamethasone; adult doses range from 4 to 100 mg, given every 6 hours. However, many physicians administer a 4- to 100-mg intravenous (IV) bolus followed by 16–96 mg/d in divided doses over several days.<sup>2,3</sup> The dose of dexamethasone, like any corticosteroid, must be tapered gradually. A common schedule for tapering calls for decreasing the dose by one third every 3–4 days. If tapering is not tolerated and neurologic deterioration occurs, a trial of an escalated dose may be attempted, followed by tapering.<sup>16</sup>

Patients who take dexamethasone must be monitored carefully for side effects of corticosteroids, such as gastrointestinal irritation, fluid retention, euphoria, depression, and hyperglycemia.<sup>8</sup> Blood glucose levels are a particular concern in diabetic patients and must be monitored closely. The diabetic patient's diet and insulin dose may need to be changed. If the patient has been treated with an oral hypoglycemic drug, insulin may need to be introduced temporarily in order to manage the higher glucose levels. Bolus injections of dexamethasone must be given slowly to avoid rectal or vaginal burning.<sup>4,17</sup>

### **Radiation therapy**

Radiation therapy is the standard of care for SCC caused by tumor involvement.<sup>1,2,8</sup> Radiation therapy resolves pain by reducing the tumor mass and relieving the SCC. There are different regimens of radiation therapy for SCC. The commonly prescribed regimen is 2–3 Gy per fraction to a total dose not exceeding 30–40 Gy, directed to the spinal cord over 2–4 weeks.<sup>1</sup>

Indicators of a response to radiation therapy include pain relief and a return to baseline function or improved function. Patients may experience some relief of symptoms within a few days after starting radiation therapy, and pain sometimes is relieved within hours. However, return to baseline function after radiation therapy can be delayed for months.<sup>5</sup>

### **Surgery**

In a small number of patients, particularly those with spinal instability or a rapidly progressing loss of neurologic function, surgery may be indicated.

Often these oncology patients are severely compromised by their underlying cancer and numerous treatment regimens. Wound healing and recovery from surgery can be difficult in this population, so patients must be selected carefully for any surgical procedure. They may have failed to respond to radiation therapy, the site of the primary tumor may be unknown, they may have local tumor that recurs at a previously irradiated site, or they may have pathologic fracture with spinal instability or compression of the cord by bone.<sup>1,2</sup>

### **Chemotherapy and hormone therapy**

Chemotherapy is indicated in adults with chemosensitive tumors such as a lymphoma or Hodgkin's disease. Chemotherapy can also be used as an adjuvant therapy with irradiation or surgery in patients with breast cancer, prostate cancer, or multiple myeloma. The choice of chemotherapeutic agents depends on the primary tumor type and the chemotherapy history of the patient. Hormone therapy is another option for patients with prostate or breast cancer.<sup>4</sup>

### **Palliative care**

Patients who have failed to respond to chemotherapy and conventional radiation therapy (external beam radiotherapy) and are not candidates for standard surgical procedures (laminectomy) have few options. Palliative care consisting of analgesic administration, nerve blocks, corticosteroid therapy, and side effect management, best performed by hospice care workers, is indicated in these patients. Optimal nursing management after treatment for SCC is paramount for success.<sup>14</sup>

Palliative care goals include prevention of further injury, good pain control, restoration and maintenance of bowel and bladder function, and provision of emotional support for both the patient and caregivers. The response to treatment depends in general on the level of function at the time of diagnosis. If a patient presents with bladder and bowel symptoms and paresthesias, it is less likely that he or she will recover bladder and bowel function or the ability to walk.

### **Implications for the health care providers**

Not only oncologists but also other health care providers, for example, the nurse specialist or general practitioner involved in oncology care, can favourably affect a patient's quality of life through timely recognition of early signs and symptoms of SCC. The current emphasis on pain control for oncology patients ought to increase awareness of the development of SCC, given that pain is usually present before the loss of sensation and motor and autonomic function begins. A thorough pain

evaluation will lead, in the case of pain, to initiation of treatment to relieve the injury to neurologic tissue before irreversible damage occurs.

Health care providers must also keep the possibility of SCC in mind when teaching cancer patients about symptoms that should be reported immediately. It is particularly important for patients with lung, breast, or prostate cancer or lymphoma to report promptly back pain that is worse in the recumbent position or chronic back pain that suddenly changes. Because back pain is a common non-malignant problem, it is not unusual for patients to ignore the pain until symptoms worsen and neurologic deterioration occurs.<sup>8</sup>

Once a diagnosis of SCC has been made, supportive nursing measures are indicated. These measures include immobilization of the spine, control of pain, paying attention to the skin, and close monitoring of bladder and bowel function. Neurologic function and vital signs are checked as often as the patient's condition warrants. Safety concerns are paramount in this population of cancer patients, many of whom have fatigue and generalized weakness because of their underlying cancer or treatment side effects. Patients should always have assistance when walking, especially at night.

After discharge, the home care doctor and nurse can continue to monitor pain control and functional status. They will also co-ordinate any rehabilitation efforts that may be indicated. A physical therapy referral may be made for range of motion exercises or an evaluation of functional capacity. The physical therapist or occupational therapist will evaluate the need for aid devices such as a hospital bed, a wheelchair, or ramps in the home.

Hospice referral is appropriate for the patient with SCC whose cancer has progressed to end-stage disease. Members of the hospice team are experts in pain control and provision of emotional support to the patient and his or her family in the face of a steady progression of losses, ultimately leading to death.

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## Superior vena cava syndrome

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The superior vena cava syndrome results from the obstruction of blood flow through the superior vena cava (SVC). The SVC is a major drainage vessel for venous blood from the head, neck, upper extremities and upper thorax; it is located in the mid mediastinum and is surrounded by the sternum, trachea, thymus, right bronchus, aorta, pulmonary artery, and perihilar and paratracheal lymph nodes. The SVC is about 2 cm wide and its wall is thin, compliant and easily compressible; hence, its vulnerability to any space-occupying process in the vicinity; the auxiliary azygos vein may be affected by the enlargement of paratracheal nodes, as well. When the SVC is obstructed, extensive venous collateral circulation may develop and the most important alternative pathway is represented by the azygos and hemiazygos veins; other collateral systems are the internal mammary vein, the lateral thoracic veins, the esophageal venous network and the subcutaneous veins.

Obstruction of the SVC may occur as an acute or subacute process producing characteristic symptoms and physical signs (superior vena cava syndrome; SVCS). Despite the presence of collateral pathways, the venous pressure is always elevated and the patient usually experiences facial edema and plethora, dilation of the chest wall and neck veins, moderate to severe respiratory difficulties and, less commonly, conjunctival edema, central nervous system complaints, headache and visual disturbances.

### **Etiology**

Malignancies are the most common cause of SVCS. Table 1 indicates the etiology of SVCS in different series of patients. Lung cancer is responsible for more than half of the cases of SVCS, while malignant lymphomas account for about 10–20% of cases. Other primary mediastinal malignancies that may cause SVCS are thymoma and germ cell tumor. Less commonly, the SVCS has a benign etiology including goiters, mediastinal fibrosis due to previous mediastinitis and thrombosis of the SVC. Most SVC thromboses develop in the pres-

ence of a central venous catheter and the increasing use of these devices for the delivery of chemotherapy agents or for hyperalimentation contributes to the development of SVCS in cancer patients.

As far as lymphoma varieties causing SVCS are concerned, about two thirds belong to the diffuse large cell (DLCL) category, while about one third are T-cell lymphoblastic lymphomas with mediastinal enlargement. Indeed, in the MD Anderson Cancer Center experience,<sup>6</sup> 4% of 915 patients with non-Hodgkin's lymphomas presented with SVCS; 64% of them had diffuse large cell lymphoma and 33% had lymphoblastic lymphoma (LBL). Altogether, in this series, SVCS was present in 7% of cases of DLCL and 21% of LBL.

In our series of primary mediastinal large B-cell lymphoma with sclerosis,<sup>7</sup> SVCS was present in 57% of cases, while in a multi-institutional retrospective study on 426 patients, SVCS was observed in 25% of the total.<sup>8</sup> SVCS is rarely observed in Hodgkin's disease, despite the high rate of mediastinal involvement in this disease. In childhood, SVCS is most commonly caused by lymphoid malignancies, especially lymphoblastic lymphoma or T-cell acute lymphoblastic leukemia (T-ALL).<sup>9</sup> Germ cell tumors, thymoma, neuroblastoma, rhabdomyosarcoma and Ewing's sarcoma have also been reported to cause this syndrome.<sup>10</sup>

### **Clinical features**

The diagnosis of superior vena cava syndrome is established by physical examination and clinical presentation. As a result of diminished blood return from the head, neck, arms and upper torso, patients with SVCS very often complain of a sense of facial swelling or head "fullness"; physical findings include venous distension of the neck in a large majority of patients (about two thirds), venous distension of the chest wall (about 50%), facial edema, cyanosis, plethora of the face, and edema of arms (about 20%). Table 2 indicates the incidence of the major symptoms occurring in SVCS. Dyspnea, cough and chest pain are the most prominent symptoms; they may be aggravated by positional changes, particularly by bending forward, stooping or lying down.

The frequency of respiratory distress is related to the underlying disease and its extent is generally less severe in lymphomas than in lung cancer, except for the case of primary mediastinal lymphoma with sclerosis.

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**Table 1. Causes of superior vena cava syndrome.**

Cause	Parish et al. <sup>1</sup>	Bell et al. <sup>2</sup>	Amstrong et al. <sup>3</sup>	Yellin et al. <sup>4</sup>
Lung cancer	52%	81%	79	48%
Lymphoma	9%	2%	14	21%
Thymoma or metastatic neoplasm	16%	3%	7	13%
Non neoplastic	23%	14%	-	18%

Modified from: De Vita V, Hellman S, Rosenberg S. Cancer: Principles and Practice of Oncology, 5<sup>th</sup> Edition, Lippincot-Raven, 1997.<sup>5</sup>

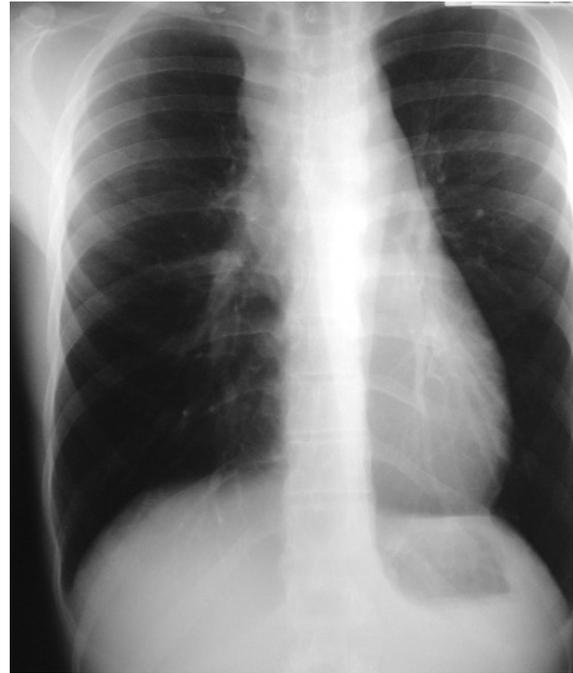
**Table 2. Symptoms of the superior vena cava syndrome.**

Symptoms	Parish <sup>1</sup>	Bell <sup>2</sup>	Amstrong <sup>3</sup>	Yellin <sup>4</sup>	Lazzarino <sup>7</sup>
Dyspnea	63%	70%	55%	30%	47%
Cough	55%	7%	23%	21%	47%
Dysphagia	12%	-	13%	6%	3%
Chest pain	20%	13%	15%	6%	43%
Neurologic	2%	-	-	-	6%
Syncope	7%	4%	-	-	3%

Modified from: Abeloff MD, Armitage JO, Lichter AS, Niederhuber JE. Clinical Oncology, Churchill-Livingstone, 1995.<sup>11</sup>

### **SVCS in primary mediastinal B-cell lymphoma with sclerosis**

Analysis of our records showed that primary mediastinal B-cell lymphoma is a tumor with distinctive clinical features.<sup>7</sup> A large majority of patients with this lymphoma presented subacutely with chest symptoms consisting of cough, chest pain, dyspnea, and dysphonia attributable to a rapidly enlarging mass of the anterior mediastinum. The overall incidence of caval obstruction was about 80%, cough and dyspnea were present in about half of the patients and not a negligible fraction (6%) complained of neurologic signs, including paralysis of vocal chords and headache related to increased intracranial pressure; tracheo-bronchial compression or displacement was present in 67% of cases (see Figures); the median time from the onset of symptoms to diagnosis was 30 days.<sup>7</sup> This type of lymphoma also showed a high propensity to early intrathoracic extension to adjacent organs; pleural and pericardial effusions were documented in 47% of cases. Extrathoracic renal tropism seems to be characteristic of this lymphoma.



**Figure 1. Superior mediastinal enlargement in a young man with primary mediastinal lymphoma with sclerosis.**

### **Imaging**

Mediastinal widening is the most common abnormality documented by standard chest radiograph. A mass is usually found in the superior mediastinum (Figure 1) or right hilum and parahilar regions (Figure 2). Pleural and/or pericardial effusions are very frequently documented by chest X-ray in patients with primary mediastinal lymphoma with sclerosis (Figure 3).

Computed tomography (CT) provides more detailed information about the mass, the superior vena cava, its tributaries, other great vessels and the air-ways. Figure 4 illustrates a narrowed left upper lobar bronchus in a young woman affected by primary mediastinal lymphoma with sclerosis; in the same CT scan, the left lung parenchyma appears to be infiltrated and obstructed. Figure 5 shows mediastinal vessels surrounded by the growing mass and a compressed left pulmonary artery. Moreover, CT scans may be helpful in the risk evaluation of diagnostic procedures such as supraclavicular lymph node biopsy, bronchoscopy, mediastinoscopy or thoracotomy.

Contrast-enhanced tomography can demonstrate collateral flow, provides visualization of extravascular and intravascular tumors, of caval thrombus and can be invaluable for presurgical evaluation. Moreover, CT scanning may be very helpful in guiding a fine-needle aspiration biopsy, when histology is not obtainable through surgery.



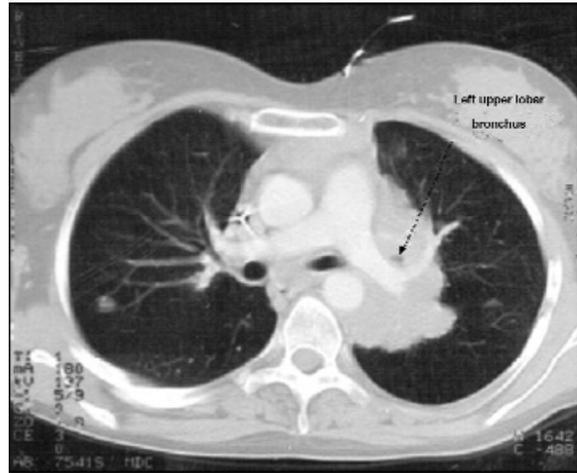
**Figure 2. Mediastinal and right hilum enlargement in a 52-yr old man with bronchus carcinoma.**



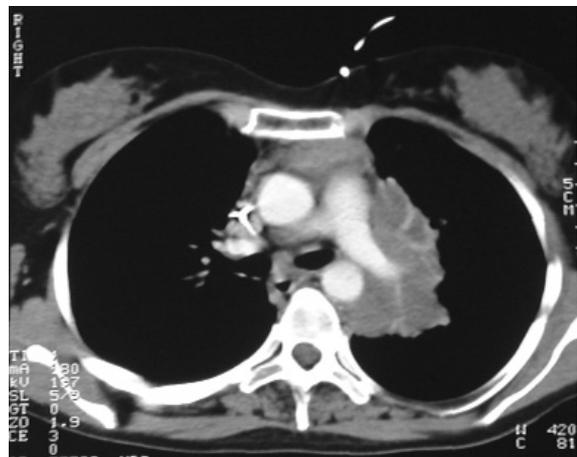
**Figure 3. Pleural effusion in a patient with primary mediastinal lymphoma with sclerosis.**

The propensity of primary mediastinal lymphomas to undergo early intrathoracic extension is illustrated by Figure 6, a CT scan of a young woman: a bulky mediastinal solid mass expands toward the left lung and narrows the left bronchus.

In the contrast-phase of the same CT scan (Figure 7), a bulky mass with areas of necrosis surrounds and narrows the main pulmonary arteries (arrows) and displaces the left bronchus (thick arrow).



**Figure 4. Left upper lobar bronchus is narrowed by a neoplastic mass and the lung parenchyma is infiltrated.**



**Figure 5. The contrast-enhanced CT scan shows mediastinal vessels surrounded by a growing mass and a compressed left pulmonary artery (arrow).**

The tendency of mediastinal lymphomas to infiltrate the surrounding structures is illustrated in the Figure 8, in which a pericardial involvement with effusion is clearly evident.

Bronchial stenosis by the neoplastic mass is the major factor predicting for the risk of complications during diagnostic procedures in patients with SVCS. Figure 9 illustrates the case of a left bronchus dramatically narrowed by a neoplastic mass growing in the antero-superior mediastinum.

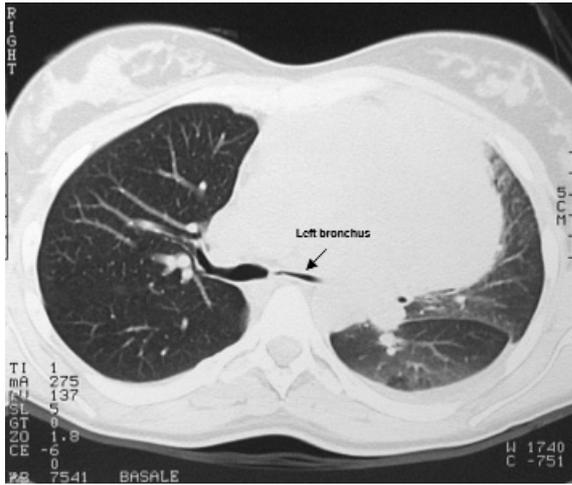


Figure 6. Large mediastinal solid mass expanding towards the left lung and narrowing the left bronchus.

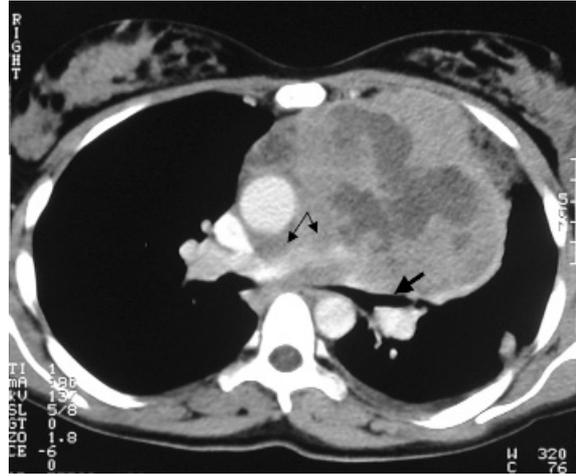


Figure 7. A necrotic mass surrounds and narrows the pulmonary arteries (arrows) and displaces the left bronchus (heavy arrow).

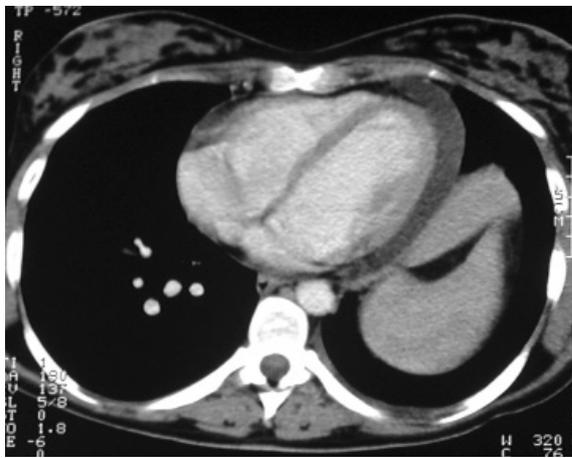


Figure 8. Pericardial effusion around the left ventricle.

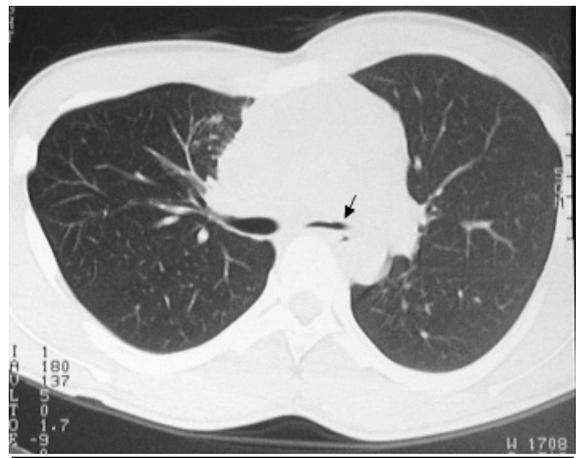


Figure 9. The left main bronchus (arrow) is dramatically narrowed by a neoplastic mass growing in the antero-superior mediastinum.

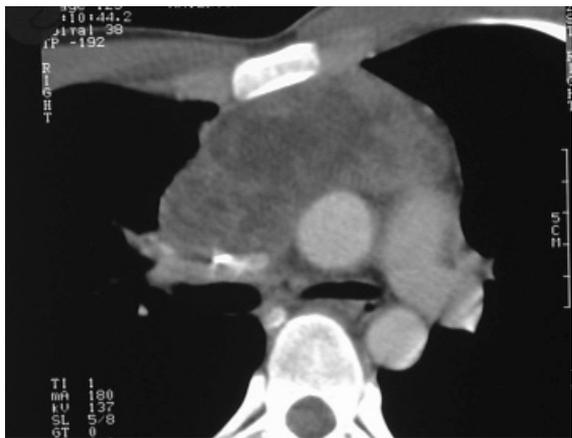


Figure 10. The ascending aorta is compressed toward the left main bronchus which is narrowed.

The patient was a 19-year old boy who had complained in the previous two weeks of cough and mild dyspnea and had developed SVC syndrome, with neck swelling and bilateral turgor of the jugular veins. This CT scan was taken at his admission to our clinic and the severe bronchial stenosis prompted us to postpone any diagnostic procedure to a debulking chemotherapy.

Contrast-enhanced CT scanning (Figure 10) shows a mass with large areas of necrosis compressing and narrowing the ascending aorta; the displaced aorta, in turn, indents the main right pulmonary artery (Figure 11). Bronchial stenosis and/or vascular compression in the context of a superior vena cava syndrome, should be considered a contraindication to any invasive diagnostic procedure under general anesthesia. The role of the CT scan-



**Figure 11.** A bulky retrosternal mass is evident; a displayed aorta indents the main right pulmonary artery.

ning and of other imaging procedures in the diagnosis of SVCS has been extensively reviewed,<sup>12-17</sup> and the importance of evaluating collateral vessels has been emphasized.<sup>18-20</sup>

#### **Diagnosis of primary neoplasia**

The most common procedures to establish the etiology of SVCS include supraclavicular lymph node biopsy, percutaneous fine needle mediastinal biopsy, bronchoscopy, mediastinoscopy and thoracotomy. In the presence of severe SVCS, all these procedures can be hazardous and their potential diagnostic yield must be carefully considered. The potential diagnostic yield from various procedures is summarized in Table 3 and ranges from 25-50% for cytology to almost 100% for thoracotomy.<sup>21,22</sup>

Fine-needle percutaneous mediastinal biopsy is often crucial for the diagnosis of primary medi-

astinal lymphoma and lymphoblastic lymphoma; indeed, in both these neoplasms, sputum cytology and bronchoscopy are ineffective and superficial nodes are normally absent. Bone marrow biopsy and peripheral blood smear can be diagnostic in T-ALL with mediastinal enlargement and SVCS. Thoracentesis may be diagnostic in primary mediastinal lymphoma, when pleural effusion with positive cytology is frequent.

SVCS secondary to lymphoma may represent an emergency requiring treatment before a histologic diagnosis is made; in cases with severe dyspnea due to tracheal compression or in the presence of neurologic symptoms (raised intracranial pressure), great care must be used in doing the biopsy, and it may be appropriate to postpone the attempt to make a histologic diagnosis until after debulking chemotherapy or radiotherapy has been administered.<sup>23</sup>

#### **General therapeutic measures**

The respiratory status must be evaluated promptly; patients with severe respiratory compromise should be treated urgently, before a histologic diagnosis is made. Historically, radiation therapy has been utilized as the primary treatment of SVC compression.<sup>24</sup> Current treatment prefers prompt chemotherapy (with or without thoracic radiation therapy) as an urgent intervention in lymphoma (see below). Measures that can alleviate symptoms related to vascular compression should be immediately instituted and include bed rest with the head elevated and oxygen administration; diuretics (beware of hypovolemia) and steroids may help as temporary palliative measures.<sup>25</sup>

Diagnostic evaluation follows the improvement of medical conditions; the least invasive procedures should be performed first, then the more invasive ones, as needed, in order to obtain the histologic diagnosis (see above).

**Table 3. Probability of a diagnostic yield for different diagnostic procedures.**

Procedure	Diagnostic yield %	Observations
Sputum cytology	20	In lung cancer only
Bronchoscopy	45	Mostly in lung cancer
Superficial lymph node biopsy	80	Rarely involved in mediastinal lymphoma
Mediastinal fine-needle biopsy	50	Often ineffective in presence of necrosis
Mediastinoscopy	80	Not exempt of risks
Thoracotomy	95	Not exempt of risks
Thoracentesis	10	In presence of neoplastic effusion
Bone marrow biopsy	10	Mostly useful in LBL and microcitoma

Modified from Abeloff MD, Armitage JO, Lichter AS, Niederhuber JE. Clinical Oncology, Churchill-Livingstone, 1995.<sup>11</sup>

In older adults, the most common cause of SVCS is lung cancer and treatment should be instituted accordingly. In young adults, the most common cause of SVCS is a lymphoma with mediastinal involvement (but rarely Hodgkin's disease).

### **The treatment of SVCS associated with mediastinal lymphoma**

Prompt chemotherapy is advocated as the treatment of choice, with full doses of an effective regimen.<sup>26</sup> One of most extensive experiences in the management of SVCS secondary to lymphoma was reported by the MD Anderson Cancer Center in 1984;<sup>6</sup> the patients were treated with either chemotherapy alone (combination chemotherapy including an anthracycline derivative) or chemotherapy combined with mediastinal irradiation; all patients obtained complete relief of SVCS symptoms within two weeks of institution of therapy. Radiotherapy should never be employed alone except when dealing with recurrent disease; consolidation RT after chemotherapy can be helpful in patients with large cell lymphoma with bulky mediastinum. At variance, in lymphoblastic lymphoma, recurrence of disease is uniformly systemic and radiotherapy is generally of no use.

### **The therapeutical experience with primary mediastinal large B-cell lymphoma**

The bulk of recent experience on the treatment of SVCS secondary to lymphoma concerns the results obtained in primary mediastinal B-cell lymphoma (PMLBCL). The discussion on the use of protocols that are more aggressive than the classical CHOP therapy in this variety of lymphoma is still open. Indeed, in historical controls treated with CHOP or CHOP-like regimens, the prognosis of patients with PMLBCL appeared worse than that of patients with non-mediastinal diffuse large B-cell lymphoma.<sup>29-34</sup> However, the use of more dose-intensive chemotherapy regimens, such as MACOP-B<sup>27</sup> or VACOP-B<sup>28</sup> plus regional radiotherapy produced remission and survival rates in PMLBCL comparable to or better than those in non-mediastinal large B-cell lymphoma.<sup>7,35-40</sup> Two large multi-institutional studies<sup>8,38</sup> may serve as reference as far as response to therapy and prognosis are concerned. Briefly, third-generation and high-dose induction chemotherapy provides a better initial response rate than first-generation chemotherapy; adjuvant radiotherapy may have an important role as far as long-term progression-free survival is concerned, especially in patients with bulky mediastinum at presentation.<sup>8,39,40</sup> <sup>67</sup>Ga SPECT and PET restaging procedures may serve to monitor the state of remission.<sup>38,40</sup> Among features at presentation, poor performance status and pericardial effusion are the two most important independent risk factors related to no response and poor survival; inadequate response to

the first course of chemotherapy is an additional feature predicting subsequent failure.<sup>38</sup>

### **Special situations**

Special situations are a SVCS due to benign causes, such a granulomatous disease with chronic fibrosing mediastinitis, an aortic aneurysm or a retrosternal goiter, and the combination of external compression, vessel wall invasion and thrombosis (of the superior vena cava or accessory veins).

### **Surgical bypass**

Surgery may have a role in the management of SVCS due to a benign cause, through direct graft bypassing of a SVC obstruction; the preferred bypass route is between an innominate or jugular vein on the left side and the right atrial appendage using an end-to-end anastomosis; symptoms usually disappear promptly and grafts remain open. In patients with malignancy-induced SVCS, surgery should be considered only when other therapeutic attempts, such as chemotherapy and radiotherapy, have failed.

### **Thrombolytic therapy**

Experience with the use of thrombolytic therapy is limited to the treatment of catheter-induced SVCS, where a thrombotic complication may ensue.<sup>41</sup> The higher success rate is related to the underlying mechanism of obstruction, to the ability of delivering thrombolytic agents (urokinase, streptokinase) directly to the thrombus and to an earlier recognition of SVCS in patients with indwelling catheters.

### **Stents**

Intravascular wire stents, placed percutaneously, may represent an adjunctive treatment in patients with SVCS, irrespective of the underlying cause.<sup>42</sup> These devices may be placed before or during the debulking chemotherapy or radiotherapy and generally produce relief from symptoms within 24-48 hours. Simultaneous antithrombotic therapy is needed and the presence of acute thrombosis superimposed on SVC obstruction is an indication for thrombolytic therapy through the stent.

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## Intensive care unit admission for hematologic malignancies: a debatable problem

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The use of intensive chemotherapy – with or without hematopoietic stem cell transplantation (HSCT) – has markedly improved the prognosis of patients with hematologic malignancies.

These aggressive treatment modalities, however, are associated, especially in acute leukemia patients and in bone marrow transplant recipients, with a number of severe and potentially life-threatening complications due to both chemotherapy-related toxicities and chemotherapy-related immunodeficiency which predisposes these patients to severe and widespread infections.

Because of the need for intensive monitoring or aggressive life support, some of these complications may require hematologic patients to be transferred to the intensive care unit (ICU), a decision which is often contentious not only because of economic costs but also because of costs in terms of emotional suffering and unmet expectations on the part of both the patients and their relatives. Ethical issues have also been raised concerning whether admission to an ICU is advisable in patients whose short-term and long-term prognosis is bleak.<sup>1</sup>

However, recent data from the literature report overall ICU mortality rates in the order of 40–60% which is higher than average ICU mortality but very close to that observed in patients with acute pancreatitis, acute respiratory distress syndrome (ARDS), severe sepsis syndrome or major burns whose admission to the ICU is not questioned.<sup>2,3</sup>

Why then are intensive care specialists usually so reluctant to offer intensive care to hematologic patients?

On one hand, hematologists often tend to overestimate the chances of survival of their patients, especially when severe complications develop during induction, consolidation or second-line chemotherapy of acute leukemia patients for whom complete disease remission is still foreseen or when they develop after bone marrow transplant has cured the patient. On the other hand, the net gain in terms of long-term survival offered by the more aggressive chemotherapy regimes available has probably not been shared in detail with intensive care specialists who still consider the overall prognosis of cancer patients very poor. Moreover, criteria for selecting hematologic patients who will most benefit from intensive care management have not been clearly established and this leaves the decision of offering intensive care largely to subjective judge-

ment rather than to established protocols. Finally, hematologic patients admitted to the ICU require a large amount of work on the part of the critical care team and high costs with little gain because of the high mortality rates, a scenario which too often discourages transfer of patients to the ICU.

It is our belief that hematologists and intensive care specialists should work more closely together in order to evaluate candidates for intensive treatment before irreversible organ failure develops: patients with good performance status and high likelihood of complete hematologic remission should be followed conjunctly and the optimal timing for ICU transfer be defined on the basis of both hematologic and physiopathologic parameters.

An overview of the more frequent complications requiring admission to the ICU and of the established predictors of mortality for hematologic patients admitted to the ICU is presented. The need for early, reproducible, prognostic factors tailored on the hematologic patients who are candidates for intensive care management and close collaboration between intensive care specialists and hematologists in evaluating candidates for intensive care before development of irreversible organ failure is stressed.

### Main causes for ICU admission

In some settings, administration of the first cycle of chemotherapy may lead to complications necessitating admission to a medical ICU. Presence of bulky disease, as seen in a subset of patients with lymphomas or in leukemic patients who present with rapidly rising or very high blast counts, can give rise to a severe metabolic imbalance with possible development of acute renal failure. Rapid lysis of neoplastic cells can acutely precipitate a number of serious metabolic derangements secondary to release of intracellular phosphate, potassium and urate with resulting hyperuricemia, hyperkalemia and hyperphosphatemia. This so-called tumor lysis syndrome is characterized by clinical features directly related to the above mentioned metabolic derangements: hyperuricemia gives rise to urate nephropathy and secondary acute renal failure; hyperkalemia is associated with potentially fatal cardiac arrhythmias; and hyperphosphatemia can cause reciprocal depression of serum calcium levels and progressive renal insufficiency, with further reduction of potassium and phosphate excretion. The hypocalcemia in turn can cause tetany, cardiac arrhythmias and muscle cramps. In spite of adequate supportive measures – e.g. fluids and electrolyte administration – cardiac and renal impairment may require intensive care and monitoring which are best provided by transient transfer of patients to the ICU.

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Pulmonary leukostasis is a serious potential problem for patients who present with a blast count of  $>50,000/\text{mm}^3$ . In this setting, leukocyte thrombi and plugging of pulmonary microvasculature may result in vascular rupture and infiltration of the lung parenchyma by leukemic blast cells. Development of hypercapnia, hypoxemia and progressive respiratory acidosis portends a very poor prognosis, despite intensive efforts to lower rapidly the blast count and the institution of ventilatory support.

As already mentioned, cardiovascular abnormalities are often due to metabolic and electrolyte derangements, and impaired pulmonary function. However, chemotherapy-related toxicities are responsible for most of the cardiovascular problems in hematologic patients. Although long-term anthracycline cardiotoxicity is dose-related and therefore easily avoided, acute toxicity – in the form of infusion-related arrhythmias and development of pericardial effusions – is well recognized and not predictable on the basis of the patient's characteristics at the time of chemotherapy administration. Moreover, anthracyclines exacerbate the cardiotoxic effect of other anti-neoplastic drugs (e.g. cytoxin) and of concomitant metabolic disturbances.

Infectious episodes, occurring during the chemotherapy-related neutropenic phase or because of underlying disease-related immunosuppression, are by far the major source of potentially ominous complications in hematologic patients. The severity and duration of immunosuppression vary according to the hematologic diagnosis, disease stage and type of therapy instituted.

As a general rule, various degrees of immunodeficiency are common in hematologic patients; impairment of humoral immunity is a characteristic feature of non-Hodgkin's lymphomas, multiple myeloma and after BMT; cell-mediated immunity is depressed in Hodgkin's lymphoma, B-cell-CLL and in all patients receiving immunosuppressive therapies. The newly introduced treatment protocols comprising monoclonal antibodies, which significantly increase the severity and duration of immunosuppression, produce an increased risk of opportunistic infections.

Chemotherapy-related severe and often prolonged neutropenia is frequently observed in hematologic patients and is a major source of both morbidity and mortality resulting from infectious complications of diverse etiologies. Patients diagnosed with acute leukemias are especially prone to the development of infectious fever of bacterial, fungal and less frequently viral origin: it is estimated that infectious fever develops in approximately 90% of cases during the chemotherapy-induced neutropenia. Most frequently cultured pathogens are *Enterobacteriaceae*, *Pseudomonas* species, and Gram-positive cocci. Most cases of sepsis during neutropenia are secondary to passage of bacteria from the gastrointestinal tract to blood because of chemotherapy-

related damage of mucosal barriers; most cases of pneumonia are due to colonization of the lower respiratory tract by pathogens present in the upper respiratory tract. Moreover, *Enterobacteriaceae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Candida* species colonize the upper digestive tract and in 90% of patients with Gram-negative pneumonia the same bacteria are present in the oropharynx.

In recent years, management of infectious bacterial complications arising in cancer patients has improved substantially: in the recent EORTC trial of empirical antimicrobial therapy, the reported 30-day mortality rates from any cause in patients with Gram-negative and Gram-positive bacteremia were as low as 10% and 6%, respectively.<sup>4</sup> Approximately 10% of patients are hypotensive at the time the first positive blood culture is obtained; septic shock, usually related to Gram-negative or polymicrobial bacteremias and evidenced by presence of hypotension, is normally associated with increased mortality<sup>5</sup> and frequently necessitates ICU admission.

Mycoses, and above all filamentous fungi infections, are critical infections in neutropenic hematologic patients, and are associated with high mortality in acute leukemia (40%) and in bone marrow recipients affected by graft-versus-host disease ( $>80\%$ ).<sup>6,7</sup> The lung is primarily involved and widespread involvement of the lung parenchyma by the invading fungus can cause acute respiratory failure; the fungus can also cause septic emboli which may disseminate all over the body, especially to the brain resulting in neurologic symptoms of varying severity up to coma.

The lung is one of the organs most severely affected by infectious complications ( $>90\%$ ) in neutropenic patients. Particular anatomic characteristics render the lung parenchyma highly susceptible to infections because pathogenic agents are allowed to reach the lung very easily through the airways and/or vascular bed and large numbers of these pathogens can accumulate in the parenchyma. The clinical outcome is determined not only by the characteristic of the pathogens (i.e. multiresistant or not) but also by interactions with polymorphonuclear cells, macrophages, lymphocytes and pulmonary cells which, by generating a wide spectrum of cytokines due to inflammatory/ immunologic reactions, are responsible for the clinical effects in response to infections, such as *Pneumocystis carinii* and cytomegalovirus infections.<sup>8</sup> Usually, the major causes prompting admission to ICU are pneumonia, septic shock and visceral failure. Infection is almost always present and responsible for septic shock, which affects 10-15% of hematologic patients admitted to the ICU.<sup>9,2</sup> Most cases of pneumonia are due to sepsis (pneumonia or septicemia); mechanical ventilation is required in 50% of ICU patients. The major complications while in the ICU are respiratory, haemodynamic and renal failure; hemodialysis for sepsis-relat-

ed anuria is performed in 15% of case.<sup>9,10</sup>

Multi-organ system failure requiring multiple life support techniques is present in approximately 20% of patients; it is often difficult to determine whether these visceral failures are due to the initial disease or to nosocomial complications.<sup>2,9,11</sup>

### **Risk factors for hematologic patients**

At the time of evaluating candidates for intensive care, both hematologic and physiopathologic parameters need to be taken into account. Unfortunately, as of now, the contributions of the underlying malignancy and acute organ failures to the outcome of neutropenic, immunodepressed hematologic patients have not been clearly defined. Several retrospective studies have tried to evaluate the impact of the patient's characteristics (e.g. age, sex) and those of the disease (primary diagnosis, disease stage, type of and response to treatment) on overall ICU and in-hospital mortality. A poor prognosis may be associated with increasing age<sup>12,13</sup> and relapsed or unresponsive malignancy,<sup>1,12,14-15</sup> which are risk factors also associated with fungal infections, often non-responsive to antifungal therapy; respiratory failure is usually the main cause for ICU admission in these patients. On the other hand, none of these features proved to be of any prognostic significance in other studies.<sup>2,10-11</sup>

Moreover, hematologic parameters may not be adequately evaluable at the time of the complication requiring intensive care ensues. For example, for patients on induction therapy or first line salvage therapy, tumor chemoresistance, a major determinant of response to therapy and of outcome, cannot be evaluated at the time when a severe complication, amenable to intensive care, develops.

Intensive care specialists too often base their judgment of eligibility of patients for ICU transfer on the prognosis of the underlying hematologic condition. Unfortunately, estimates of outcome are not so clear cut in many cancer patients and no single clinical feature (e.g. age, primary diagnosis, disease stage) or diagnostic parameter (e.g. cytogenetics, blast count) by itself is predictive of short-term outcome. Therefore, as far as concerns the hematologist's contribution to the decision about candidates for intensive care and monitoring, the decision still needs to be tailored on the individual patient's characteristics, independent by of predetermined cut-off parameters which are not yet available.

In this setting, the second set of parameters (i.e. presence of organ failures) may help to identify patients who may be eligible for intensive care. Blot *et al.*<sup>10</sup> attempted to determine factors predicting the outcome of a stay in an ICU before the patients were referred to such a unit, rather than evaluating them retrospectively. Several factors were recorded at ICU admission; none of the prognostic factors was related to any characteristics of the underlying malignancy,

while the number of organ failures at the time of admission proved to be the only relevant prognostic indicator of outcome. Although in many retrospective studies the need for mechanical ventilation was a strong predictor of poor outcome,<sup>9,14</sup> in a study by Brunet *et al.*<sup>2</sup> the etiology and initial severity of lung injury did not appear to carry prognostic relevance.

Other factors have been associated with poor short-term outcome including hypotension, administration of inotropes or vasopressors, and increased number of failed organs. Finally, time to ventilation and time to admission to ICU are also negative predictive factors.<sup>14</sup>

Among cancer patients admitted to the ICU, neutropenic patients have the worst prognosis<sup>16,17</sup> with a mortality rate as high as 70% to 80% in some series.<sup>10,18</sup> In hematologic patients neutropenia was previously shown to be associated with a poorer prognosis than that noted in the treatment of solid tumors, because this former neutropenia is usually more severe and lasts longer.<sup>19,20</sup>

In a recent paper by Blot *et al.*<sup>10</sup> the prognosis of neutropenic patients in an ICU is clearly independent of the type and progression of cancer, and depends only on the presence, nature and number of acute organ failures; among them the presence of respiratory failure was the strongest predictor of death. Granulocytopenia at admission turned out not to be of prognostic significance, but absence of leukocyte recovery is a prognostically bad sign.<sup>21</sup>

### **Outcome**

The reported overall mortality in hematologic patients admitted to ICU varies from 32% to 61% with an increase in mortality rate up to 80% in those with respiratory failure.<sup>14</sup> High mortality (>60%) is present also in patients who need hemodialysis.<sup>9</sup> The median duration of survival following discharge from hospital is in the region of 12-23 months, but a few patients survive much longer, a some must be presumed cured of cancer; their quality of life is good.<sup>14</sup>

In recent years short-term mortality after ICU transfer of patients with hematologic malignancies has improved. Several factors may account for these encouraging results: better selection of patients and infection prophylaxis, use of hematopoietic growth factors to shorten the duration of neutropenia, earlier recognition and optimized management of organ failures while the patient is still in the hematology ward may all be viewed as measures able to influence the outcome of these critically ill patients positively.

### **Conclusions**

Over the years hematologists have had to broaden their clinical knowledge in order to manage complications arising from the introduction of more aggressive chemotherapy protocols. Anthracycline toxicity

has been recognized and ways to assess and monitor cardiac dysfunction early have been adopted from cardiologists. Close collaboration with nephrologists has resulted in optimal prevention and treatment of acute renal failure secondary to tumor lysis, hypercalcemia and paraproteinemia. Protocols for the prevention and treatment of infectious complications have been established and have greatly reduced morbidity and mortality secondary to neutropenia-related infections. Nevertheless, both the severity of the underlying hematologic condition (especially acute leukemias and immunosuppression secondary to bone marrow transplant) and the prolonged cytopenias that result from the more aggressive chemotherapy protocols often employed to obtain long-lasting remissions expose hematologic patients to a number of potentially life-threatening complications: it is these for complex and multidisciplinary problems that often necessitate consideration for intensive care management.

To date, in spite of the large body of published studies specifically addressing this issue, there does not appear to be any single factor that allows selection of those patients who would best benefit from intensive care.<sup>2</sup> This low impact of the hematologic condition on ICU survival may be due to a bias in the selection of patients admitted to the ICU: most likely, patients with unresponsive malignancies, older patients with substantial comorbidities undermining both survival and chances of response to chemotherapy, patients with acute onset organ failure and rapid deterioration of vital organ functions were not even evaluated for ICU transfer. Indeed, as Groeger said: «...in the near future, it may become necessary to demonstrate that certain types of health care services are worth the cost. Subjective value judgements may be required, but treatment or care that is costly and is deemed to be of marginal benefit may not be routinely available. Medical professionals need to provide guidance and leadership for cancer patients and their families when considering admission to the ICU».<sup>1</sup>

It is in this prospective that closer collaboration between hematologists and intensive care specialists becomes mandatory: a common ground based on both hematologic and physiopathologic parameters needs to be found in order to identify patients whose vital organ function is deteriorating and needs closer monitoring and more aggressive support measures while the patient is still in the hematology ward. Consideration for ICU transfer would then be made on sounder grounds. Simple measures can also be implemented in a hematology ward: in patients with incipient organ failures, increasingly frequent monitoring of blood pressure, pulse, urine output, respiratory rate, blood gases, and blood chemistry profile can be implemented and evaluated in collaboration with the intensive care specialists allow optimal timing for ICU transfer.

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## Intensive care unit admission for patients with hematologic malignancies: beyond emotions

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In recent years, the appropriately aggressive treatment of patients suffering from hematologic malignancies (HM) has markedly improved both the patients' prognosis and their life expectancy.<sup>1</sup>

This treatment, however, may be associated with severe and life-threatening therapy-related complications.<sup>2</sup> Since many of these acute events are potentially reversible and chemotherapy may improve the patients' prognosis overall, admission to the intensive care unit (ICU) to treat critical conditions or life-threatening organ dysfunctions may be appropriate.<sup>2,3</sup>

HM patients suffering from acute organ dysfunction and in a critical condition requiring admission to the ICU<sup>2,4</sup> are usually considered to have poor short-term and long-term survival.

This assumption is largely derived from studies carried out in the late 1980s which reported a short-term mortality rate in the range of 70-80% for hematologic patients admitted to the ICU for different life-threatening conditions, such as critical hypotension needing vasopressors, acute renal and hepatic failure, and acute respiratory failure needing mechanical ventilation (MV). Mortality rate figures were even worse in bone marrow (BM) recipients who required MV: in this subset of critically ill patients, short-term mortality was reported to be as high as 85%.<sup>2,5</sup> In 1989, commenting on mortality in MV patients undergoing bone marrow transplantation, an editorial view by Carlon ended with a lapidary: «Just say no» when asked for ICU admission.<sup>6</sup> Based on this early literature, in many hospitals, cancer patients and particularly HM patients, because of their assumed dismal prognosis, are frequently not considered suitable candidates for ICU admission and intensive care therapies.<sup>3,5</sup>

However, recent European and US published series show a rather different picture, with progressive over time improvement of the prognosis for hematologic patients admitted to the ICU.<sup>7-9,13</sup> Rubinfeld *et al.*<sup>10</sup> found an increased survival rate from 5% to 16% in the period between 1988 and 1992 in allogeneic BMT recipients requiring MV. Azoulay *et al.* found a ten-fold lower risk of death in patients with multiple myeloma who required ICU support between 1996 and 1998 as compared to those in the period 1992-1995.<sup>11</sup> The same group reported a four-fold lower risk of death in can-

cer patients who required MV between 1996 and 1998 as compared to those in the period 1990-1995.<sup>12</sup>

Better patient selection, new insights in hematologic treatment, optimization of failing organ management and specifically the use of non-invasive ventilation (NIMV) have been quoted as the most probable reasons for this net improvement in results.<sup>8,9,12</sup>

This improved hematologic and intensive care management of patients, leading to improved survival rates, compels re-evaluation of the eligibility of hematologic patients for admission to the ICU: ideally, the admission criteria should be the same in patients with malignancy (solid or hematologic) as in patients with severe congestive heart failure, acute pancreatitis, severe burns, cirrhosis, chronic obstructive pulmonary disease (COPD) with acute respiratory failure due to pneumonia, and acute renal failure requiring continuous renal replacement therapy (CRRT), all conditions long recognized to be at high risk of mortality but rarely under contention as far as concerns ICU admission.<sup>9</sup>

The decision to admit cancer patients to the ICU is often complex. Specific, prospectively validated tools (such as the severity of illness scoring systems - APACHE II, APACHE III, SAPS II, OSF or SOFA) since long used to assist ICU physicians in estimating patient's survival do not seem to be suitable as such for cancer patient evaluation. In this specific subset of patients, they have been shown to grossly correlate with outcome but their accuracy is not such to be confidently used for decision making, especially when decisions about an individual patient need to be taken.<sup>5,7,8,15,18,19</sup>

Very recently, Benoit *et al.*<sup>9</sup> suggested that urea levels, leukopenia, need for vasopressors and presence of bacterial infection may represent more reliable prognostic indicators than the APACHE II and SAPS II scores in discriminating future survivors from non-survivors at the time of admission to the ICU. Their results confirm the limited use of the available scoring system for the assessment of prognosis in critically ill hematologic patients and underline the need for developing and validating alternative scoring systems specifically designed for this patient population and easily applicable at the bedside.

A different way of using available scoring systems was presented by Guiguet *et al.*<sup>16</sup> They proposed a so-called *multiple assessment* of the severity scores (SAPS II and OSF), with assessment of the scores on admission and reassessment 48-72 hours after ICU admission. This new modality of assessment could provide information

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in neutropenic patients, allowing the patients to be allocated into homogeneous subgroups according to risk of mortality.<sup>16</sup>

In Guiguet's series, the mean number of acute organ system failures decreased in survivors over the first 72 hours. In contrast, no changes or worsening in the patient's profile was associated with a deteriorating prognosis. The pattern of change in the scores between ICU admission and 72 hours later was also considered of value for assessing a patient's chance of recovery.<sup>16</sup> In this setting, life-support measures can be offered to all patients for whom the approach is indicated, a new assessment being performed on day 3 or 4; in the author's opinion the «*aggressive treatment can be reasonably withdrawn if the number of OSFs has not decreased or is more than 3 on the third day in ICU*».<sup>16</sup>

A similar approach has been proposed by Rubenfeld and Crawford for BM recipients undergoing MV<sup>17</sup> and by Blot *et al.* in febrile neutropenic patients<sup>19</sup> evaluated while still in the hematology ward.

Persistently high ICU mortality rates render admission policies a critical point of discussion: both excessive obstructionism to admission (the *just say no* policy) and emotional, aggressive but useless consumption of resources (so-called *futile treatment*) need to be avoided.

For HM patients becoming critically ill or frankly unstable during their clinical course, directives for intensive caring in the hematology ward must be developed:<sup>19</sup> early, close physiological monitoring of critical patients, more aggressive treatment of potentially but not yet *full blown* failing organs, frequent consultation with the ICU specialists and reassessment should become everyday practice. The time has come for a high dependency unit within the hematology ward, a sort of *step-up unit*, where semi-invasive monitoring and treatments such as NIMV are available. Early treatment of the unstable HM patient in this semi-intensive unit should precede (and sometimes, eventually, avoid) admission to the ICU. Implementation of such directives (locally developed, with a daily assessment of score systems as suggested by Guiguet *et al.*,<sup>16</sup> Rubenfeld<sup>17</sup> and Blot *et al.*<sup>19</sup>) might become a valuable tool to standardize a correct approach to the acute HM patient.

While the optimal timing for ICU referral has yet to be defined, it might be effectively preceded by efforts to reverse initial organ failures while the patient is still on the hematology ward.<sup>19</sup>

As underlined before, proper indications for ICU admission of HM patients rely upon both physiologic and hematologic parameters.

In a recent study, Massion *et al.* were able to demonstrate that severity of the underlying hematologic malignancy does not influence ICU or hospital mortality, the short-term prognosis (mainly

hospital mortality) being exclusively predicted by acute organ failures, aggressiveness of pathogens (fungi) and transplant status.<sup>2</sup>

Among risk factors able to influence short and long term prognosis in hematologic patients, neutropenia is under great debate and the importance of leukopenia per se as a risk factor for mortality is controversial. Many studies have reported a higher mortality in patients with (prolonged) neutropenia, particularly when mechanically ventilated; however, this has not been confirmed by other studies.<sup>2</sup> In Benoit's study,<sup>9</sup> leukopenia on admission, which was in most cases chemotherapy-related, was an independent risk factor for adverse outcome. However, the higher mortality in this subgroup of patients was not related to the duration of leukopenia before or during ICU admission.<sup>9</sup>

A good selection of patients likely to benefit from ICU admission seems to have played, at least in part, a role in the relatively good outcomes reported in the most recent studies.<sup>2,8,9,11,12</sup> Admission criteria should be discussed and shared between primary care physicians (the hematologist) and the intensive care specialists, keeping two milestones in mind.

First, admission to the ICU must be considered only for patients who have a potential long-term survival or a treatable relapse.<sup>9</sup> This same policy was proposed by Massion *et al.*,<sup>2</sup> Guiguet *et al.*<sup>16</sup> and Rubenfeld and Crawford<sup>17</sup> whose admission criteria were life expectancy exceeding 6 months or, in the case of progressive disease, chemotherapy expected to allow partial or complete remission. The proper definition of this item is the total responsibility of the hematologist.

Second, the criteria to ask for an ICU consultation (e.g. simple *preemptive consultation*, use of NIMV in the ward or call for urgent admission) must be very clearly planned (*CCM guidelines, Crit Care Med, 1999*) discussed, shared and implemented. Since the consultation is requested by the hematologist, the call must be neither too early (useless) nor too late (futile). Directions to orient the care of HM patients whose clinical course worsens and for whom ICU consultation is warranted need to be implemented as cornerstones of the program of quality of care.<sup>19</sup> An earlier referral to the ICU during the evolution of the critical illness and advanced ICU management could reduce the number of failing organs or preserve these patients from intractable or irreversible organ failure (severe hemodynamic, respiratory, neurologic impairment). As reported in several studies, multiple organ failure and the combined need for ventilation and renal replacement therapy have a profound adverse effect on survival in both the general ICU population and HM patients.<sup>19</sup>

Reductions in morbidity and mortality in critically ill HM patients administered intensive care

treatments may be the result of two more factors: on the one hand, the very early detection of worsening clinical conditions, as assessed by daily evaluation of OSF score;<sup>19</sup> on the other, better tuning and tailoring of the supportive care. These could be the rationales for early non-invasive monitoring or the application of NIMV while in the ward (or, better still, in a high dependency unit), or admission to the intensive care setting in a *quasi* preemptive treatment. As emphasized by Benoit *et al.*,<sup>9</sup> commenting on their very recent crude ICU and in-hospital mortality rates of 42% and 54%, «*the reluctance to admit patients with hematologic malignancy to the ICU may be unjustified*». This, in spite of the severity of their population of patients, as suggested by the length of stay, the high prevalence of ventilation and its long duration, the use of vasopressors, and the need for renal replacement therapy during ICU stay. Using a well-planned ICU admission policy and providing advanced and in some cases prolonged supportive care to these patients, Benoit *et al.* were able to achieve a 6-month survival that was better than the 6-month survival of 20% observed in a general ICU population in the same institution with acute renal failure who needed renal replacement therapy.<sup>9</sup> ICU management cannot be routinely considered futile in critically ill HM patients.<sup>13</sup> According to the results recently proposed by Azoulay in HM patients with acute respiratory failure undergoing NIMV, «*improvements in ICU treatments and onco-hematologic management have stripped classic predictors of ICU mortality of much of their value*».<sup>13</sup> As proposed by Groeger<sup>7</sup> commenting on Benoit's study, the old statement made by Carlon<sup>6</sup> could be rewritten as *Consider saying yes*.

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## Intensive care unit admission in patients with hematologic diseases

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Recent therapeutic developments have significantly contributed to the increase in successful treatment of patients with hematologic malignancies (HM).<sup>1</sup> Such patients form a growing number of severely immunocompromised subjects, exposed to life-threatening infectious complications, which contribute substantially to the mortality associated with this condition.<sup>2</sup>

Most of these complications require admission to the Intensive Care Unit (ICU) and can require tracheal intubation and mechanical ventilation (MV).

Unfortunately in neutropenic patients this approach is associated with significant morbidity and mortality, with in-hospital mortality rates as high as 90 to 97%.<sup>3</sup> According to recent data, the need for MV was a strong predictive factor of mortality both in the univariate and multivariate analyses in a population of patients with HM (with an odd's ratio = 28.4), confirming this variable as the most important determinant of mortality.<sup>4</sup>

Evison *et al.* showed that the presence of multiple organ failure, in particular sepsis with cardiovascular failure requiring vasopressors, respiratory failure requiring MV, and renal failure requiring hemodialysis, is associated with a mortality rate as high as 90% in patients with HM.<sup>5</sup>

The prognosis in these patients correlates well with the severity of the disease as indicated by the SAPS II score and/or APACHE score: SAPS II values at admission higher than 50 are associated with a survival rate lower than 10%.<sup>6</sup>

The outcome in this population of patients is uniformly poor: decisions about ICU admission (and particularly institution of MV) must be made taking into consideration the dismal prognosis of these patients.

In this context it is clear that although every effort is mandatory in order to try to decrease the mortality rate so far observed, a more titrated approach to this population of patients is also necessary in order to avoid futile treatments.

### Personal experience

In a 5-year period (1998-2002) 34 patients with HM were admitted to the general ICU of Ospedale Niguarda Milan for acute, severe (multi-) organ failure; all required tracheal intubation and MV.

The main clinical characteristics (hematologic disease, primary diagnosis and reason for ICU admission, SAPS II value at admission, age, outcome, duration of stay in ICU) are reported in Table 1.

The distribution of the patients according to the primary hematologic disease and final ICU outcome is reported in Table 2.

The overall ICU mortality was 26/34 (76,5%); 12 patients out of 12 with a diagnosis of septic shock and 13 patients out of 15 with a diagnosis of acute respiratory distress syndrome (ARDS) died; the mean SAPS II value in this group of patients was 64±15. Only 2 patients with ARDS survived. In the survivor group, the mean SAPS II value was significantly lower, 37±11; the diagnoses at admission are reported in Table 3.

Twenty-seven patients were admitted because of either acute respiratory failure (ARF=ARDS) or severe sepsis or septic shock (SS); among these patients the mortality was 25/27 (92.6%). Seven patients were admitted with less severe disease, for miscellaneous reasons, including pulmonary edema, neurologic disturbances, post-operative monitoring, hypovolemic shock, diagnostic procedures (broncho alveolar lavage): none of these patients died.

The number of deaths in the more severely ill patients was higher than expected (26 versus 20.5, with a ratio of 1.27) according to the predicted risk of death in ICU as estimated by the SAPS II scoring system. It is worth noting that among other populations of patients with comparable severity of SAPS II values, but different diagnoses (ARDS, septic shock, severe burns, multiple organ failure), the observed mortality rate is much closer to the expected one (ratio 1.05), suggesting that in patients with HM (and in general in patients with cancer) the severity scores are not accurate enough to be used in the routine management and that the underlying disease may play a more relevant role.<sup>7</sup>

In a substantial proportion (61%) of non-survivors, the duration of stay in ICU was less than 72 hours: this can be interpreted as admission being *too late*, thus emphasizing the need for a more aggressive approach to these patients.

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**Table 1. Characteristics of the patients.**

<i>Year</i>	<i>No.</i>	<i>Hematologic</i>	<i>SAPSII score</i>	<i>ICU admission</i>	<i>Age (years)</i>	<i>Outcome</i>	<i>Time spent in ICU (days)</i>
1998	1	ALL	66	Septic shock	70	D	2
	2	NHL	29	Hypov. shock	66	S	2
	3	AML	69	ARDS	40	D	55
	4	CML	59	Septic shock	55	D	5
	5	Plasma cell	27	Monitoring	48	S	1
	6	NHL	68	ARDS	71	D	20
1999	7	CLL	43	Pulmonary edema	74	S	9
	8	NHL	64	ARDS	20	D	3
	9	NHL	74	ARDS	72	D	5
	10	AML	67	ARDS	61	D	7
	11	CLL	58	ARDS	64	D	4
	12	NHL	47	Septic shock	37	D	2
	13	ALL	40	Pulmonary edema	68	S	7
2000	14	AML	n. a.	Cerebr hemorrhage	6	D	1
	15	Bone marrow aplasia	58	Septic shock	56	D	11
	16	NHL	35	Monitor	50	S	2
	17	NHL	68	ARDS	58	D	2
	18	NHL	66	Septic shock	67	D	1
	19	Multiple myeloma	48	ARDS	69	S	15
	20	HSCT	61	Septic shock	32	D	14
	21	CML	63	Septic shock	64	D	5
2001	22	HSCT	44	ARDS	59	D	29
	23	AML	65	Septic shock	64	D	1
	24	HSCT	36	ARDS	32	S	15
	25	HSCT	58	Septic shock	27	D	1
	26	AML	59	Septic shock	49	D	1
	27	AML	71	Septic shock	40	D	2
	28	Multiple myeloma	68	ARDS	75	D	4
	29	HSCT	73	Septic shock	45	D	7
2002	30	NHL	73	ARDS	71	D	4
	31	ALL	63	ARDS	56	D	12
	32	NHL	41	Pulmonary edema	70	S	7
	33	HSCT	64	ARDS	46	D	3
	34	HSCT	74	ARDS	30	D	2

SAPS II: Simplified Acute Physiologic Score II; D: deceased; S: survived; n.a.: not applicable (age).

NHL: non-Hodgkin's lymphoma; AML: acute myeloid leukemia; CML: chronic myeloid leukemia; ALL: acute lymphoblastic leukemia; CLL: chronic lymphocytic leukemia; HSCT: hemopoietic stem cell transplantation; Plasma cell L: plasmacell leukemia.

**Table 2. Distribution of patients for hematologic disease and outcome.**

<i>Hematologic disease</i>	<i>No.</i>	<i>Survivors</i>	<i>Non survivors</i>
ALL	3	1	2
n-H LYMP	10	3	7
AML	6	0	6
CML	2	0	2
CLL	2	1	1
Bone marrow aplasia	1	0	1
Multiple myeloma	2	1	1
HSCT	7	1	6
Plasma-cell L	1	1	0

**Table 3. Diagnosis at ICU admission among survivor and non survivor patients with HM.**

<i>Diagnosis</i>	<i>Total</i>	<i>Non survivors</i>	<i>Survivors</i>
ARDS	15	13	2
Septic shock	12	12	0
Cerebral hemorrhage	1	1	0
Monitoring post-operative	2	0	2
Congestive heart failure	3	0	3
Hypovolemic shock	1	0	1
Total	34	26	8
SAPS II		64±15	37±11

## Discussion

Our data are consistent with those reported in the literature. Hilbert reported on 52 patients with HM, 32 of whom intubated for ARF, with an ICU mortality rate higher than 87% (all intubated patients died).<sup>8</sup> Raño reported, in a study of non-HIV immunocompromised patients, 105 cases of HM+HSCT, with 55 patients submitted to MV and a mortality rate, in this subgroup, higher than 90%.

In this series, the multivariate analysis shows that the factors associated with mortality were the need for MV, the severity of illness, and a delay longer than 5 days in establishing a specific diagnosis.<sup>4</sup>

Price reported on 115 patients with HSCT, 48 of whom underwent intubation and MV with a mortality as high as 83%. Among non-intubated

patients, the mortality rate was 34%. An infectious complication was one of the major determinants of poor outcome.<sup>9</sup>

Ewing reported on 89 patients treated over a 10-year period with an overall ICU mortality rate of 79%, and as high as 90% among HSCT patients treated with MV. Evison reported on 48 critically ill patients with HM, 42 with either ARDS or septic shock, treated with MV, and 38 deaths.<sup>2</sup>

Despite this discouraging context, some favorable points can be picked out. Some reports have suggested that the prognosis of these patients might be improving, especially within certain groups of immunocompromised patients; new molecular diagnostic techniques, more effective prophylactic treatments, and reduced toxicity of conditioning regimens might be contributing to this improvement in prognosis.<sup>1,3,10</sup>

Critical care medicine may also give its contribution: in selected immunocompromised patients with pneumonia and acute respiratory failure, early initiation of non-invasive ventilation (NIMV) is associated with a significant reduction in the rates of endotracheal intubation and serious complications and an improved likelihood of survival to hospital discharge. Hilbert was able to use NIMV (CPAP) to manage 16 out of 64 patients with HM and ARF: all patients survived, whereas only 4 out of the 48 intubated patients left the ICU. The latter had significantly higher SAPS II scores than those who were treated with NIMV so it is possible that the less severe degree of illness allowed less invasive treatment with favourable results. This approach was used as a way to improve gas exchange, reduce the work of breathing and avoid MV, with its detrimental effects on pulmonary function.<sup>8</sup>

CPAP and NIMV have been used successfully for years to correct refractory hypoxemia in various clinical conditions<sup>11</sup> and may also prove useful in (selected) patients with HM.<sup>8</sup> It has also been shown that prognosis in patients with HM, respiratory failure and pulmonary infiltrates can be significantly improved by achieving an earlier diagnosis of the infectious etiology of the disease, thus allowing quicker and more appropriate therapy.<sup>4</sup>

The diagnostic procedures, within the first 24 to 48 hours after the identification of the pulmonary infiltrate, include blood samples for hemocultures and antigen testing, sputum samples and Gram stain, samples of nasopharyngeal washes for tissue culture, bronchial aspirate, bronchoalveolar lavage, protected-specimen brush and, in selected cases, transbronchial and open lung biopsy.

The combination of early diagnosis and non-invasive respiratory treatment may result in a substantial improvement of the outcome.

In a recent study it was observed that patients

who develop ARF and severe sepsis during chemotherapy, but who are expected to have an increase in granulocyte counts within days, have a surprisingly good prognosis. The authors suggest that such patients should, therefore, be admitted to the ICU and treated aggressively.<sup>12</sup>

In general there is growing evidence that many of the complications observed in patients with HM are the result of a systemic inflammatory disorder that has escaped biological control, such as the inflammatory process begun by the preparative regimen (particularly in HSCT) and perhaps added to by intercurrent infections, tumor cell death and other as yet unidentified stimuli. If this is true, this syndrome has many similarities with the multiple organ dysfunction syndrome (MODS) seen in critically ill non-HM, non-HSCT patients.

This hypothesis has 2 main corollaries, 1) looking for or empirically treating a reversible, organ-specific cause of single organ dysfunction (such as infectious pneumonia, intracranial hemorrhage), is unlikely to be rewarding as the defect causing the organ dysfunction is often systemic at the time of its presentation, and 2) that MODS is the toxic limit of the preparative regimens, suggesting that a better understanding of pathophysiology and the development of therapies for MODS will allow the intensity of these regimens to be intensified, thus curing more patients of their malignancy. For instance, manipulation of the hemostatic system may prove to be one of these therapies, but there is little doubt that other interventions designed to modulate the inflammatory process will prove to be even more useful in these cases.<sup>13</sup>

The above considerations emphasize the necessity of an increasingly closer and closer relationship between the primary physician, the hematologist, and those involved in the care of HM patients when severe complications ensue: this approach may help in the selection of patients who need aggressive, full therapy and avoid futile treatment when the prognosis is exceedingly poor.

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## Intensive care for hematopoietic stem cell transplant recipients: futile or mandatory option?

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Life-threatening complications requiring intensive care (IC) in hematopoietic stem cell transplant (HSCT) recipients must be discussed separately from those in patients with other hematologic conditions (such as acute leukemia patients in induction chemotherapy) for two main reasons:

- Transplantation establishes a different biological status.
- Recipients have undergone high dose radiochemotherapy for conditioning and consequences such as mucositis, the *cytokine storm*, and barrier damage are to be expected in addition to secondary effects of treatment on the liver, lung, heart and bladder;
- a more profound phase of aplasia is obviously expected;
- in the field of allogeneic transplantation, the immunologic relationship between donor and recipient and immunosuppressive therapy for tolerance induction lead to pathological patterns that are very rare or inexistent in non-transplant patients: veno-occlusive disease (VOD), graft failure, acute or chronic graft versus host disease (GVHD), viral reactivation, and idiopathic pneumonia syndromes (IPS).

Transplant is a very different *human condition* being an elective procedure.

In fact, for a patient in remission (sometimes with a life expectancy of years without transplantation), the decision to face the risks of a transplant in order to have a possibility of cure, produces a condition very different from that of a patient with acute leukemia undergoing induction chemotherapy.

I would like to stress the enormous responsibility that the medical and nursing team has in this situation to reduce transplant related mortality (TRM). Adequate equipment to minimize bacterial and fungal infections, and safe platelet support are mandatory, as is the possibility of early diagnosis of infections to allow for pre-emptive treatments. It is a general rule to pay particular attention to iatrogenic risks whenever performing any procedure (even a simple central line insertion) in a person doing well.

Obviously the relative importance of these conditions depends on transplant characteristics (autologous or allogeneic), disparity between donor and recipient (matched,

mismatched, related, unrelated, haploidentical), hematopoietic stem cell source (bone marrow, peripheral blood stem cells or cord blood). Reduced intensity transplantation shows an extensive, but delayed, pattern of complications.

The variable incidence of complications requiring ICU admission, reported by transplant Centers (7–40%) mainly reflects the characteristics of the transplants performed in the center and the age range of the patients subjected to the procedure. Moreover, the phase of transplant (early during transplantation, post-transplantation or after a relapse) in which the critical complication occurs, may require different approaches. At least in the first two conditions the intervention must be prompt and intensive (possibly even planned). On the other hand, when a relapse after transplantation has unfortunately occurred, intensive treatment must be evaluated in the context of a full prognostic judgement and not automatically undertaken. Certainly we still have to offer complete medical care to our patient but we must take a holistic view of the person we have in front of us when making choices.

A transplant patient is often a *critical* patient; however in this discussion we intend to limit *critical* to a patient who needs a period of intensive care to support one or more vital functions because of cardiac, respiratory, or renal failure or septic shock or neurologic complications.

Regarding infections, transplanted patients are similar to other immunosuppressed patients but clinical pictures are usually less confusing because specific complications tend to occur within well-defined time-periods; the time and intensity of cytoreductive therapies and the type of transplant, driving the immunorestitution, dictate these intervals. So clinical controls and diagnostic procedures can also be scheduled on this time-table.

Table 1 shows factors influencing the risk of a *critical* situation in the different phases of transplantation. The time-relation of the most frequent critical complications is illustrated in Figure 1.

### Clinical situations most frequently involved in intensive care admissions

- *Sepsis*. The clinical picture is similar to that of the well-known septic shock occurring in hematologic patients during aplasia. The prevalence of bacterial agents in such decontaminated patients with central lines is summarized in Figure 1: Gram positive, Gram negative and, then, later encapsulated bacteria. Fluid and sodium overload, frequent in early post-transplant days, may complicate the picture causing edematous syndromes,

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**Table 1. Factors influencing the risk of a critical situation, divided by transplant phases.**

Pre-transplant factors
Age
Focal infections but also donor and recipient serologic status for infections and recipient bacterial and fungal contamination with their eventual antibiotic resistance
Function of heart, liver, lung, kidney and gastrointestinal system
Degree of matching donor/recipient
Immunization of donor and recipient with particular attention to platelet refractoriness.
Psychological and social conditions severely interfering with treatment compliance (behavior or regular drug assumption)
Transplant-related factors
Foreseen aplasia (neutropenia, anemia, thrombocytopenia)
Severe combined immunosuppression (secondary to conditioning treatment and standard GVHD prophylaxis) and other eventual immunosuppressive prophylaxis (T-depletion, ATG, Campath-1) or therapy (steroids) for GVHD
Regimen-related toxicity on heart, liver, lung and barriers (skin and mucosae)
Graft failure and secondary cytopenia and additional immunosuppression
Acute GVHD and its treatment
Post-transplant factors
Immune reconstitution in presence of particular serologic pattern (such as HBV or HCV positivity)
Chronic GVHD, its treatment and infection risk (bacterial, fungal, viral)
Relapse

cardiac dysfunction or pleuropericarditis. Radiotherapy and cyclophosphamide may contribute to cardiovascular damage.

It must be noted that when respiratory failure requiring intubation is associated with septic shock, the reported mortality rate is very high: only 1% of intubated patients leave the ICU.<sup>1,2</sup>

In allogeneic transplantation the onset of acute GVHD, manifested with fever, rash, and tachycardia, may mimic infection and a differential diagnosis is required for targeted treatment.

- *The heart* may be a primary cause of requiring intensive care in up to 5% of patients: left heart failure, ischemic problems, pericardial tamponade but also myocarditis which may be infectious or toxic (conditioning or previous treatments with anthracyclines) may all occur.

- *Renal failure* requiring hemofiltration may follow

hypotension or liver failure, drug toxicity, and cyclosporine A (CSP-A) overdose. It seriously worsens the prognosis.

- *Gastrointestinal complications* by themselves rarely necessitate transferring a patient to the ICU (except for massive hemorrhage); however, they actively facilitate infectious problems and respiratory failure. Mucositis, esophagitis and enterocolitis lead to barrier damage increasing the risk of infections. Sedative drugs must be used cautiously in these patients because of risk of ingestion. Acute diarrhea can rapidly reduce absorption of life-saving drugs, (such as CSP-A), and is a risk for hyperacute flaring GVHD.

- *The liver* is a critical organ early after transplant not only as target for GVHD, but also for VOD, which may be a critical clinical picture or a more insidious syndrome complicating an impending critical situation. Liver decompensation may also follow viral reactivation or toxicity. Prevention and early treatment are crucial.

- *Graft failure* with its consequences (infections and viral reactivation because of neutropenia and immunosuppressive treatment) may trigger a critical condition.

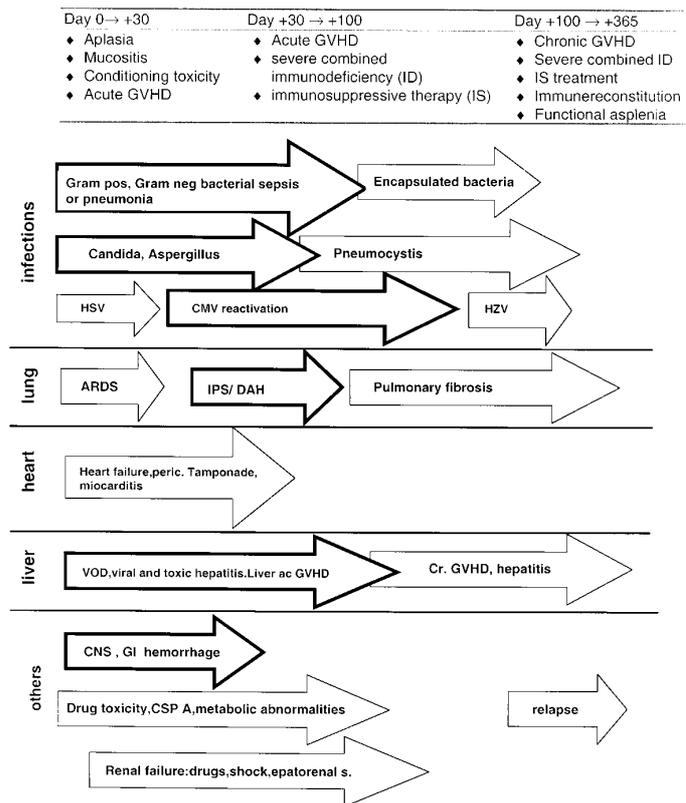
- Acute GVHD is a specific complication which may be severe. Later, chronic GVHD with its typical immunosuppressed status and required immunosuppressive treatment, classically increases bacterial, viral, and fungal infections even later in the history of a transplant. *Pneumocystis carinii* infections often require IC and neurotoxoplasmosis may be a reason for intensive support.

- *Relapse of neoplasm* may sometimes require IC (for example for hypercalcemia).

- *Respiratory distress* remains the most frequent indication for IC. Up to 50% of transplant patients are reported to have a lung complication at some time during the course of their transplant. Some of them become critically ill. Some lung complications are common to non-transplant patients, like pneumonia, invasive fungal infections and acute respiratory distress syndrome (ARDS, a severe acute lung complication related to radio-chemotherapy toxicity and sepsis).

Other clinical pictures are typical of the transplant patient and some of non-infectious complications have recently been better defined.

*Idiopathic pneumonia syndrome (IPS)*, according to the recommendations of the 1991 National Institutes of Health Workshop, is a clinical syndrome with «evidence of widespread alveolar injury in the absence of lower respiratory tract infection» after marrow transplantation.<sup>3</sup> The term *syndrome* is used to emphasize the inherent heterogeneity of the clinical expression and severity, histopathology and multiple, probably interacting, potential causes (conditioning, GVH immune reactions, unrecognized viral infections and inflammation related lung injury as in



**Figure 1. Time-relation of most frequent complication requiring ICU.**

endotoxemia and cytokine reactions).<sup>4,5</sup>

Chest radiography shows diffuse pulmonary infiltrates (intra-alveolar or interstitial); the clinical picture is one of non-specific fever, non-productive cough, and hypoxemia. Progression to respiratory failure is usually rapid with 69% of patients requiring mechanical ventilation within 2 days from the detection of infiltrates.

A recent study<sup>6</sup> by the Fred Hutchinson Cancer Research Center reviewing 1.165 transplants, found 85 cases of IPS (7.3%). The median onset was day +21 post-transplantation. Overall mortality was 74%. The diagnostic criteria are very selective: bronchoalveolar lavage (BAL) must be negative for infectious agents including PCR studies for cytomegalovirus, respiratory syncytial virus, influenza, parainfluenza and adenovirus. The BAL lymphokine pattern seems to be significant.<sup>7,8</sup> No proven effective treatment exists for IPS: high dose steroids have been used in addition to respiratory support.

*Diffuse alveolar hemorrhage (DAH)* is a variety of IPS with typical progressively bloody return from the BAL. DAH is often associated with mucositis, renal failure, and low platelet counts without signs of coagulopathy. The picture is diffuse alveolar damage in the presence of thrombocytopenia. The etiology is still cryptic and associated variables remain confusing. It appears more frequent in second trans-

plants and in patients who have had previous chemotherapy.<sup>9</sup>

The Minneapolis team<sup>10</sup> reported an incidence of DAH of 23/922 adult transplants (2.5%); the median onset was day +17 (range: 5-34), the mortality was 74%, and 21/23 patients required mechanical ventilation. High dose steroids (250-2000 mg daily dose) have provided some improvement and perhaps need to be continued for a week after resolution to avoid relapse.

Another severe lung complication (*de novo* or following IPS) is *lung fibrosis*, a syndrome of multifactorial origin requiring ICU and usually progressing to death.

The recently reported lower incidence of IPS has to be ascribed to a better diagnosis of infectious pneumonia (especially related to CMV and opportunistic pathogens), earlier treatment (pre-emptive therapy for CMV reactivation) and standard *Pneumocystis carinii* prophylaxis. Early antigenemia, PCR techniques and BAL are main steps; more invasive diagnostic procedures are usually not indicated in transplanted patients, nor indeed are they safe.

A useful flow-chart can be suggested, based on chest X-rays and time after transplantation.<sup>1</sup>

If infiltrates are diffuse, and early after transplant, edema syndromes must be first ruled out or treated (diuretics and/or prompt correction of hypoalbuminemia).

minemia), then an ARDS or IPS suspected. From transplant to day +30 multiple infiltrates do not usually have an infectious origin, but may be rapidly complicated by secondary infections and by VOD or hepatorenal syndrome. When possible BAL should not be delayed. If the infiltrates are focal, infection is most probable; the infections are usually bacterial but if they are not resolved by antibiotics, a fungal cause must be suspected.

During the second and third months after transplantation bacterial, CMV and opportunistic pneumonias are possible as well as idiopathic pneumonia. After this period and especially in the presence of chronic GVHD the same lung infections are possible but obliterative bronchiolitis can also occur.

### **Incidence of intensive care utilization**

The frequency of intensive care use varies from 7 to 40% according to type of transplant and age of the recipient. Nursing by skilled care-givers experienced in both critical care and transplanted patients is crucial to the efficient care of these patients. Close co-operation with specialist consultants familiar with the complications of immunosuppressed patients, especially gastroenterologists, surgeons, otolaryngologists, neurologists, and neurosurgeons, is also very important.

In our Bone Marrow Transplant (BMT) Unit, of 370 adult HSCT recipients, 16 required intensive medical care (13 were transferred to the ICU and 3 were followed by intensive care specialists in BMT unit).

Six had had an autologous transplant (out of 240: 2.5%) and 10 had undergone allogeneic transplantation (out of 130: 7.7%). Our personal opinion is that a rate of 4.3% makes the transfer of critical patients to ICU preferable for better nursing and experienced medical intensive treatment. Of course occasional exceptions can be discussed in some particular cases or when a delay allows a patient to stay in a more sterile environment until favorable blood counts are reached. We prefer a close linkage with a particular intensive unit in order to enable better cooperation and the growth of common experience. It is the responsibility of the treating hematologist to follow the transferred patient; nurses can also cooperate with their colleagues in the ICU enhancing the continuity of care (such as sterile procedures and decontamination). In any case, seeing your own doctor or one of your nurses from the BMT unit at the door of the ICU, is certainly not a negative event for the patient!

If complete intensive care material seems useless on a transplantation ward, the availability of equipment other than the basic resuscitation equipment, for example, non-invasive bedside monitoring (cardiac and respiratory), and some non-invasive ventilation devices, seems mandatory for first intensive care needs. In our experience the possibility of bedside echocardiography and color Doppler ultra-

sonography has been very useful.

Table 2 shows the causes necessitating intensive care for our patients, divided in autologous and allogeneic (of whom 35 were unrelated) transplant recipients. Nine out of 16 (56%) left the ICU (60% of allogeneic and 50% of autologous) cases and 38% were alive 30 days after.

If we match these data with our TRM (which is 25/370, that is 7.6% split into 15% in allogeneic recipients and 2.5% in autologous recipients) we find that 28% of transplant-related deaths occurred in the ICU and 40% of patients who died from transplant-related causes, required IC. This raises the very important question: what can we do to reduce TRM?

### **Importance of pre-transplant evaluation, prevention and pre-emptive treatments on TRM rate**

In our opinion the first responsibility of the transplant team is to give the best care in order to prevent ICU admission become necessary. We think we can continue to do a lot of work in this field: apparently insignificant details may prevent irreversible complications.

#### *What should we do before the transplant?*

- careful investigation (and treatment) of every infectious focus (teeth, sinuses, lung and genitoperineal region);
- evaluation of heart, lung, kidney, and liver function;
- extensive assessment of donor and recipient serology;
- a study of immunization (especially platelet refractoriness).

#### *What prevention strategies can we routinely employ during the transplant?*

- laminar air flow or filtered air rooms;
- completely sterile equipment and diet;
- total enteral decontamination starting some days before admission;
- weekly surveillance cultures from nose, throat, urine, stools and blood;
- body weight and fluids balance registration every work shift;
- heparin for VOD prophylaxis from admission;
- donor platelets for refractory recipients at hemorrhagic risk.

#### *Pre-emptive therapies*

- Gancyclovir for early CMV antigenemia is the universally known *pre-emptive* therapy, but some simple choices have also resulted very useful in our experience.
- In allogeneic transplantation any weight increase needs prompt diagnosis and treatment (fluid restriction, diuretics and albumin)
- We perform frequent CSP-A dose adjustments according to blood levels and CSP-A is tem-

porarily discontinued when bilirubin rises (obviously in the absence of hepatic GVHD) and substituted by a prophylactic dose of 1 mg/Kg of steroids.

- Fluconazole is added in contaminated patients or when there is mucositis.
- CMV-screened blood is planned when the recipient and donor are both CMV negative.

The real task of a Unit is to anticipate risks and to try to avoid or reduce them.

## Discussion

Firstly we would like to stress that the true medical responsibility of the transplant team and intensive care consultants is to prevent IC problems or to treat them very early. So the transplant clearly appears as a continuous period of care in which an eventual request for intensive life support should be considered only as a particular moment during the total care. Moreover during the long course of a transplant, many other choices have to be made: of course this one may seem more crucial or emotionally laden, but it is not really of a different nature from the others. We recently appreciated a debate about the decision to withhold or withdraw life support, in which an ICU director wisely stated that the problem is not to withhold or to withdraw support, but the care of the patient before and after. He also explained that the decision in his Unit is taken collegially: if one of the doctors does not agree with withdrawing support, the IC continues, in this way being recognized that nobody can be sure of a fatal outcome.

Sometimes, however, we do have to face the difficult decision to withhold or to withdraw life support. Decision-making in these usually young patients is complicated by many factors: the potential for a cure of the underlying disease, the uncertainty of the outcome, the emotional and physical burden endured by patients and their family, limited community resources, competing demands and availability of a tremendous quantity of blood products. A guaranteed system to identify patients who will benefit is impossible: but some points can be focused on, keeping in mind that in this field more than in others, guidelines should be considered as what they actually are: knowledge given to men who have to take the entire and dramatic responsibility for the decision they have to make to collaborate towards the *good* of another man. In any case, this remains the definition of every medical act!

In 1996 Rubenfeld<sup>2</sup> in a review based on 11 studies including the most consistent group from Seattle (3,635 transplants of whom 25% were admitted to the ICU), reported a survival of 0-11% among ventilated patients in years 1980-1992. No factors were found to affect predict survival significantly except age and early intensive treatment; however, even if

**Table 2. Transplanted patients in our BMT Unit who required IC: causes and outcome.**

Type of transpl.	Cause of IC adm.	N. of TX	IC adm.	ICU disch.	Alive 30 d. after
Autologous		240	6 (2.5%)	3 (50%)	2
	Septic shock		3	0	0
	Cardiac failure		2	2	1
	Pneumonia		1	1	1
Allogeneic		130 (MUD 35)	10 (7.7%)	6 (60%)	4
	Septic shock		1	0	0
	PC pneumonia		2	2	1
	Fungal pneumonia		1	0	0
	IPS+fibrosis		2	1	1
	CNS hemorrhage		1	1	0
	CNS Abscess		2	1	1
	GIT hemorrhage		1	1	1
<b>Total</b>		<b>370</b>	<b>16 (4.3%)</b>	<b>9 (56%)</b>	<b>4 (25%)</b>

PC: Pneumocystis carinii; CNS: central nervous system; GIT: gastrointestinal tract.

considerable overlap was found between survivors and non survivors, some combinations were very predictive of an unfavorable outcome. A mortality of 100% was estimated among 398 similar patients at Seattle ICU who were ventilated because of lung injury and had either hepatic and renal insufficiency or hemodynamic instability requiring vasopressors. Of course absolute certainty is not attainable for the individual patient, but these data could help in the decision not to prolong IC treatment after some days without improvement.

They also reported an increased survival from 6% in 1980 to 16% in 1992. It should be noted that, in this paper, the reported patients could also have been a negatively selected population because Seattle is a reference center for transplantation and very high risk patients are consequently referred there. The authors' conclusions were in favor of undertaking IC treatment, but not prolonging it if high risk combinations appear. In 1999 Shorr<sup>11</sup> tried to record similar data for IC treatment in autologous transplant recipients, a theoretically low risk population: 11% required intubation and 17% survived (higher percentage in some subgroups). Nichols, in the editorial of Chest,<sup>12</sup> reviewed other recent improved results<sup>13,14</sup> and formulated 3 main statements for IC in HSCT: a) transplant recipients can survive ICU: it is not futile treatment. Moreover, substantial advances in outcome are reported by different ICUs. This probably also reflects better infection prophylaxis, diagnosis and therapy, especially for CMV, and

optimized management of organ failures; b) even low risk autologous transplants may require ICU (up to 10% in some reports) and c) survival in HSCT patients is not so different from that of other patients usually admitted to the ICU.

Looking for prognostic indicators for patients admitted to ICU, Price *et al.*<sup>15</sup> showed an important difference between intubated and non-intubated patients (survival 18.8% versus 65.7%, respectively). Other ICUs have claimed the protective effect of non-invasive mechanical ventilation.<sup>12,16-18</sup> These authors also prospectively studied the influence of the source of hematopoietic progenitors: peripheral blood stem cells seems better than bone marrow. Interestingly, after an educational diffusion of data on IC survivors to medical and nursing teams, no substantial behavior changes have been observed.<sup>19</sup> This shows that, in the decision-making process, compelling hope is more important than statistical data. Every transplant doctor knows the absolute diversity between two similar patients and therefore he considers a study population a cohort of very different patients. The hypothesis of asking for written pre-transplant consent including the patient's wishes in the case of IC requirement seems very unrealistic to us and in some way even damaging for a person beginning a very burdensome procedure requiring patience, strength and hope.<sup>20</sup> Moreover can a person really want something like this in such a different situation? Even the legal validity of such documents seems very questionable.

Decisions about IC do not appear to be very different from any other decision taken by doctor and patient together; they are just a more acute problems to be faced by the same therapeutic alliance between the patient and his doctors. In our opinion it is this alliance that can, using science and humane comprehension of the totality of the person, co-operate in an attempt to shift the limit further away. The responsibility for humane care lasts during the entire course of this successful or unsuccessful attempt. A lot of less debated questions could be more important for the patient's survival and to reduce TRM.

In conclusion: to undertake intensive care does not automatically mean that it must be continued. An early offer of intensive care could be followed by evaluation of improvement, in a climate of comprehension and extensive explanation to the family. The responsibility definitely remains dramatic and personal; it can be supported and shared but never guaranteed. The decision is neither mathematical nor logical but entirely human, based on an essential concept: that of staying at the side of the patient and his family, doing our best to ameliorate a life whose destiny we know is definitely not in our hands.

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## Acute hemolysis: differential diagnosis

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At the end of their normal life-span of approximately 120 days, red blood cells (RBC) undergo lysis being destroyed within the reticulo-endothelial (RE) system in the spleen, liver and bone marrow. The hemolytic anemias are a heterogeneous group of RBC disorders all characterized by a shortened red cell life-span whatever the underlying cause. The causes of increased hemolysis leading to anemia are: a) loss of structural integrity of red cell membrane and cytoskeleton (i.e. hereditary spherocytosis, elliptocytosis, paroxysmal nocturnal hemoglobinuria (PNH), immune and drug-associated antibody damage); b) defects of red cell metabolism [e.g. glucose-6-phosphate dehydrogenase (G6PD), pyruvate kinase deficiency] c) defects of hemoglobin synthesis (e.g. thalassemias and abnormal hemoglobins); d) red cell damage by outside factors (e.g. mechanical trauma, microangiopathic conditions, thrombotic thrombocytopenic purpura and chemical toxins). In some hemolytic anemias, the hemolysis may occur predominantly in the RE system (extravascular) and the plasma hemoglobin concentration is moderately raised, whereas in some others, a major degree of hemolysis occurs within the bloodstream (intravascular) and the plasma hemoglobin is substantially increased. In some cases the severity of hemolysis leads to hemoglobin excretion in the urine (hemoglobinuria) (Figure 1). A combination of both mechanisms is often observed in severe acute hemolytic crises.

Increased hemolysis may be suspected from either clinical or laboratory abnormalities and can be acute or chronic, hereditary or acquired. Anemia, jaundice and splenomegaly are the most suggestive clinical features; the nature of the hemolytic mechanism, where the hemolysis is taking place and the bone marrow response are suggested by different laboratory data; the family and personal clinical history provides helpful information for differential diagnosis between hereditary and acquired forms. However *the diagnosis of hemolytic anemia, in some instances may be obvious from a glance down the microscope at the patient's blood film* as reported by Sir John V. Dacie.<sup>1</sup>

### Investigation of hemolytic anemias

Once a hemolytic anemia has been suspected, the first step is to provide evidences of increased hemolysis by simple and unexpensive tests, namely, Hb estimation, reticulocyte count, inspection of a stained blood film, unconjugated serum bilirubin, haptoglobin and urine examination.

In the presence of anemia and an increased reticulocyte count, the differential diagnosis between acute or chronic blood loss and hemolysis has to be considered taking into account the unconjugated bilirubin and the haptoglobin values (Figure 2). If evidence is found that the anemia is of hemolytic nature, the next step will be to establish the type of hemolytic mechanism and to differentiate the acquired from the inherited forms. For this purpose the history, blood film examination and the direct antiglobulin test (Coombs test) are mandatory. Which further tests should be done to reach the diagnosis of the precise form of hemolytic anemia depend upon the results of the tests which have already been carried out, considering that not all are appropriate in every case. A tentative flow chart for the diagnosis of different hemolytic anemias is reported in Figure 3.<sup>2</sup>

### Hereditary hemolytic anemias: membrane defects

Spherocytosis (HS) is the most common hereditary red cell membrane disorder, characterized by hemolytic anemia of varying severity, spherocytes on the blood film, increased red cell osmotic fragility and a favorable clinical response to splenectomy. In recent years several distinct molecular defects of both skeletal and transmembrane proteins have been identified. Polyacrylamide gel electrophoresis of red cell membrane proteins (SDS-PAGE), generally only possible in reference laboratories, will identify qualitative or quantitative alterations in the specific proteins.<sup>3</sup> The pathophysiology of HS is a multi-step process resulting from a primary inherited deficiency or dysfunction of one of the RBC membrane proteins which leads to destabilization of the membrane lipid bilayer followed by loss of membrane material. The subsequent loss of cell surface area and a decrease in the surface/volume ratio cause the formation of poorly deformable spherocytes that are selectively retained and damaged in the spleen. The clinical expression of HS is extremely variable, ranging from an asymptomatic condition to a severe life-threatening hemolytic anemia. Because of the asymptomatic course of HS in some patients, diagnosis of HS should be considered during

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Modified from: Dacie and Lewis, 2001

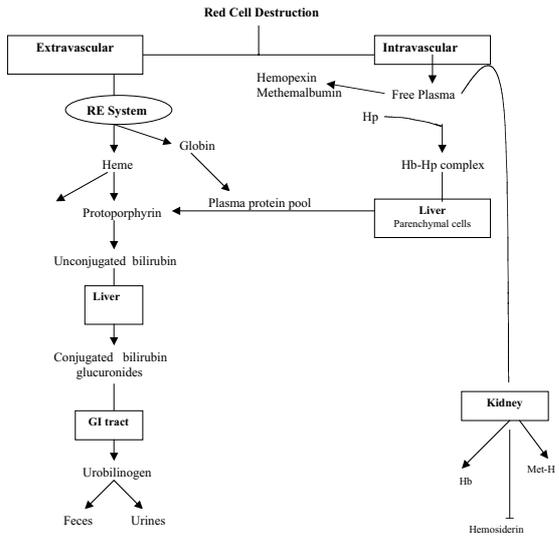


Figure 1. Catabolic pathway of hemoglobin (Modified from Dacie and Lewis, 2001).

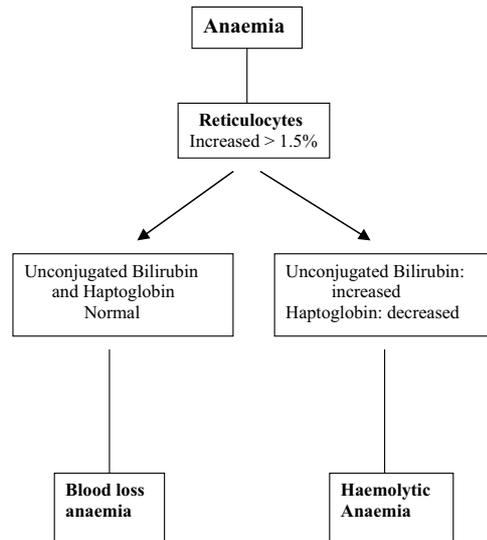


Figure 2. First step for approaching the diagnosis of hemolytic anemia.

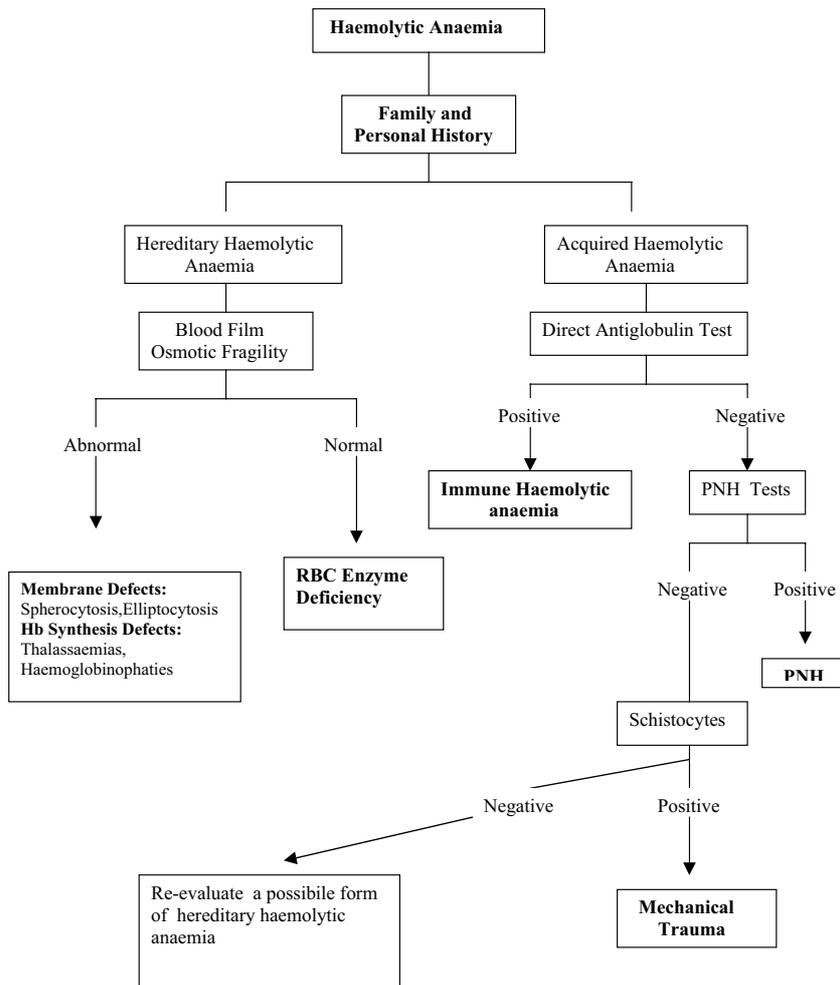


Figure 3. Second step for approaching the hemolytic anemias. (Modified from Boschetti et al., 1999).

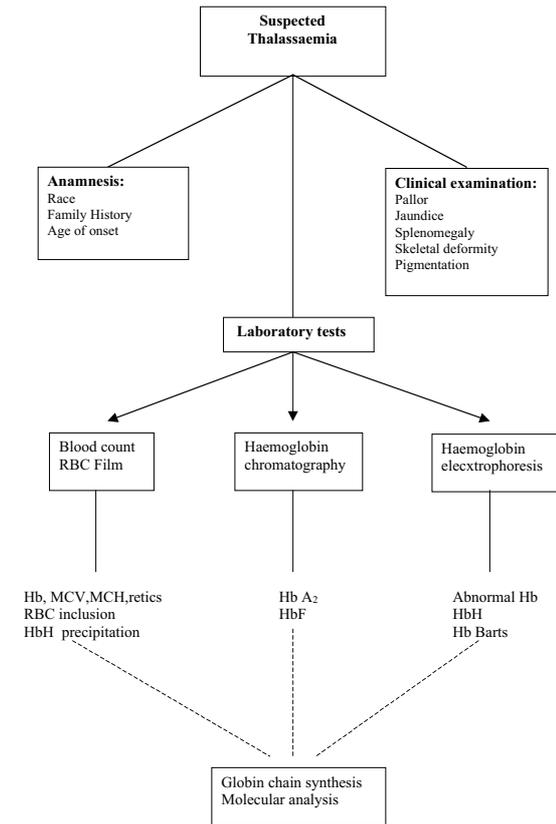
evaluation of incidentally noted splenomegaly, gallstones at a young age, or anemia resulting from parvovirus infection, infectious mononucleosis or during pregnancy, which can increase the hemolytic rate in HS. HS should be distinguished from other spherocytic hemolytic anemias, such as autoimmune hemolytic anemia by a Coombs' test, unstable hemoglobins by Heinz body as well as the rare Rh deficiency syndrome. Among the HS complications, aplastic, megaloblastic and hemolytic crises have been reported in association with parvovirus infection.<sup>4</sup>

Elliptocytosis (HE) is a term which designates a clinically, genetically and biochemically heterogeneous group of inherited disorders, having in common the elliptical shape of red cells. The most common defects in HE are  $\alpha$  or  $\beta$  spectrin mutations leading to an impairment of the self-association of spectrin heterodimers into tetramers. This *horizontal defect* leads to a disruption of the membrane skeletal structure and, consequently, to whole cell destabilization followed by red cell fragmentation and poikilocytosis. Such fragments can be seen on stained peripheral blood films. Elliptocytes and poikilocytes are commonly found in a variety of conditions including iron deficiency, thalassemias, megaloblastic anemias, myelofibrosis, myelodysplastic syndromes and pyruvate kinase deficiency, however in these conditions the percentage of elliptocytes rarely exceeds 60%.<sup>5</sup>

#### **Hereditary hemolytic anemias: Hb synthesis defects**

The inherited defects of Hb synthesis can be classified broadly into two groups. The first includes inherited structural alterations in one of the globin chains; the associated clinical abnormalities result from the physical properties of the abnormal hemoglobin. The second group includes *the thalassemias* which are caused by inherited defects in the rate of synthesis of one or more of the globin chains. This causes imbalanced globin chain production, ineffective erythropoiesis, hemolysis, and a variable degree of anemia.

The structural variants of hemoglobin, namely, *hemoglobinopathies* are usually caused by point mutations affecting one or, in some cases, two or more bases coding for amino acids of the globin chains. An example of such a point mutation is HbS caused by the substitution of valine for glutamic acid in position 6 of the  $\beta$  globin chain. HbS causes red cell sickling under deoxygenation. After the discovery that HbS was electrophoretically abnormal, additional variants were identified and assigned letters of the alphabet (C,D,E etc), however the letters were rapidly exhausted and subsequent abnormal hemoglobins were named after the geographic location in which they were found.<sup>6</sup> Many hemoglobin



**Figure 4. A flow-chart for approaching the diagnosis of the thalassemia syndromes.**

variants are hematologically and clinically silent because the underlying mutation causes no alteration in the function, solubility or stability of the hemoglobin molecule. Many of these variants are identified by electrophoresis or chromatography separation, but some are not and remain undetected. At the other end, some structural variants are associated with severe clinical phenotypes in the homozygous or even heterozygous state; these mutations affect the physical or chemical properties of the hemoglobin molecule resulting in changes in hemoglobin solubility, stability or oxygen-binding properties. The most common hemoglobin variants which have clinical or genetic relevance, such as HbS, HbC, HbE, HbD are detectable by electrophoretic or chromatographic techniques. HbS is the most common hemoglobin variant in the world: it is estimated that almost 7.8% of the world population carry one HbS gene. The highest prevalence of HbS is in tropical Africa where the heterozygous frequency is usually 20 to 40%. The sickle cell trait has a frequency of about 8% in American black popu-

lations and is also found in Caucasians especially in areas where racial mixture has occurred.<sup>7</sup> The term *sickle cell diseases* refers to those disorders in which sickling produces relevant clinical manifestations and includes the double heterozygosity HbS/HbC (hemoglobin SC disease), HbS/HbD (hemoglobin SD disease), sickle cell  $\beta$  thalassemia and sickle cell anemia. The red cell life-span is shortened in all the varieties of sickle cell disease and it can be further reduced for different reasons increasing the rate of hemolysis (hemolytic crises). The etiology and pathogenesis of acute hemolytic crisis in sickle cell diseases are discussed elsewhere. (*L. De Franceschi in this issue*).

The thalassemia syndromes are extremely heterogeneous both at molecular and clinical levels. The clinical manifestations range from completely asymptomatic microcytosis to severe anemia which is incompatible with life and can cause death *in utero*. The heterogeneity of the phenotypes is the result of the variable severity of the primary genetic defect in hemoglobin synthesis and the co-inheritance of modulating factors such as the capacity to synthesize increased amount of HbF or the co-inheritance of modifier genes unlinked to the globin genes which are capable of ameliorating or aggravating the thalassaemic phenotype (modifier genes, e.g. HFE gene responsible for increased iron absorption, UDFPG gene for increased bilirubin level).<sup>8</sup> In severe cases of thalassemias such as the homozygous  $\beta$  thalassaemia and hemoglobin H disease, the clinical and hematologic findings are so typical that little difficulty in their diagnosis is usually encountered. A simple flow chart for laboratory investigations to be performed when a thalassemia is suspected is reported in Figure 4.<sup>9</sup>

#### **Hereditary hemolytic anemias: RBC enzyme deficiency**

Deficiencies in the activities of a number of erythrocyte enzymes may lead to a short red cell life-span. G6PD deficiency was the first of these to be recognized and is the most common. More than 400 G6PD variants have been described all over the world. The common forms (polymorphic) are associated with acute hemolysis and subsequent severe anemia only under conditions of stress, such as the administration of oxidative drugs, ingestion of fava-beans, infection or the neonatal period. Chronic hemolysis in the absence of oxidative stress occurs in the presence of uncommon, particularly severe G6PD variants or in some other enzyme deficiencies. These conditions are named *hereditary (congenital) non-spherocytic hemolytic anemia*: the diagnosis of hereditary non-spherocytic hemolytic anemia is reserved for those patients who have no major abnormalities of red cell morphology (Figure 2).<sup>10</sup> Hereditary ovalocytosis, pyropoikilocytosis,

stomatocytosis and even sickle cell disease and thalassaemia major are hereditary non-spherocytic hemolytic anemias but are non included in this category because of their RBC morphological abnormalities. Most of the enzyme deficiencies are inherited as autosomal recessive disorders, but G6PD deficiency and phosphoglycerate kinase deficiency which are X linked. The induced hemolysis in G6PD deficient cells is generally accompanied by the formation of Heinz bodies, particles of denatured hemoglobin and stromal protein formed only in the presence of oxygen. Drug-induced hemolytic anemia due to G6PD deficiency has similar clinical features and certain laboratory features as those of drug-induced hemolytic anemia associated with unstable hemoglobin: an accurate family and personal history of the patient often provides adequate information for the differential diagnosis. PK deficiency, like G6PD deficiency is heterogeneous with different mutations causing different kinetic and electrophoretic changes in the enzyme. In the case of a putative metabolic defects, an attempt should be made, when possible, to pinpoint the enzyme involved in order to approach the hemolytic crisis appropriately. Commercial kits are available for some quantitative enzyme assays and they can be used for the preliminary screening. Further characterizations of the enzyme defect should be performed by laboratories that are experienced in the field.<sup>11</sup>

#### **Acquired immune hemolytic anemia**

Acquired immune-mediated hemolytic anemias can be due to auto-antibodies to a patient's own red cell antigens or to allo-antibodies present in the serum or sometimes completely bound to red cells. Auto-immune hemolytic anemia (AIHA) may be idiopathic or secondary associated with lymphoproliferative disorders or auto-immune diseases such as systemic lupus erythematosus. AIHA may also be associated with certain infections, certain non-lymphoid neoplasms (e.g. ovarian tumors), chronic inflammatory diseases (e.g. ulcerative colitis) or with ingestion of certain drugs (e.g.  $\alpha$ -methyl dopa). The diagnosis of AIHA requires evidence of anemia, hemolysis and the demonstration of immunoglobulin and/or complement bound to the patient's RBC. The *broad spectrum* antiglobulin test (Coombs' test) is the screening test that allows the immune nature of the hemolysis to be identified (*details are presented in this issue by A. Zanella*).

The severity of anemia ranges from being life-threatening to very mild; the reticulocyte count is usually very high and the blood film shows spherocytes, RBC fragments, nucleated RBC, and occasional erythrophagocytosis by monocytes. Acquired AIHA can resemble hereditary spherocytosis because of spherocytes in peripheral blood; however, a positive Coombs' test is usually confirmatory.

**Acquired non-immune hemolytic anemia**

In the presence of reticulocytosis and a negative antiglobulin test, having excluded any hereditary form of hemolytic anemia, paroxysmal nocturnal hemoglobinuria (PNH) must be suspected. PNH is commonly regarded as a type of hemolytic anemia but in reality is a clonal hematopoietic disorder in which the patient's red cells are abnormally sensitive to lysis by normal constituents of plasma. The most convenient screening tests for PNH are the sucrose hemolysis test and the examination of urine for hemosiderin. If the sucrose test is positive, the diagnosis should be confirmed using the complete Ham acid hemolysis test.<sup>12</sup>

Microangiopathic or mechanical hemolytic anemia should be suspected when a blood film shows red cell fragments. The blood film examination is the most important laboratory procedure in making this diagnosis.

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## Immune mediated hemolytic anemias

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### Summary

Immune-mediated hemolytic anemias are a heterogeneous group of disorders characterized by the presence of red cell antibodies. The clinical picture and the severity of hemolysis mainly depend on the nature of the antibodies (auto or alloantibodies), or naturally occurring agglutinins of the ABO blood group system. Autoimmune hemolytic anemias (AIHA) can be distinguished into *warm* and *cold* based on the thermal properties of the antibody, and into primary (idiopathic) and secondary forms. Warm idiopathic forms are often insidious, although sometimes rapidly worsening. Life-threatening hemolytic episodes are more common in warm AIHA cases secondary to infections or in cold-antibody AIHA, which comprises idiopathic or secondary cold hemagglutinin disease (CHD) and paroxysmal cold hemoglobinuria (PCH). The patient who has failed to respond to first- and second-line treatment (steroids and cytotoxic drugs) represents a critical clinical problem. Life-threatening immune-mediated hemolytic diseases require a therapeutic decision in emergency. In refractory and hyperacute cases the therapeutic options include blood transfusion, plasma-exchange or plasmapheresis, i.v. immunoglobulins, i.v. cytotoxic drugs, and monoclonal antibodies. Critical clinical situations are also frequent in some drug-induced immune hemolytic reactions and in hemolytic transfusion reactions (HTR), mainly those due to *transfusion of the wrong blood*.

Immune-mediated hemolytic anemias are a group of disorders in which components of the immune system (mainly antibodies) are involved in red-cell destruction. The clinical picture and the severity of hemolysis mainly depend on the nature of the antibody. The anti-erythrocyte antibodies are auto- or allo-antibodies, or naturally occurring agglutinins of the ABO blood group system (Table 1). An immune-mediated destruction of red cells may be induced by drugs with different mechanisms, and may also occur in paroxysmal nocturnal hemoglobinuria (PNH), due to abnormal membrane sensitivity to the lytic action of the complement components.

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### Autoimmune hemolytic anemias

Autoimmune hemolytic anemias (AIHA) are a heterogeneous group of disorders characterized by the presence of red cells autoantibodies which result in increased erythrocyte destruction. The degree of hemolysis varies markedly from patient to patient, from being fully compensated to causing very severe anemia. AIHA can be distinguished into two broad clinical categories: primary (idiopathic) AIHA, in which hemolysis dominates the clinical picture in the absence of any other co-existing disorder, and secondary AIHA, accompanying and complicating an underlying disease.

Since the clinical signs depend not only on the amount of the anti-red cell antibody but also on its thermal properties, AIHA are further conveniently classified into AIHA due to *warm* antibodies (which bind to erythrocytes most avidly at 37°C) and AIHA due to *cold* antibodies (which react strongly at 4°C, progressively less as the temperature rises and usually fail to react at all at normal body temperature). Cold-antibody AIHA comprises two different clinical entities, the cold hemagglutinin disease (CHD) and paroxysmal cold hemoglobinuria (PCH). Some cases escape, however, this classification, such as the mixed-type AIHA in which the hemolysis is sustained by both warm and cold autoantibodies.<sup>1-3</sup>

Table 2 reports the percent distribution of the various types of AIHA, together with male to female ratio, computed through the analysis of data published in the last thirty-five years. The overall ratio of primary to secondary AIHA in the above quoted series, calculated only in the 4,575 cases in which this information was available, was 1.04 (0.96 in warm antibody AIHA, 1.32 in CHD, 0.53 in PCH and 1.22 in mixed-type AIHA). It is worth noting that PCH, which remains a rare disorder in adults, has been recently reported to be one of the most common types of acute AIHA in young children, accounting for some 30-40% of all cases of AIHA in patients less than 16 years of age.<sup>4-6</sup>

### Warm-antibody AIHA

Warm-antibody AIHA is by far the most common type of AIHA (Table 2) with an incidence of approximately 1 in 75,000 – 1 in 100,000 per year.<sup>1,7</sup> In our series the overall male to female ratio was 1.2 and the median age of idiopathic warm-antibody AIHA was 52 years, similar to that reported by others.<sup>8</sup> The age incidence of secondary warm-antibody AIHA mirrors the age of the associated diseases. Secondary warm-antibody AIHA occur more frequently in association with chronic lymphatic

**Table 1. Immune-mediated hemolytic anemias.**

Autoimmune hemolytic anemias (AIHA)
<i>Warm autoimmune hemolytic anemia</i>
<i>Cold hemagglutinin disease (CHD)</i>
<i>Paroxysmal cold hemoglobinuria (PCH)</i>
Drug-induced immune hemolytic anemias
Hemolytic transfusion reactions (HTR)

**Table 2. Percent distribution of the various types of AIHA, together with male to female ratio, computed through the analysis of data published in the last 35 years.**

Type	No.	%	M/F
Warm-antibody AIHA	5,125	72.3	0.86
Cold-antibody AIHA			
<i>Cold agglutinin disease</i>	1,595	22.6	0.88
<i>Paroxysmal cold hemoglobinuria</i>	138	1.9	2.0
Mixed-type AIHA	227	3.2	0.81
Total AIHA	7,085	100	0.86

leukemia, Hodgkin's and non-Hodgkin's lymphomas, infections, immunodeficiency states and autoimmune disorders, such as systemic lupus erythematosus.<sup>1,8</sup>

Warm-antibody AIHA are characterized by great variability in terms of onset, grade of severity and clinical course. The onset of idiopathic forms is often insidious, although in some patients it may be sudden, with rapidly worsening anemia and jaundice. Life-threatening hemolytic episodes are more common in AIHA cases secondary to infections. Massive, usually short-lasting hemoglobinuria may also occur in acute cases, albeit rarely. Some patients may be not significantly anemic and indeed may be symptomless. The spleen was enlarged in half cases, and the liver in approximately one third.<sup>7</sup> Purpura is not commonly found, except in Evans' syndrome, in which AIHA is associated with idiopathic thrombocytopenic purpura. As regards the clinical course, the disease may be in some cases, particularly in children, of short duration, but more often it is a chronic disease extending over years. In this latter case, the course is unpredictable, often characterized by clinical relapses alternating with periods of remission lasting months or even years.

Laboratory findings include a hemoglobin concentration ranging from 3 g/dL to normal values,

raises mean cell volume (MCV), reticulocyte number, unconjugated bilirubin and lactate dehydrogenase (LDH), and increased consumption of haptoglobin. Spherocytes are often detectable at peripheral blood smear examination. Occasionally, massive hemoglobinemia, hemoglobinuria and hemosiderinuria are noted, usually in patient with hyperacute diseases. A positive Coombs' test (direct antiglobulin test, DAT) is the cornerstone of the diagnosis of AIHA. The traditional agglutination technique, which is usually performed with broad spectrum Coombs' reagents, may however give false-positive and false-negative results.<sup>9</sup> Monospecific antisera against IgG, IgM, IgA or components of complement may be employed to characterize the pattern of sensitization further. Anti-IgG antibodies are found in most cases of *warm* AIHA, being unusual to have isolated IgA or IgM warm autoantibodies,<sup>9,10</sup> whereas cold agglutinins are, with few exceptions, virtually always IgM.<sup>3,9,11</sup> More sensitive DAT techniques, such as the complement-fixing antibody consumption test,<sup>12</sup> various immunoradiometric, ELISA and cytofluorimetric assays,<sup>13-17</sup> and the solid phase antiglobulin test<sup>18</sup> have been reported to give positive results in some patients in whom the conventional DAT gave negative results.<sup>19</sup> In DAT-negative hemolytic anemias in which an immune-mediated pathogenesis is suspected, the use of mitogen-stimulated DAT can be of great diagnostic aid, since *in vitro* mitogen stimulation may result in the DAT becoming positive in these cases.<sup>20,21</sup> Corticosteroids represent the first-line treatment of warm-antibody AIHA with overt hemolysis. Prednisone<sup>8,22</sup> at an oral dose of 40 mg/m<sup>2</sup> per day in adults for up to 3 weeks is usually adequate to keep the hemolysis under control in 80-90% of cases;<sup>7,8</sup> larger doses very seldom elicit a better therapeutic response. If hemolysis is critical, high-dose prednisone should be given intravenously (prednisolone 250-1000 mg per day for up to 5 days). When an adequate and stable hemoglobin level has been reached (10 g/dL or more), steroids may be gradually reduced, the aim being to take the patient off the drugs completely in 3-6 months.

If the patient fails to respond to steroids, or is intolerant of the drug or is unable to achieve long-term remission on acceptable dosages, second-line treatment should be considered, and a choice has then to be made between splenectomy and immunosuppressive drugs. Splenectomy has the advantage that it has the potential for complete and long-term remission and that the beneficial effect, if any, is likely to be evident within a very short time, whereas immunosuppressive agents are slow-acting and may lead to unwelcome complications. Most authors<sup>8,22,23</sup> suggest splenectomy first for those patients who are fit for the operation; in patients unfit for splenectomy or not responsive to surgery, immunosuppressive drugs should be introduced and

the steroids gradually tailed off. Splenectomy leads to a complete remission in more than 50% of patients, and in the remainder the hemolysis tends to be more easily managed with drug therapy.<sup>8,23</sup> The major concern of splenectomy is the increased susceptibility to infections in the long term. The risk of serious infectious complications in asplenic patients may be decreased by immunization against *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Neisseria meningitidis*, which should be performed at least 2 weeks prior to splenectomy. In view of the uncertain protection obtained by immunization, most authors recommend antibiotic prophylaxis until the age of 18 in children, and for at least 5 years in adults.<sup>24</sup>

Among cytotoxic drugs the most commonly used is azathioprine which, at a mean daily dose of 80 mg/m<sup>2</sup> (1–1.5 mg/kg), is reported to give good results in some 2/3 of cases. Similar results have also been obtained with cyclophosphamide 60 mg/m<sup>2</sup> daily for at least six months before starting a gradual reduction.<sup>8</sup> More recently cyclosporin at doses of 5 mg/kg/day is being increasingly used in autoimmune cytopenias, including AIHA, with beneficial effects in many cases, although no controlled clinical studies are available.<sup>25,26</sup>

The patient who has failed to respond to the first and second line treatment presents as a critical clinical problem. Possible remedies, besides blood transfusion, include high doses of i.v. immunoglobulins, plasmapheresis (plasma exchange or specific immuno-absorption of Ig), intravenous cyclophosphamide and vinca alkaloids. Other more recent options are rituximab, Campath-1H, mycophenolate and bone marrow transplantation (BMT).

The indications for blood transfusion in warm-antibody AIHA patients and the inherent risks of transfusing have been the object of many reviews.<sup>7,8,27</sup> There is common agreement that blood transfusion should be avoided as far as is possible and that the decision to transfuse should be based on clinical criteria rather than laboratory data. However, blood transfusion should not be refused or delayed if really necessary, simply because *in vitro* compatible blood cannot be found. In fact, the presence of strongly reactive autoantibody interferes with compatibility testing and may make it difficult to detect co-existing, clinically significant red cell alloantibodies potentially capable of provoking severe hemolytic transfusion reactions;<sup>27</sup> the occurrence of alloimmunization is not a rare event in AIHA, its prevalence ranging from 13% to 38%.<sup>11</sup> The best technique for determining whether alloantibodies are present in addition to autoantibodies in not recently transfused patients is to adsorb the autoantibody from the patient's serum at 37°C using the patient's own red blood cells (autologous adsorption) prior to proceeding with the antibody screening and cross-match.<sup>27-30</sup> The specificity of autoan-

tibodies in AIHA is usually very complex. In the case of simple, clear-cut autoantibody specificity, there may be some benefit in providing antigen-negative blood. Although there is some evidence that red cells carrying the corresponding antigen (antigen-positive blood) may have a reduced *in vivo* survival,<sup>8</sup> the specificity of the autoantibody is more often ignored in the selection of blood for transfusion.<sup>8,11,22,27,31</sup> In fact the decreased red cell survival of antigen-positive blood may be more acceptable than the risk of alloimmunization induced by antigen-negative blood. Sokol *et al.*<sup>27</sup> reported good transfusion efficacy and no hemolytic reactions in more than 2,000 AIHA patients transfused without taking into account the autoantibody specificity.

The efficacy of treatment with intravenous gammaglobulins (i.v. IgG) has been variable, some studies reporting efficacy particularly in children<sup>32</sup> others showing a lack of response. At first, dosages similar to those administered in idiopathic thrombotic purpura (ITP), e.g. courses of 0.4 g/kg/day for 5 days, were used. Subsequently, it was found that higher doses, e.g. up to 1 g/kg/day might be necessary for a favorable response.

Plasma exchange has been applied in recent years to a number of patients seriously affected by warm-antibody AIHA refractory to conventional treatment, with the aim of transiently reducing the titer of autoantibodies. Although the efficacy of this procedure is limited by the continuous production of antibodies and by the widespread extravascular distribution of IgG, a good response was obtained in some, but not all, cases of hyperacute AIHA;<sup>8,33</sup> some of these cases were young children.<sup>34</sup> Extracorporeal specific immunoabsorption of IgG by protein A is an alternative to plasmapheresis and it seems to be an effective procedure which is considered more efficient and selective than plasmapheresis.<sup>35</sup>

Promising results have been obtained from the use of monoclonal antibodies, although the number of cases is still rather limited, and follow-up too short to evaluate how sustained the response will be. In particular, rituximab is being increasingly used in the management of refractory and severe warm type AIHA, producing a response rate of 73%,<sup>36-38</sup> while treatment with Campath-1H is limited to very few patients.<sup>39</sup> Mycophenolate mofetil has also been used for the treatment of AIHA, but information is so far scanty.<sup>40-42</sup>

BMT has been carried out in some patients with very severe AIHA, most of whom had Evan's syndrome or with AIHA associated with other diseases, but this therapeutic option should be considered still experimental.<sup>43,44</sup>

### **Cold-antibody AIHA**

Cold-antibody AIHA are less frequent than warm-antibody AIHA, representing 8 to 25% of all AIHA. They comprise different clinical entities, the cold

hemagglutinin disease (idiopathic or secondary) and paroxysmal cold hemoglobinuria.

Primary chronic CHD is usually a clonal, non-malignant clinical entity. Men are more frequently affected than women and the maximum incidence occurs in the sixth decade of life. Patients are often in good general condition: pallor and/or acrocyanosis affecting mostly ears, nose-tip, fingers and toes occur due to autoagglutination of red cells in the skin capillaries when the temperature falls to a critical level, which varies from patient to patient. There is neither peripheral lymphadenopathy nor marked splenomegaly, in contrast to in the secondary forms of CHD accompanying a malignant lymphoproliferative condition. Patients with very high titer and/or wide thermal amplitude cold agglutinins may have a chronic hemolytic process independently of exposure to cold. The chronic form of secondary CHD usually accompanies lymphoproliferative disorders: in these cases the hemolytic disease does not usually dominate the clinical picture. The direct Coombs' test is positive against C3dg, negative against Ig. Hemoglobin concentration is more or less reduced, but rarely drops below 7.0 g/dL. Blood smears usually show strong agglutination. The laboratory findings are in fact dominated by the high titer (up to 1:256,000 or even more) cold agglutinins which, with rare exceptions, are virtually always IgM.<sup>11</sup> They usually display anti-I/iH or less frequently anti-i specificity, although specificity against Pr antigens<sup>45</sup> and more rarely against other antigens<sup>11,46</sup> has been reported.

In contrast with chronic primary or secondary CHD, the acute transient form of secondary CHD, usually associated with *Mycoplasma pneumoniae* infection or with infectious mononucleosis, is characterized by an abrupt onset, sometimes fulminant,<sup>45</sup> with rapidly worsening anemia, jaundice, spleen enlargement and, very seldom, hemoglobinuria. Complete recovery usually occurs spontaneously within a few weeks. The specificity of cold agglutinins, which are usually polyclonal, is anti-I in cases due to *Mycoplasma pneumoniae*, EBV and cytomegalovirus infections, often anti-i in infectious mononucleosis, and more commonly anti-Pr in rubella and Klebsiella infections.<sup>11</sup>

Patients with mild chronic hemolysis do not require specific therapy. The more efficient treatment is to avoid cold as far as is practical. Other forms of treatment have been used in patients with severe symptoms despite efforts to avoid exposure to cold. Corticosteroids are almost always ineffective, except in the case of cold agglutinins with a high thermal range and low titer, or in the presence of IgG antibodies reactive at low temperature.<sup>47</sup> Splenectomy is not expected to be beneficial in CHD, since the red blood cells damaged by cold agglutinins are mainly sequestered by the liver. Among cytotoxic drugs, chlorambucil proved to be effective

in some patients with marked anemia, given either as a continuous low-dose regime (2-4 mg daily) or at a higher intermittent dose (10 mg daily for 14 days in a 28-day period).<sup>23</sup> Satisfactory results were also obtained in some cases with cyclophosphamide 100-200 mg daily over long periods.<sup>19</sup> Intravenous pulse therapy with cyclophosphamide was shown to be very effective as a remission-inducing regimen<sup>22,48</sup> particularly if combined with steroids and/or plasmapheresis.<sup>48</sup> Among monoclonal antibodies, rituximab is being increasingly used in the management of refractory and severe CHD with very promising results.<sup>36-38</sup> Plasma exchange, possibly performed using a commercially available in-line blood warmer,<sup>49</sup> has been employed to lower transiently the cold agglutinin titer in a number of severely ill patients suffering from CHD.<sup>48,49</sup> It is, however, unlikely that the procedure could be applied on a long-term basis, and the removal a substantial mass of cold antibody from time to time can hardly be expected to diminish the activity of the monoclonal cells producing the protein. Blood transfusion is occasionally necessary in CHD. Because in almost all cases the cold antibody is of anti-I specificity and because I-negative adult blood is extremely rare, it is almost always impossible to obtain compatible blood. Anyway, the transfusion of adult I erythrocytes to CHD patients usually results in a satisfactory rise in hemoglobin, provided that the blood is run at a slow drip rate (or by using an in-line blood warmer in severe cases), and that the presence of alloantibodies in the patient's serum has been excluded.<sup>8</sup>

Paroxysmal cold hemoglobinuria (PCH) was classically described in patients with syphilis, but is now frequently associated with viral infections. There are chronic and acute, transient forms, these latter being more frequent in children under the age of 5 years,<sup>56</sup> especially following definite viral infections (measles, mumps, chicken pox, infectious mononucleosis) or even vague flu-like disorders. Symptoms are due to acute hemolysis after exposure to cold, and include general malaise, headache, cramps, and pain in the back, legs, and abdomen, followed by severe shaking chills and fever. Usually, the first urine passed after the chills is dark-brown or black, and the hemoglobinuria disappears in several hours. Modest jaundice can be present the day after the attack. Vasomotor disturbances such as urticaria have also been described. In some patients, the disease is precipitated by brief exposure to moderate cold, while in others prolonged exposure to chilly temperatures is required. The resultant anemia can be very severe. Recovery from the attack is usually rapid. The antibody causing PCH is the Donath-Landsteiner *biphasic* hemolysin, a complement-binding IgG that binds to red cells most avidly at 4°C, and becomes hemolytic after incubation with complement at 37°C. The specificity of antibody is

almost invariably anti-P, with few exceptions.

Treatment for syphilis is given when the disease is present, and clinical improvement occurs in most patients with this condition. Avoidance of cold is the only effective measure for patients affected by chronic idiopathic PCH, as steroids and splenectomy are useless. In acute post-infective cases recovery is spontaneous.<sup>6</sup> Transfusion has been reported to be necessary in approximately 50% of patients.

### **Drug-induced immune hemolytic anemia**

Drug-induced immune hemolytic anemia was common in the past when penicillin and  $\alpha$ -methyl-dopa were widely administered, but is unusual in present-day clinical practice. Three distinct mechanisms are associated with the disorder.<sup>50</sup>

In the first, typical of penicillin, antibodies against the drug react with erythrocyte-bound drug, resulting in red blood cell destruction. Clues to the diagnosis are a positive DAT, a negative indirect antiglobulin test, and the failure of antibodies eluted from the patient's red blood cells to bind to normal erythrocytes. The diagnosis is established when both the eluate and the patient's serum react with penicillin-coated cells. The clinical picture is seldom acute and severe, and the discontinuation of the drug rapidly brings the hemolytic anemia to a halt. Other drugs able to induce hapten-mediated hemolytic anemia are cephalotin, cephaloridine, ampicillin, methicillin, carbenicillin, and cephotaxime.

The second mechanism involves immune complexes formed by the drug and an anti-drug antibody, usually IgM. The clinical picture is frequently acute and severe, with intravascular hemolysis, hemoglobinemia, hemoglobinuria and even renal failure. Laboratory diagnosis includes DAT positivity for complement only, a positive reaction of the patient's serum with red blood cells (lacking anti-drug antibodies) in the presence of the offending drug, and lack of reaction of the patient's eluate with normal erythrocytes. The drugs capable of inducing immune-complex-mediated hemolysis are stibophen, quinine, quinidine, phenacetin, hydrochlorothiazide, rifampin, p-aminosalicylic acid, antihistamines, sulfonamides, isoniazid, chlorpromazine, pyramidon, melphalan, tetracycline, acetaminophen, hydralazine, probenecid, cephalosporins, sulindac, fenoprofen, and radiographic contrast medium.

The third mechanism involves a drug-induced *in vivo* modification of the red blood cell membrane with consequent formation of autoantibodies. The serologic findings are indistinguishable from those of idiopathic autoimmune hemolytic anemia. There is a positive DAT but rarely severe hemolytic anemia. The reaction is typically induced by methyl-dopa, but also by mefenamic acid, procainamide, ibuprofen, diclofenac, thioridazine, and interferon- $\alpha$ .

### **Hemolytic transfusion reactions**

Typically, hemolytic transfusion reactions (HTR) occur when antigen-positive red blood cells are transfused to a patient who has an alloantibody to that antigen. HTR may also result from the infusion of fresh-frozen plasma or platelets containing antibodies directed against an antigenic determinant on recipient red cells.<sup>51</sup> HTR are subdivided into acute and delayed, on the basis of whether they occur within 24 hr of the transfusion or later. The hemolysis is usually intravascular in the former and extravascular in the latter type of reaction.<sup>11</sup> The incidence per red cell units transfused is approximately 1:25,000 for the acute<sup>52</sup> and 1:5,000 for the delayed<sup>53</sup> reactions. The overall incidence of HTR per transfused patient is approximately 1:500.<sup>54</sup>

HTR result from either the failure to detect potential incompatibility or the inadvertent or deliberate (as in the case of platelet transfusions, urgent transfusions in immunized patients, bone-marrow transplantation) administration of incompatible blood components. Among 158 transfusion-related fatalities due to acute hemolysis, 86% were the result of process errors (10% occurring in phlebotomy and ordering, 33% within the blood bank, and 57% during transfusion administration).<sup>55</sup> Similar results were reported in a more recent survey.<sup>56</sup>

The clinical presentations of HTR are diverse, and depend on the patient's condition, the amount of incompatible blood involved, and the nature of serologic incompatibility. The most common signs and symptoms are fever, chills, nausea and vomiting, pain, dyspnea, tachycardia and/or hypotension (rare in extravascular reactions), and jaundice. In all cases there is an unexpected degree of anemia due to the loss of transfused red cells. The most feared complications of a hemolytic transfusion reaction are hypotension, disseminated intravascular coagulation, and renal failure. The risk of death is approximately 1:630,000 units and 1:190,000 patients transfused for the acute reactions, and approximately 1:3.35 million units and 1:1.15 million patients transfused for the delayed reactions.<sup>55</sup>

The antibody specificities associated with HTR involve numerous blood group systems, in particular ABO, H, Lewis (Le<sup>b</sup> rarely), P (rarely P1), I/i, Rh, Duffy, MNS (N unusual), Lutheran (Lu<sup>b</sup>), Kell, Kidd, Cartwright (Yta), Diego (Di<sup>a</sup>, Di<sup>b</sup>), Scianna (Sc1, Sc2), Colton (Co<sup>a</sup>, Co<sup>b</sup>), Dombrock (Do<sup>a</sup>, Do<sup>b</sup>), Vel, Gerbich, Lan, Sid.<sup>57</sup>

It is worth noting that many clinical conditions should be considered in the differential diagnosis of HTR. These include thermal injury due to improper storage or improper deglycerolization, use of incompatible fluids, autoimmune hemolytic anemia, hemolytic anemia associated with G-6-PD deficiency or hereditary spherocytosis, hemoglobinopathies such as sickle cell anemia, drug-induced hemolysis, microangiopathic hemolytic anemia, artificial heart

valve dysfunction, paroxysmal nocturnal hemoglobinuria, and infections.

Blood substitutes are under development for transfusion in place of donor blood during emergencies and lengthy surgery. The first generation of blood substitutes is currently in clinical trials. Blood substitutes are solutions intended to replace transfusion of banked red blood cells. Several variations of products based on either hemoglobin (animal or human) or perfluorocarbon emulsions are in advanced stages of clinical development. The need for such products is pressing as shortages of banked blood worsen and awareness of the dangers of blood transfusion increases.<sup>58,59</sup>

### Conclusions

Immune-mediated hemolytic anemias are a heterogeneous group of disorders in which the clinical picture and the severity of hemolysis largely depend on the serologic characteristics of the autoantibodies and thus on the mechanisms of red blood cell immune destruction. Critical clinical situations are frequent in hyperacute or refractory warm AIHA and CHD, as well as in some drug-induced immune hemolytic reactions. HTR, mainly those due to *transfusion of the wrong blood*, can be fatal. A prompt, correct diagnosis is fundamental for good, effective treatment. Other causes of acute hemolysis (G-6-PD deficiency, hemoglobinopathies, microangiopathic hemolytic anemia, artificial heart valve dysfunction, paroxysmal nocturnal hemoglobinuria, and infections) should be considered. Life-threatening immune-mediated hemolytic diseases can require a therapeutic decision in emergency. In this case the therapeutic options include blood transfusion, plasma-exchange or plasmapheresis, i.v. immunoglobulins, i.v. cytotoxic drugs, and monoclonal antibodies. It is to be hoped that the specific role of the various forms of treatment may be better defined by appropriate clinical trials and that new therapeutic options will become available for patients with immune-mediated hemolytic anemia.

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## Diagnosis and initial treatment of acute events in sickle cell disease

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Sickle cell disease (SCD) is a genetic disorder characterized by a mutation in the  $\beta$  globin gene, which specifies the insertion of a valine in place of glutamic acid in the synthesized  $\beta$  globin chain.<sup>1</sup> Sickle cell hemoglobin (HbS) has the unique property of polymerizing when deoxygenated.<sup>1,2</sup> The fundamental process of HbS polymerization has been studied in great detail, and much is known about the kinetics of HbS polymerization in solution and in cells.<sup>1,2</sup> The lag time preceding the rapid phase of deoxygenation induced HbS polymerization is inversely proportional to the 20–40<sup>th</sup> power of the HbS concentration.<sup>1–4</sup> Thus, even a slight reduction in HbS concentration is likely to have a large beneficial effect on the kinetics of HbS polymerization. Intracellular Hb concentration is determined by red cell water, potassium and chloride content, which are regulated by cation and anion transport proteins of the red cell membrane.<sup>5,6</sup> Polymerization of HbS generates dense, dehydrated rigid sickled red cells.<sup>1–6</sup> Repeated cycles of HbS polymerization, red blood cell sickling and dehydration play a major role in the pathogenesis of vaso-occlusive and ischemic events, which result in recurrent acute painful crises and, ultimately, irreversible damage of various organs.<sup>1–8</sup> Dehydrated and sickled red blood cells are trapped in the microcirculation, resulting in frequent and diffuse microinfarctions that are responsible for severe acute and chronic organ disease.<sup>1–8</sup> Since many cellular and molecular events participate in the pathophysiology of the vaso-occlusive crises, it has been difficult to distinguish causative from secondary mechanisms and, therefore, devise effective therapies. Vaso-occlusive events in the microcirculation may result from the interactions between plasma factors and different cell types, including dense, dehydrated sickle cells, reticulocytes, endothelial cells, leukocytes and platelets.<sup>8,9</sup> For instance, endothelial cells are abnormally activated, displaying increased expression of adhesion molecules in association with a pro-coagulant phenotype.<sup>9</sup> Furthermore, it has been observed that the severity of SCD increases with the white cell count, most likely related to the fact that leukocyte adhesion to abnormally activated endothelium contributes to vaso-occlusion.<sup>10,11</sup>

These pieces of evidences support the hypothesis that sickle cell disease is a chronic inflammatory state, further exacerbated by acute events.<sup>6,9</sup>

Clinical and epidemiological studies have identified the organs that are the target of sickle cell disease as those with the common characteristics of a slowing down of the circulation, high level of oxygen extraction and acid pH, all conditions favoring HbS polymerization and sickling.<sup>13,14</sup>

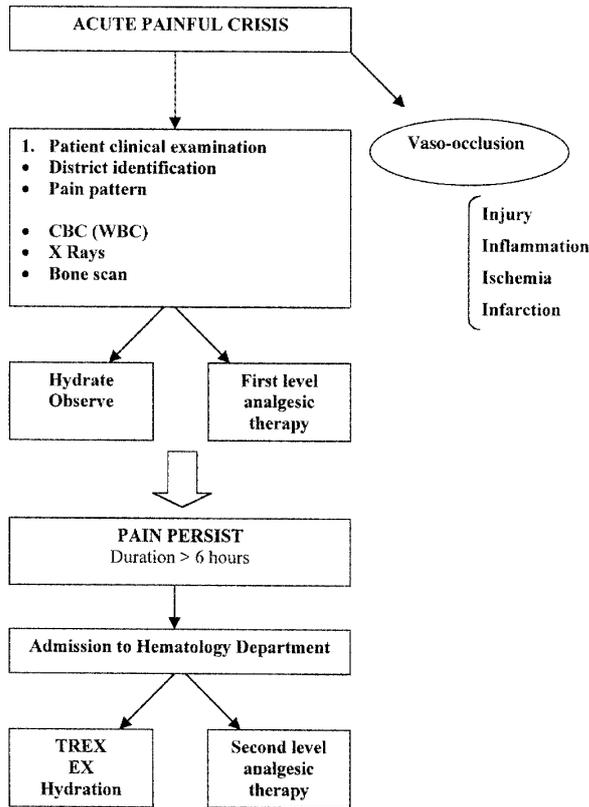
Here, we will consider the diagnosis and management of the most common acute events in sickle cell disease. Table 1 shows the most frequent acute events responsible for bringing sickle cell patients to the Emergency Department.

### Acute painful crisis

Painful crises are the most frequent type of sickle cell pain in all ages and may be acute or chronic. The *Co-operative Study of Sickle Cell Disease* (CSSCD) has reported that painful crises are the most common complication in sickle cell patients occurring at a rate of 0.8 episodes per year.<sup>14</sup> The events promoting a sickle cell painful crisis are still under investigations; however, conditions favoring or accelerating HbS polymerization play a crucial role in the pathogenesis of the painful crisis. Thus, the sickled, rigid, dense red cells may be trapped in districts in which the circulation slow down, determining organ ischemic/reperfusion injury, further amplifying the inflammatory response. Bone has a peculiar anatomic organization that is characterized by enclosed spaces with a single incoming artery and outgoing vein. The rigid, dense red cells may be trapped in the areas of slowed down circulation resulting in increased tissue pressure within the enclosed space. The increased pressure reduces arterial input with resultant hypoxia of the marrow and bone.

Figure 1 is an algorithm for the evaluation and management of an acute painful crisis in sickle cell patients. First step: clinical examination, immediate brief history of the pain crisis and identification of the muscle/bone district involved, blood tests. *Second step.* Since the pain is often associated with reduced fluid intake and increased water losses, the patient's hydration is crucial in the acute phase; this is combined with the initiation of specific analgesic treatment. The efficacy of pain control is related to combined use of therapies with different pharmacologic targets: the non-steroidal anti-inflammatory agents (NSAIDs) affect transduction while the opioids influence transmission

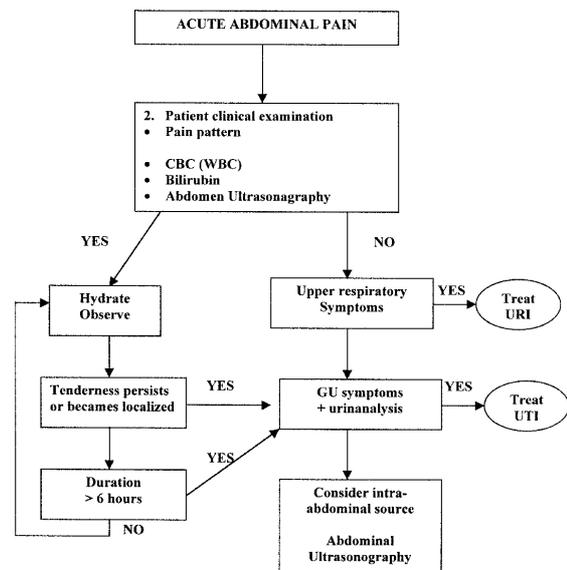
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**Figure 1 (left).** Algorithm for evaluating and managing acute painful crises in sickle cell patients admitted to the Emergency Department. *CBC: complete blood count; WBC: white cell count; TRES: erythrocyte apheresis; EX: manual red cell exchange.*

**Table 1. Acute events responsible for the admission of sickle cell patients to the emergency department.**

Acute painful crisis
Acute chest syndrome
Acute abdominal pain
Stroke
Acute anemic episodes (→ aplastic crisis)
Priapism



**Figure 2.** Algorithm for evaluating and managing acute abdominal pain in sickle cell anemia patients (modified from Scott-Conners and Brunson, 1994 and Ohene-Frempong K and Steinberg MH, 2001). *CBC: complete blood count; WBC: white cell count; URI: upper respiratory infection; UTI: urinary infection.*

and modulation of nociception and if used in systemic form, can influence pain perception.<sup>12,15</sup> The possible cause(s) of acute pain involving the bone-muscle district(s) may be: bone infarction, aseptic necrosis of the bone (epiphyseal segments of the humeri and especially the femora) or osteomyelitis. When the pain is in a joint and is associated with fever and local signs of arthritis, a septic arthritis must be excluded. *Third step.* The persistence of pain indicates admission to a Hematology department and a second level of analgesic treatment associated with transfusion treatment based on erythrocyte apheresis, manual red cell exchange, or transfusion of red cell units (Figure 1).

**Acute thoracic pain**

In sickle cell patients, the differential diagnosis of acute thoracic pain presents several difficulties. The possible causes are: pneumonia, thoracic vertebral collapse, pulmonary thromboembolism or acute chest syndrome. The rapid and correct diagnosis of acute chest syndrome (ACS) is crucial in sickle cell patients. ACS is the second most common complication (rate of 12.8 cases per 100 patient-years) and is the most common condition at the time of death in sickle cell patients.<sup>14,16,17</sup> The ACS is defined as *the new appearance of an infiltrate on chest radiograph or, in the presence of pulmonary symptoms (coughing, wheezing and*

**Table 2. Main causes of abdominal pain in sickle cell patients.**

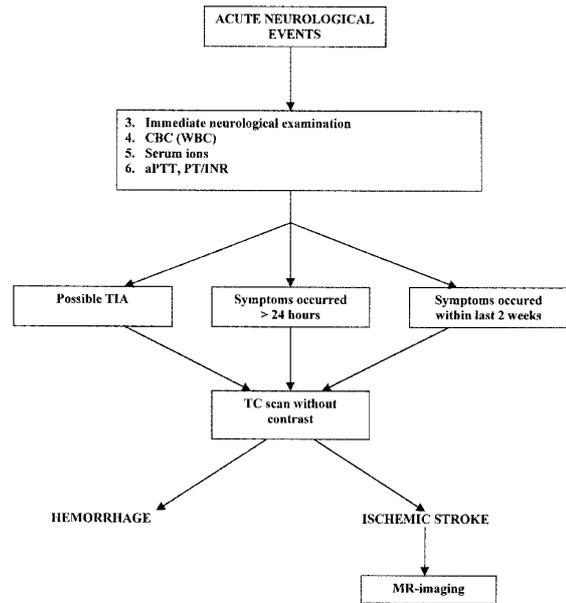
Hepatobiliar disease
Spleen origin: hemorrhage, infarction, sequestration abscess
Mesenteric ischemia/infarction
Renal origin: obstructive uropathy, stone, clot, papillary necrosis
Bone infarction: ribs, spine, femoral head
Osteoporosis and vertebral collapse
Nerve root compression
Cystitis
Gynecological origin

Modified from Scott-Conner and Brunson, 1994 and Ohene-Frempong K and Steinberg MH, 2001.

tachypnea) and negative chest radiograph, abnormalities on an isotopic scan of the lungs.<sup>18,19</sup> Lungs are particularly vulnerable to vaso-occlusive events because of their anatomic features. Dehydrated and sickled red blood cells are trapped in the pulmonary microcirculation, before reoxygenation and unsickling can occur, and this phenomenon results in frequent, diffuse microinfarction that results in severe acute and chronic lung disease. Subsequently, areas of lung ischemia caused by vaso-occlusion of large vessels are more prone to infection, playing part in the pathogenesis of ACS. The most frequent causes of ACS are fat embolism from bone marrow, infections (*Staphylococcus aureus*, *Streptococcus pneumoniae*, *Mycoplasma hominis*, parvovirus B19 and rhinovirus), iatrogenic fluid overload, hypoxia and atelectasis secondary to splinting from painful rib and sternal infarctions and pulmonary vascular obstruction.<sup>20,21</sup> Repeated episodes of ACS with pulmonary infarction are responsible for the evolution into pulmonary hypertension, pulmonary failure and terminal adult respiratory distress syndrome (ARDS).<sup>21,22</sup> A prospective study of sickle cell patients admitted to the Emergency Department for acute thoracic pain shows that the presence of fever is *per se* an indication for a chest X-ray.<sup>23</sup>

### Acute abdominal pain

Abdominal pain is frequently experienced by sickle cell patients. Table 2 shows the principal



**Figure 3. Algorithm for evaluating and managing acute neurologic events.** CBC: complete blood count; WBC: white cell count; aPTT: activated partial thromboplastin time, PT/INR: prothrombin time. TC scan: computerized tomography (CT) scan; MR: magnetic resonance imaging.

causes of abdominal pain in sickle cell disease. Studies by Scott-Conner and Brunson have shown that more than half of the episodes of acute abdominal pain in sickle cell disease are related to vaso-occlusive events, 40% of the episodes are due to gallbladder disease or appendicitis, 10-15 % are related to renal events, the others are due to pneumonia and gynecologic disease.<sup>22,24</sup> A recent study of sickle cell patients admitted to the Emergency Department for pain indicates that the routine use of a urinary dip stick is a rapid instrument for aiding differential diagnosis.<sup>25</sup>

### Acute neurologic events

Figure 3 shows the decision-making process for sickle cell patients presenting with acute neurologic signs. *First step.* Neurologic evaluation and patient's personal history. In sickle cell patients, the neurological symptoms are generally related to ischemic stroke, which frequently presents as focal signs, hemisensory deficits or visual disturbances.<sup>26</sup> The presence of additional risk factors for stroke events, other than the sickle cell disease, should be considered. Whenever patients presents with severe headache associated with different degrees of altered consciousness, intracranial hemorrhage should be considered.<sup>26,27</sup> The CSSCD identified the following risk factor for infarctive stroke: prior transient ischemic attack, steady-state hemoglobin (Hb) level, systolic blood pressure, acute chest syndrome within 2 weeks of the stroke event and rate

of ACS per year. The same study identified low steady-state Hb level and high leukocyte count as significant risk factors for hemorrhagic stroke.<sup>28</sup> *Second step.* The differential diagnosis is based on the results of cranial computerized tomography (CT) scanning without contrast, which is able to identify intracranial hemorrhage or brain ischemia after 3 hours or other possible neurologic causes such as abscess, tumors and some infections.<sup>27</sup> When these latter causes have been excluded, the next step is represented by the use of cranial magnetic resonance (MR) and/or perfusion MR imaging.<sup>29</sup>

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## Antibody-mediated thrombosis

GUIDO FINAZZI

Antibody-mediated thrombosis is an area of medicine that is currently receiving a great deal of attention<sup>1</sup> and a partial list of thrombotic diseases caused by antibodies is reported in Table 1. The pathophysiologic mechanisms by which antibodies may induce thrombosis are still incompletely clarified, although many interesting proposals have been put forward. While previous concepts mainly concentrated on inhibition of pathophysiologically important antithrombotic antigens by the antibody, current views emphasize tight attachment of antibody through various proteins to blood cells or endothelial cell membranes, followed by activation of the prothrombotic mechanisms within these cells. These concepts are better illustrated by heparin-induced thrombocytopenia and thrombosis and the antiphospholipid syndrome. These two clinical examples of antibody-mediated thrombosis are briefly reviewed herein.

### Heparin-induced thrombocytopenia

**Pathophysiology.** Heparin-induced thrombocytopenia (HIT) is an autoimmune disease mediated by an antibody that causes platelet activation in the presence of heparin (for a review, see ref. #2). The antigenic target of this antibody is a multimolecular complex formed by platelet factor 4 (PF4) and heparin. The mechanism responsible for platelet activation in patients with HIT has been elucidated: following heparin administration, or as a consequence of the thrombotic process for which heparin is administered, platelets release PF4; heparin-PF4 complexes form in the circulation and on the platelet surface. Antibodies to the heparin-PF4 complex may then develop. Binding of heparin-PF4-antibody complexes to the platelet surface leads to tight occupancy of the platelet FcγRII receptors by the IgG Fc-moiety. Strong platelet activation results, with further release of PF4; a vicious circle is activated, ultimately leading to thrombosis.

Generation of the antigen and induction of HIT antibody appear to depend on the molecular weight of the oligosaccharide. In a clinical trial of patients undergoing hip replacement surgery, Warkentin *et al.*<sup>3</sup> found significantly fewer HIT antibodies in patients receiving low-molecular-weight heparin (LMWH) than in those receiving unfractionated heparin (UFH) (2% vs. 8%, respectively). Theoretically, very small LMWH preparations (eg. pentasaccharide) will not cause HIT.

### Diagnostic and clinical aspects

The clinical diagnosis of HIT is usually made on the following criteria: a) a fall in platelet count by >50% of basal, typically occurring after 5 to 10 days of heparin use. Importantly, HIT can begin more rapidly (within 2 to 18 hours after the start of heparin) in patients who had already received heparin within the previous 100 days; b) exclusion of other causes of thrombocytopenia; c) possible contemporaneous occurrence of a new thromboembolic complication; d) resolution of thrombocytopenia after cessation of heparin; this last criterion, however, can only be applied retrospectively. Whenever possible, the clinical suspicion of HIT should be confirmed by a specific laboratory test, such as a now commercially available ELISA measuring the PF4-heparin complexes.<sup>4</sup>

Both venous and arterial thromboses may complicate HIT. Deep venous thrombosis and pulmonary embolism are the most frequent events. Other unusual venous thrombotic complications include warfarin-induced venous limb gangrene, cerebral sinus thrombosis and adrenal hemorrhagic infarction secondary to adrenal vein thrombosis. Arterial thrombosis commonly involves the large arteries of the lower limbs, leading to acute ischemia. Other complications that involve arteries include acute cerebrovascular accidents and myocardial infarction.

### Management

Discontinuation of heparin therapy has long been the cornerstone of management of HIT, but this step alone is not enough even for patients with isolated thrombocytopenia. The risk of thrombosis is 10% at 2 days, 40% at 7 days and 50% at 30 days despite stopping heparin. Thus, administration of another rapidly acting anticoagulant is recommended until the platelet count is restored. The major treatment options include danaparoid, hirudin and argatroban. However, only recombinant hirudin (lepirudin), a direct inhibitor of thrombin, is currently licensed in Italy. Lepirudin is given as a slow i.v. bolus, 0.4 mg/kg, followed by a continuous infusion at 0.15 mg/kg per hour, with dose adjustments to maintain the activated partial thromboplastin time (aPTT) between 1.5–2.5 times baseline. Lepirudin is highly effective in the treatment of patients with HIT but the risk of bleeding should be carefully considered.<sup>5,6</sup> Warfarin alone, LMWH and platelet transfusions are contraindicated in the acute phase of HIT. Warfarin should be given together with lepirudin until the platelet count has recovered. Then, warfarin can be continued alone.

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**Table 1. Main clinical syndromes characterized by antibody-mediated thrombosis.**

Heparin-induced thrombocytopenia
Antiphospholipid syndrome
Acute idiopathic thrombotic thrombocytopenic purpura (antibodies to vonWillebrand factor-cleaving protease) <sup>21</sup>
Postvaricella purpura fulminans (antibodies to Protein S) <sup>22</sup>

### The antiphospholipid syndrome

**Pathophysiology.** Antiphospholipid (aPL) antibodies are a large and heterogeneous group of immunoglobulins that include, among others, lupus anticoagulants (LAs) and anticardiolipin (aCL) antibodies.<sup>7</sup> LAs are acquired inhibitors of coagulation, first described in patients with systemic lupus erythematosus (SLE), which prolong phospholipid-dependent coagulation reactions. Despite this *in vitro* behavior, LAs are not usually associated with bleeding complications. aCL antibodies react with anionic phospholipid in solid phase immunoassays, and are responsible for the biological false positive test for syphilis. LAs and aCL antibodies are closely related antibodies, as they are concurrently present in approximately two thirds of the patients.

In the 1990s, work from different laboratories made it clear that LAs and aCL antibodies do not recognize anionic phospholipids, as had long been believed, but rather plasma proteins bound to suitable anionic (not necessarily, phospholipid) surfaces. Among such proteins,  $\beta$ 2-glycoprotein I ( $\beta$ 2-GPI), and prothrombin (PT) are the most common and investigated antigenic targets.  $\beta$ 2-GPI is required by the great majority of aCL antibodies to react with cardiolipin in immunoassays, whereas LA activity in phospholipid-dependent coagulation tests is caused by both  $\alpha$  $\beta$ 2-GPI and aPT antibodies. Other proteins recognized by aPL antibodies are activated protein C, protein S, annexin V, low- and high-molecular weight kininogens, factor XII, and tissue-type plasminogen activator. As most of these proteins are involved in the regulation of the coagulation processes, it is conceivable that antibodies that reduce their plasma concentration and/or hamper their function may produce an imbalance between the pro- and anti-coagulant systems, thus explaining the increased thrombotic risk of the patients.

Interestingly, a pathogenetic scenario for antiphospholipid-mediated thrombosis based on parallelism with HIT has been proposed:<sup>8</sup> a small initial activation results in local exposure of negatively charged phospholipid on the surface of platelets, endothelial cells and probably leukocytes; binding of

$\beta$ 2-GPI (or other phospholipid-binding proteins) to this surface is facilitated by specific IgG with lupus anticoagulant properties; this antibody subsequently attaches tightly through interaction of its Fc portion with the surface Fc $\gamma$ RII receptor; further cellular activation ensues, resulting in a localized prothrombotic vicious circle and ultimately thrombosis. It should be recognized, however, that other potential thrombogenic mechanisms of antiphospholipid antibodies have been reported.<sup>7</sup>

### Clinical features and predictors of thrombotic risk

The clinical importance of aPL derives from their association with a syndrome of vascular thrombosis and complications of pregnancy, named *antiphospholipid syndrome* (APS).<sup>9</sup> Cumulative retrospective literature data indicate that a history of thrombosis is present in approximately 30–40% of patients with aPL and that 70% of the events are venous and 30% arterial. Deep vein thrombosis and pulmonary emboli are the most common venous events while the cerebral circulation is the most commonly affected arterial site. Thrombosis tends to be recurrent and recurrences tend to occur in the same vascular district (venous or arterial) as the initial event.

The natural history and risk factors for thrombosis in patients with aPL have been analyzed in detail in a prospective study from the Italian Registry.<sup>10</sup> Three hundred and sixty consecutive patients (males/females 118/242, median age 39 years, range 2–78), fulfilling the currently accepted criteria for diagnosis of lupus anticoagulant (n=326) and/or raised IgG anticardiolipin antibodies (n=185), were collected from 16 institutions. After a median follow-up of 3.9 years (range 0.5–5), 34 patients developed a thrombotic complication, with a total incidence of 2.5% patient-year. Multivariate logistic regression analysis identified a previous thrombosis as the most important clinical risk factor for thrombotic events. Patients with a history of vascular events showed a 5.4% patient-year incidence of further complications, whereas the incidence in asymptomatic subjects was 0.95% patient-year. Age, sex, previous miscarriages, underlying SLE or related disease, thrombocytopenia and smoking were not independent risk factors for thrombosis. Thus, patients with aPL at presentation might be divided into two groups: the first, the asymptomatic subjects, have a low risk of vascular complications and needs only careful observation; the second, patients with previous thrombosis and/or recurrent abortion, need active therapy.

A considerable number of studies have been performed in the attempt to establish the role for the different aPL antibodies as risk factors of arterial and/or venous thrombosis in the APS. By reviewing the relevant literature from 1988 to 2000, the sen-

**Table 2. Type of antibody and risk of thrombosis in patients with the Antiphospholipid Syndrome. Cumulative analysis of the literature 1988-2000 (see text and refs.11 and 12 for details).**

Type of antibody	Strength of association with thrombosis	
	Retrospective studies	Prospective studies
Lupus Anticoagulant	++	++
Anticardiolipin	+	+
High titers	+	+
Low titers	-	-
Anti- $\beta$ 2-glycoprotein	+/-	+/-
Antiprothrombin	+/-	+/-

++ strong association; + significant association; +/- uncertain association; - no association; \* heterogeneous results with different reagents.

sitivity, specificity, and *odds ratio* (with 95% confidence interval, CI) for arterial and venous thromboses of the different aPL antibodies were either taken from each study or, whenever possible, calculated<sup>11,12</sup> (Table 2). This analysis suggests that LAs are the strongest risk factor for thromboembolic events for aPL-positive patients. Therefore, each case with clinical manifestations of APS should undergo testing for LAs, irrespective of the laboratory methodology employed for their detection. The results are less clear for aCL antibodies, although high-titers were more associated with thrombosis than low-titers. These findings also support only in part the concept that  $\alpha\beta$ 2-GPI and aPT antibodies may be an independent risk factor for thrombosis. The measurement of these latter antibodies should, therefore, be performed only in the setting of *ad hoc* clinical studies.

### Management

The optimal treatment of patients with aPL and thrombosis was first evaluated in retrospective studies.<sup>13-14</sup> These studies showed that high-intensity warfarin therapy (INR>3) was significantly more effective than standard-intensity warfarin (INR 2.0-3.0) or aspirin alone in preventing recurrent vascular events (recurrence rates 1.3%, 23% and 18% per year, respectively).<sup>14</sup> However, there is concern about the implications of recommending such therapy on the basis of retrospective and non-randomized data. Fatal, cerebral or uncontrollable bleeding was reported during anticoagulation in such patients<sup>15,16</sup> and the cumulative risk of hemorrhage is expected to increase with duration and intensity of treatment. The need for intensive anticoagulation was challenged by the results of a randomized clinical trial

recently published in abstract form. Crowther *et al.*<sup>17</sup> reported 114 patients with aPL and thrombosis treated with standard intensity (INR 2.0-3.0) or high intensity (INR 3.1-4.0) warfarin therapy and followed for an average of 2.68 years. Five of 58 (8.6%) patients allocated to standard intensity warfarin and 10 of 56 (17.8%) allocated to high intensity warfarin suffered an objectively confirmed recurrent thromboembolism or a major bleeding complication. Thus, the appropriate therapeutic range of oral anticoagulation for patients with aPL and thrombosis is disputed and the results of other controlled clinical trials, such as the recently completed WAPS study,<sup>18</sup> are awaited. In the meantime, it is probably wise to prefer standard intensity oral anticoagulation for most patients with aPL and a first thrombotic episode, reserving high intensity warfarin therapy for those with recurrent thrombosis despite conventional treatment.<sup>19</sup>

A minority of patients with APS present with an acute and devastating syndrome characterized by multiple simultaneous vascular occlusions throughout the body, often resulting in death. This syndrome, termed *catastrophic APS*, is defined by the clinical involvement of at least three different organ systems over a period of days or weeks with histopathologic evidence of multiple occlusions of large or small vessels.<sup>20</sup> The mortality rate is 50%, and death is usually due to multiorgan failure. Recommendations for the treatment of catastrophic APS are based entirely on case reports. In a series of 50 patients,<sup>20</sup> recovery occurred in 14 of 20 patients (70%) treated with a combination of anticoagulants and steroids plus either intravenous immune globulin or plasmapheresis. The rationale for plasmapheresis derives from its documented effectiveness in treating thrombotic thrombocytopenic purpura, which is, at least in some cases, another immune-mediated thrombosis,<sup>21</sup> emphasizing the concept of a spectrum of thrombotic diseases underlaid by impaired autoimmunity.

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## Acquired hemophilia and its treatment

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Acquired hemophilia is a rare clinical syndrome characterized by the sudden onset of bleeding, either spontaneously or after surgery or trauma, which is usually severe (87% of the cases) and occurs in patients with a negative family or personal history for bleeding.<sup>1-4</sup> The depletion of factor VIII (FVIII) and much less frequently of factor IX, is mediated by specific autoantibodies. The auto-antibodies are usually IgG (mainly IgG4) directed against specific functional epitopes that neutralize FVIII and/or accelerate its clearance from the plasma.<sup>5</sup> The incidence of acquired hemophilia varies between 0.1 to 1.0 per million/population per year.<sup>1,2,6,7</sup> The age of presentation averages 65 years with a wide range of distribution. The incidence increases with age, with equal sex distribution except in the younger group because of the cases related to pregnancy.<sup>1-4,8,9</sup>

Acquired haemophilia is commonly associated with a variety of clinical conditions, autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis, asthma), solid tumors, lymphoproliferative diseases, drug hypersensitivity and pregnancy; 50% of the cases are idiopathic<sup>1,3,8-12</sup> (Table 1).

### Clinical picture

The clinical picture is characterized by the acute onset of severe bleeding or diffuse bruising occurring either spontaneously or following minor trauma or after a procedure (positioning of an intravenous catheter, surgery, intramuscular injection). Common sites of bleeding are the skin (large ecchymoses), the mucosae (epistaxis, gingivorrhagia, metrorrhagia), and the muscles; hemarthroses are unusual.<sup>3,4,9,11,12</sup> Retroperitoneal hemorrhages are common and sometimes fatal. If the bleeding occurs in critical sites, compression problems may ensue. Bleeding is more severe than in congenital severe hemophilia with or without antibodies in spite of the higher observed levels of FVIII. The severity of bleeding is not proportional to the inhibitor titer.<sup>8</sup> Spontaneous disappearance of the inhibitor occurs in 5-30% of the patients (mainly in the post partum cases) over a period of weeks or months;<sup>6</sup> mortality related to bleeding is 8-22% of the cases<sup>1-4,7-12</sup> with the majority of deaths occurring within the first weeks after presentation.<sup>1,3,8,9</sup> The high rate of death may

be related to the invasive procedures carried out to control bleeding, to a delay in diagnosis and to inadequate replacement therapy.<sup>9</sup>

Pregnancy is a frequent concomitant condition (7-21%);<sup>1-4,7-9</sup> in general the inhibitor occurs in the first pregnancy<sup>13-17</sup> and does not recur in subsequent pregnancies although recurrence was reported in some series.<sup>18</sup> The inhibitor may disappear spontaneously or may persist for months or years with a consequent high risk of bleeding. The inhibitor is in general identified on occasion of overt bleeding, which usually occurs in the post-partum period but may also happen during pregnancy, pre-partum and after delivery. The time of the development of the inhibitor in relation to the bleeding cannot be retrospectively determined. Severe metrorrhagia is common, but bleeding may be delayed, mild, and self-limited with stable hemoglobin and may not require therapy.<sup>9</sup> It must be emphasized that in patients who undergo hysterectomy, it may already be known that the APTT is prolonged, but this is overlooked and the inhibitor recognized because of the excessive surgical bleeding.<sup>9</sup> With adequate diagnosis and replacement therapy hysterectomy could be avoided. The inhibitor titer is not usually correlated with the intensity of bleeding although this correlation has been reported.<sup>13,18</sup> No fatalities were reported in our series<sup>9</sup> or in that of Solymoss;<sup>18</sup> the death rate was 10% in the survey of Michiels.<sup>16</sup> Inhibitors may cross the placenta and may persist for up to three months in the neonate, usually without causing bleeding complications.<sup>19,20</sup> However Ries reported a case of intracranial hemorrhage in a neonate.<sup>21</sup> These data suggest that delivery should be managed as in hemophilia.<sup>22</sup>

Five to 15% of the patients with acquired hemophilia have a concomitant malignancy, three times more common in male than in females, without any relation to the tumor type although solid tumors are much more commonly associated with bleeding than lymphoproliferative diseases.<sup>3,8,23-25</sup> Chemotherapy, immunosuppressive therapy and radiotherapy are not in general associated with the disappearance of the inhibitor but low titer inhibitors, associated with early stages of neoplastic disease, are more likely to disappear with effective treatment of the tumor than are high titer ones.<sup>23,25</sup> The persistence of the inhibitor may condition survival because of bleeding complications.<sup>25</sup>

### Diagnosis of acquired hemophilia

The diagnosis of acquired hemophilia is suggested by the clinical picture and confirmed by laboratory tests. The prolonged activated partial thromboplastin time

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**Table 1. Clinical conditions associated with acquired FVIII/FIX inhibitors.**

Clinical conditions	Green D <sup>1</sup>	Morrison AE <sup>3</sup>	Bossi P <sup>8</sup>	Baudo F <sup>9</sup>
Number of patients	215	65	34	96
Idiopathic	46.1	52.5	47.1	46.8
Autoimmune disorders	20.4	21.5	17.6	16.6
Drug related	3.0	5.6	2.9	0
Pregnancy and <i>post-partum</i>	11.0	7.3	8.9	21.0
Malignancies	13.5	5.5	14.6	9.4
Other	1.5	11.8	8.8	6.2

(APTT), not corrected by incubation with normal plasma, with a normal prothrombin time is the hallmark of the laboratory diagnosis. The APTT of a mixture of the patient's plasma with normal plasma must be carried out before and after incubation at 37°C for 2-4 hours because the inactivation of FVIII is time- and temperature-dependent. The diagnosis is confirmed by the specific factor assay and by dosage of the inhibitor.<sup>2,11,12</sup>

### Therapy of acquired hemophilia

The objectives of therapy are control of the bleeding and suppression of the antibodies.

### Therapy to control bleeding

No prospective randomized trial comparing the efficacy of various agents has been reported and none of the available agents is effective in all patients. The studies reported so far include a limited number of patients with primary disorders of different etiology. Efficient hemostasis can be achieved by the normalization/correction of FVIII plasma level (human, porcine or recombinant FVIII concentrates, desmopressin), bypassing the inhibitor (activated prothrombin complex concentrate, recombinant FVIIa), by neutralization of the inhibitor (high dose immunoglobulin for the high content of idiotypic anti-FVIII antibodies) or by its removal. Immunoadsorption and plasmapheresis are methods of removal. Combined modalities may be necessary.

The selection criteria for anti-hemorrhagic therapy are the site and entity of bleeding, age, underlying disorders, co-morbidity states, inhibitor titer, cross-reactivity with porcine FVIII, and anamnestic

**Table 2. Agents used and recommended dose in the treatment of acute bleeding in acquired hemophilia.**

Agents	Initial dose	Subsequent doses
Human FVIII	50-100 IU/kg	50-75 IU/kg 2-3 times/ day or 4-14 U/kg/h by c.i.
Porcine FVIII	50-100 IU/kg	50-75 IU/kg 2-3 times/ day or 4-14 U/kg/h by c.i.
R FVIII	50-100 IU/kg	50-75 IU/kg 2-3 times/ day or 4-14 U/kg/h by c.i.
DDAVP	0.3 µg/kg	0.3 µg/kg/day
High dose Ig	1 or 0.4 g/kg	1 or 0.4 g/kg for 2 or 5 consecutive days
APCC	50-100 IU/kg	50-75 IU/kg 2-3 times/ day or c.i.
rFVIIa	90 µg/kg	90 µg/kg every 3-6 hours or 10-20 µg/kg/h by c.i.

response. Life- or limb-threatening bleeding must be treated aggressively. Only in the case of *minor bleeding* (e.g. ecchymoses) observation is justified. The bleeding-related mortality rate approaches 15%, mainly due to early hemorrhagic complications, which underscores the importance of quick and effective diagnosis and treatment. The therapeutic agents and the recommended doses for the management of acute bleeding are reported in Table 2.

### Patients with low-titer inhibitor (<5 BU/mL)

Replacement with human FVIII concentrate is the treatment of choice.<sup>11,12,26</sup> In acquired hemophilia the anamnestic responses to FVIII infusion are rarely reported.<sup>17,18,27,30</sup> The recovery and half-life of the infused FVIII cannot be predicted because of the variable kinetics of FVIII.<sup>2,5</sup> An initial dose (75-100 U/kg) is given to neutralize the inhibitor and then followed by a continuous infusion of 4-14 U/kg/h to achieve and maintain the hemostatic level.<sup>28,29</sup> The advantages of FVIII concentrates are better predictability of therapeutic efficacy and ease of laboratory monitoring. High doses of intermediate-purity FVIII concentrates have the potential side-effects of inducing immune hemolysis because of their anti-A isoantibody content.<sup>31,32</sup> Various FVIII concentrates are commercially available with comparable therapeutic efficacy and safety.

DDAVP (1-deamino-8-D-arginine) infusion at the dose of 0.3 µg/kg results in a rapid increase of FVIII sufficient to treat minor bleeding.<sup>33,35</sup> The tachyphylaxis phenomenon limits its use to 3 or 4 consecutive days. The well-known antidiuretic and vasomotor

side-effects should be carefully considered in older patients.<sup>11,35</sup>

Intravenous high dose immunoglobulins (1 or 0.4 g/kg for 2 or 5 consecutive days, respectively) induced complete or partial remission in 23–37% of patients, mainly in those with low titer inhibitors.<sup>36</sup> Multiple courses are needed to obtain a sustained response. The high costs have limited its uses.

#### *Patients with high inhibitor titer (>5 BU/mL)*

*Recombinant FVIIa* has represented a major advance in the treatment of bleeding in congenital hemophilia with inhibitors; however, its use in acquired hemophilia, details of administration, efficacy and safety are poorly defined. Favorable reports in patients who failed to benefit from other treatments suggest that it may be suitable as first-line therapy. The disadvantages are its high cost, the lack of laboratory monitoring and its short half-life (6 hours) necessitating frequent administrations; thromboembolic complications are rare.<sup>37-40</sup>

*Bypassing concentrate* (FEIBA) promotes hemostasis by mechanisms not fully understood. Efficacy is not predictable and laboratory monitoring is not satisfactory.<sup>41-43</sup> Only clinical endpoints can be used to monitor treatment. Thromboembolic complications are possible.<sup>44</sup>

FVIII autoantibodies have a lower cross-reactivity to *porcine* FVIII than to human FVIII; therefore a satisfactory hemostatic level may be obtained even in patients with high inhibitor titer.<sup>45-48</sup> Reactions, such as pyrexia, flushing, and urticaria, may be seen during the initial infusion; mild thrombocytopenia or severe anaphylactic reactions are rarely observed with the recent formulations obtained by serial polyelectrolyte fractionation.<sup>49-5</sup>

In particular clinical conditions (e.g. prior to surgery) effective hemostasis can be restored by the removal of the inhibitor by *plasmapheresis* or by *immunoabsorption* (sepharose-bound staphylococcal protein A, protein A bound to silica matrix, or sepharose-bound polyclonal sheep anti-human antibodies). Extracorporeal methods have only temporary effect and replacement therapy with FVIII is needed immediately after the procedure. Because of the subsequent rebound in the inhibitor titer after the procedure, simultaneous immunosuppression is needed. Limitations of the use of immunoabsorption are the need of special equipment and expertise, but in the case of life-threatening hemorrhages it can be lifesaving.<sup>54-58</sup>

#### **Therapy to suppress the inhibitor**

The aim of immunosuppressive therapy is to suppress the cellular clone responsible for synthesis of the inhibitor. Predictive factors for a positive response are a low inhibitor level and a short time interval between the appearance of the inhibitor and the start of immunosuppressive therapy.<sup>11,12,59</sup>

Several reports have addressed the question of controlling the acquired inhibitors by immunosuppressive therapy. Prednisone, cyclophosphamide, azathioprine, vincristine, and cyclosporine are all currently used as monotherapy or in combination. There are no prospective, controlled clinical studies to evaluate their efficacy. The available studies are retrospective and include a limited number of patients with different clinical conditions. On the other hand it would be difficult to carry out sufficiently powered prospective, controlled studies to evaluate the efficacy of the different therapeutic agents. Efficacy is also difficult to assess because of the possibility of spontaneous remissions (mainly in children, post-partum cases and drug-associated cases).<sup>6,13</sup> Severe and life-threatening hemorrhages may occur in 80-90% of patients in the course of the disease, suggesting that immunosuppressive therapy must be started as soon as the diagnosis is established.<sup>60,61</sup> In the post-partum cases, the prognosis is generally favorable.<sup>16,18</sup>

Immunosuppressive treatment with steroids alone is the initial preferred treatment. In children, in post-partum women and in drug-associated cases complete disappearance of the inhibitor was reported in 33-96% of the patients.<sup>1,9,62,63</sup> The patients unresponsive to steroids were treated with chemotherapeutic agents alone or combined with steroids with an overall response rate of 58-80%.<sup>1,9,63</sup> The relapse rate averaged 23%<sup>9,62</sup> but a second remission was obtained in 90% of the patients with combined therapy.<sup>9</sup> Inhibitors associated with pregnancy should be considered separately. In over 60% of the cases the inhibitor disappears spontaneously after a mean period of 3 months. In the Italian survey immunosuppressive treatment with steroids alone or in combination with other agents was the preferred treatment. The response rate was high (94%), the relapse rate was also high (42%) but all the patients were rescued.<sup>9</sup> Immunosuppressive therapy may shorten the time to response without influencing the response rate. Hauser *et al.* reviewed the *post-partum* data in the literature comparing the results of immunosuppressive therapy and no treatment. The time to response was shorter in the treated patients but the overall response rate was not different.<sup>13</sup> Similar results were reported by Michiels.<sup>16</sup> These studies must be considered with caution for a number of reasons. They were retrospective, referred to a small number of patients with heterogeneous characteristics and had no predefined criteria for treatment.

Different strategies may be suitable for different subgroups of patients.<sup>3</sup> A *watch-and-wait* approach may be appropriate for children and pregnancy-related and drug-associated cases; combined immunosuppressive therapy is indicated for idiopathic, autoimmune and malignancy-related cases.

Current evidence from the literature suggests that prednisone at the dose  $\geq 1$  mg/kg per day for a minimum of three weeks induces inhibitor disappearance in 1/3 of patients, generally those with low titer inhibitors, but that sustained remission after prednisone discontinuation is rare; cyclophosphamide (2 mg/kg per day) combined with prednisone and/or vincristine, azathioprine, induces complete and continuous remissions in a high percentage of cases (78-92%) provided that the therapy is continued until the inhibitor disappears completely and that it is administered at adequate doses.<sup>11,12,59</sup> Previous experience in hemophiliacs emphasized the importance of carrying out the treatment according to hematologic tolerance.<sup>64</sup> A low inhibitor titer and a short time interval between inhibitor appearance and start of immunotherapy are favorable prognostic factors.<sup>3,65</sup>

Immune tolerance is an accepted and effective treatment in patients with congenital hemophilia and as inhibitor but has rarely been applied in acquired hemophilia. Evidence of its effectiveness and safety in acquired hemophilia was provided by the Budapest protocol<sup>66</sup> [human FVIII 30 U/kg/day for the first week, 20 U/kg/day for the second week and 15 U/kg/day for the third week combined with i.v. cyclophosphamide 200 mg/day (total dose 2-3 gr) and i.v. methylprednisolone 100 mg/day for the first week, tapering the dose gradually over the next two weeks]. A complete and sustained remission was reported in more than 90% of the patients. Similar results have been reported by the Heidelberg group,<sup>67</sup> which used a modified Malmö protocol (immunoabsorption, high doses of FVIII, cyclophosphamide and corticosteroids). Very recently promising results have been reported with an anti-CD20 monoclonal antibody (rituximab).<sup>68,69</sup>

The majority of cases of acquired hemophilia occur in general hospitals and bleeding manifestations may be life-threatening. In the presence of an unexplained, often severe hemorrhage with an abnormally prolonged APTT it is important to seek immediate specialist advice. A prolonged APTT is often observed and overlooked. Because of the rarity of the disorder, the complex treatment and the potential risk of severe bleeding, these patients should be managed in hemophilia centers or under their supervision.<sup>3</sup>

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## Hemorrhagic complications of oral anticoagulation

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Oral anticoagulant therapy (OAT) is increasingly used for the prevention and treatment of thromboembolic complications from vascular diseases, on the basis of accumulating evidence of its effectiveness in many clinical indications. OAT is, however, associated with a not negligible risk of adverse effects. Bleeding is the most important complication and is a major concern for both physicians and patients, limiting the more widespread use of OAT. Consensus on the true incidence of bleeding is, however, difficult to reach since rates vary widely across published studies. First of all, since the adopted classification of bleeding events (major or minor) differs significantly in clinical studies, reported rates are hardly comparable. Moreover, reliable data on the true incidence of complications in patients commencing OAT are scanty because the available studies have often been affected by methodological limitations. Many studies were performed before the introduction of the international normalized ratio (INR) system for expressing prothrombin time results (PT) while others either did not adopt the INR system or calculated INR values via retrospective analysis of the observed PT ratios. Most recent studies using INR system have been experimental in nature and have included only highly selected patients, whose expected bleeding risk was lower than that found in the varied mix of patients treated in clinical practice. Some observational studies were either retrospective or descriptive and were not performed on a clearly defined inception cohort of patients;<sup>1,2</sup> others, which included an inception cohort of patients, were retrospective and either did not use INR values<sup>3</sup> or included patients who were treated for selected indications.<sup>4</sup> Earlier studies used higher intensity anticoagulation, while only very few recent studies have been of an observational nature, including an inception cohort of unselected patients and adopting well defined therapeutic ranges as endorsed by the scientific community.<sup>5</sup>

### Definition of major hemorrhage

The expected rate of bleeding complications, especially major ones, is the crucial factor when determining the evaluation of risks/benefits in OAT and a wider use of this therapy. The adopted classification of bleed-

ing events markedly influences the rate of complications reported in clinical studies. Unfortunately, a wide variety of classifications have been adopted in clinical studies on OAT, probably accounting for the major differences in the bleeding rates reported in the different studies. In this regard the following should be considered: a) a classification of bleeding episodes is acceptable if it is easily reproducible and adequately reflects the clinical relevance of hemorrhage; b) the most important difference in the various adopted classifications regards the definition of major hemorrhage; and c) the more clinically irrelevant events are included in classification the greater the difference may be between observed rates in clinical studies.<sup>6</sup> The definition of major hemorrhage should reflect the severity of an outcome. If it includes hospitalization- without concomitant decrease in hemoglobin or need for blood transfusion, as adopted in some studies<sup>1,7</sup> - it will overestimate the severity of bleeding, especially in elderly patients, since the decision to hospitalize a patient may be subjective and may reflect differences in health system procedures in different countries, different practices between physicians, presence of concomitant diseases and even social factors such as lack of family or social support. Some authors<sup>7</sup> consider bleeding to be major when it prompts cessation of therapy; this may also lead to an overestimation of the rate of major bleeding.

A largely adopted and validated classification of hemorrhages is reported in Table 1.

### Rates of bleeding complications in experimental and observational studies

As pointed out above, information from observational studies may differ from that derived from experimental trials on selected patients. In a review of controlled trials, the rate of fatal bleeding ranged from 0 to 4.8%, and that of major bleeding from 2.4% to 8.1% patient/years.<sup>8</sup> On the other hand, observational studies reported an average annual rate of fatal, major and minor bleeding episodes of, respectively, 0.8%, 4.9% and 15%.<sup>2</sup> However the reliability of these data is debatable, as most of the observational studies were either retrospective or descriptive rather than prospective, and the INR system was generally not used as the reference for the degree of anticoagulation.

The ISCOAT study (*Italian Study on Complications of Oral Anticoagulant Therapy*)<sup>5</sup> was a collaborative, prospective, inception cohort, nation-wide study offering an *on field* picture of what can be expected, in terms

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of bleeding complications, in a European country with a good network of anticoagulation centers. The study was conducted in 2745 consecutive patients observed from the start of their anticoagulation course, with a total follow-up of 2011 patient/years. Patients with various indications for oral anticoagulation were included: venous thromboembolism (32.5% of cases), non-ischemic heart disease (24.1%), ischemic heart disease (14.7%), peripheral arterial or cerebrovascular disease (10.2%), heart valve prostheses (10.8%) and heart valve disease (6.7%). The ISCOAT study showed that, in the normal practice of Italian Centers, the rates of fatal, major and minor bleeding were, respectively, 0.25, 1.1, and 6.2 per 100 patient/years, figures consistently lower than those previously reported in the surveys of both experimental and observational studies. The low bleeding rate was not connected with lower efficacy of anticoagulation, as the rate of thrombotic recurrences was also lower than in other studies.<sup>9</sup>

#### **The major determinants of oral anticoagulant-induced bleeding-intensity of anticoagulant effect**

The actually achieved intensity of anticoagulation is likely the most important determinant of bleeding risk. In clinical trials, subjects randomized to a higher level of anticoagulation had a higher risk of bleeding than those who were treated at a lower anticoagulation intensity.<sup>10-13</sup>

In line with the results of other studies,<sup>1</sup> the observational ISCOAT study<sup>5</sup> did not find a significant relationship between risk of bleeding and target zone; however, a relationship between intensity of anticoagulation achieved and temporally related risk of bleeding was clearly evident. In the ISCOAT study the incidence of bleeding events at different achieved intensities of anticoagulation was investigated by dividing the number of events occurring in patients with temporally related INR values in increasing INR categories (< 2, 2-2.9, 3-4.4, 4.5-6.9, > 7.0 INR) by the total number of patient-years accumulated in these categories. The lowest rate of bleeding (4.8% patient-years) was found in the 2.0-2.9 INR category, whereas many bleeding events occurred at a very low anticoagulation intensity (7.7% patient-years in the < 2 INR category). Along with a further increase in INR levels there was an increase in the bleeding incidence which became exponential for INR values > 4.5. The multivariate analysis confirmed that the risk of bleeding was markedly higher when INR values exceeded 4.5 ( $p < 0.0001$ ). The finding of a substantial risk of bleeding even in conjunction with very low INR (< 2.0) is in line with other reports<sup>3</sup> and suggests that some bleeds during OAT are not related to the intensity of anticoagulation but rather to the possible presence in some patients of

**Table 1. Classification of bleeding events.**

Major bleeding
• Fatal (due to hemorrhage)
• Intracranial (confirmed by CT or MRI)
• Intra-ocular (with visual loss)
• Intra-articular (major joints)
• Retroperitoneal (confirmed by CT or MRI, or by surgery)
• If surgery or invasive procedures are required to arrest bleeding
• If hemoglobin falls 2g/dL or more, or 2 units or more blood transfusion are needed
Minor
All those that are not major
• Hematuria (macroscopic)
• Bruising (over 5 cm diameter, or at 3 or more sites)
• Muscle hematoma
• Rectal bleeding (without local cause)
• Menorrhagia/metrorrhagia
• Gastrointestinal bleeding
• Hemoptysis
• Post-dental bleeding requiring intervention
• Nose bleeds requiring intervention
• Other sites
The following should not be considered as bleeding outcomes: small bruising, small ecchymoses, self-limiting nose-bleeds, occasional bleeding from hemorrhoids, microscopic hematuria.

**Table 2. Major determinants of OAT-induced bleeding.**

• Intensity of anticoagulant effect
• Patient's characteristics
• Age
• (Sex)
• History of past bleeding
• Co-morbid conditions
• Underlying pathologic lesions
• Duration of OAT
• Indication for OAT
• Services provided and surveillance

a local bleeding source that may be unmasked by anticoagulant therapy.<sup>14</sup>

### **Patient characteristics**

**Sex.** While some studies have noted an increased rate of bleeding in women treated with warfarin,<sup>1,2,15</sup> others have not confirmed this finding.<sup>5,16</sup>

**Age.** It has long been a matter of debate whether the risk of bleeding during OAT is higher in older patients.<sup>17-20</sup> In the ISCOAT study patients > 70 years old showed a relative risk of 1.75 ( $p < 0.01$ ) compared to all the others. Similar results have been found by several recent observational studies,<sup>1,3,15,16</sup> though not by all.<sup>2</sup>

In a more recent paper, reporting the results of a large, prospective, multicenter, nested, case-control study,<sup>21</sup> it was shown that the trend for overall, rates of bleeding being higher in patients aged 75 years or older (9.9% patient-years) than in matched (for sex, main indication for therapy and treating center) younger controls aged less than 70 (6.9% patient-years) was not significant. However, there was a higher risk of major (2.1% patient-years versus 1.1% patient-years) and fatal complications in elderly patients than in controls (6 versus only 1, all due to intracranial bleeding). These results are in keeping with the findings of recent studies in which the risk of life-threatening or fatal bleeding was significantly higher in older patients treated with oral anticoagulants than in younger ones.<sup>22,23</sup> Others have also reported that the risk of intracranial bleeding during OAT is higher in older people.<sup>3,24,25</sup> In their review, Hart *et al.*<sup>26</sup> concluded that predictors of intracerebral hematoma during OAT are advanced age, prior ischemic stroke, hypertension and intensity of anticoagulation.

Though most physicians are aware of the higher risk of OAT in the elderly, an increasing number of elderly patients are treated with anticoagulants. More than one third of all the patients included in our study were > 70 years old. We are thus faced with the dilemma that, although older patients are likely to benefit most from OAT, they have an increased risk of major bleeding complications. It is, therefore, important to assess the individual risk of anticoagulation-related bleeding in older patients in order to consider avoiding treatment in those at higher risk. Elderly patients on anticoagulants should be: treated at a low target range; monitored closely to keep their INRs within the therapeutic range; carefully followed so that conditions which may potentially interfere with OAT (such as intercurrent illnesses, co-interventions, treatment compliance and diet) can be monitored, detected and modified as appropriate.

### **Type of indication for treatment**

There are data showing that the risk of bleeding is higher when the indication for anticoagulant

treatment is the presence of arterial disease. In the ISCOAT study<sup>5</sup> bleeding was particularly frequent in patients treated for cerebrovascular disease (14.5% patient-years). The higher incidence of bleeding in cerebrovascular or other *arterial* patients than in other types of patients (those with deep vein thrombosis, atrial fibrillation, prosthetic valves) raises the question of whether the risk of bleeding during anticoagulation outweighs the benefits in these conditions.

### **Concomitant diseases and co-medications**

Some patients have more than one indication for OAT, a condition which seems to increase the risk of bleeding. About one third of the patients who presented bleeding complications during the ISCOAT study<sup>5</sup> had other clinical indications for OAT beyond the main one, most frequently the presence of peripheral and/or cerebral arterial disease, ischemic heart disease and atrial fibrillation. At least one co-morbid condition or general risk factor was present from the beginning of OAT in more than half of the patients who experienced bleeding. In a few cases it was possible to correlate the occurrence of a bleeding episode with the onset of specific pro-hemorrhagic conditions, such as trauma, urinary infections and/or nephrolithiasis, heparin co-administration, thrombocytopenia and lung disease. A history of gastrointestinal hemorrhages is a risk factor for bleeding during OAT;<sup>27</sup> however, peptic ulcer disease without previous hemorrhages has not been associated with a higher risk of bleeding.<sup>28</sup>

In some patients the occurrence of venous thromboembolism is associated with a malignancy. These patients should be treated with warfarin for an undefined period to reduce the risk of recurrence even though their risk of bleeding during OAT is markedly higher than in patients without cancer. A recent study<sup>29</sup> compared the outcome of anticoagulation courses in 95 patients with malignancy and in 733 patients without malignancy. All patients were participants in a large, nation-wide population study and were prospectively followed from the initiation of their oral anticoagulant therapy. The rates of major (5.4% vs 0.9%), minor (16.2% vs 3.6%) and total (21.6% vs 4.5%) bleeding were statistically significantly higher in cancer patients than in non-cancer patients. Bleeding was also a more frequent cause of early anticoagulation withdrawal in patients with malignancy (4.2% vs 0.7%;  $p < 0.01$ ; RR 6.2 (95%CI 1.95-19.4). In the group of patients with cancer, the bleeding rate was high across the different INR categories and was independent of the temporally associated INR. In contrast, in the group of patients without cancer the bleeding rate increased only in cases with INR values over 4.5. Similar results have recently been reported by other authors.<sup>30</sup>

Except for patients anticoagulated for venous thromboembolism, who are often treated only by OAT, many other patients, especially the elderly, are plurimedicated. It is known that a higher frequency of bleeding is associated with the concomitant use of aspirin or other antiplatelet drugs<sup>31</sup> and non-steroidal antiinflammatory drugs.<sup>32</sup>

### **Compliance**

Most authors, though not all,<sup>33</sup> believe that non-compliance may be a problem in the elderly.<sup>34</sup> It has been demonstrated<sup>35</sup> that a reduction in mental ability/attention levels can be found in a fairly significant proportion of elderly, anticoagulated patients monitored in an anticoagulation clinic. Such a condition, which seems to be more frequent with age, affects the quality of anticoagulant therapy by increasing the period of either under- or over-anticoagulation and exposing the patients to a higher risk of failure or bleeding complications. We, therefore, consider it wise to recommend that anticoagulation clinics carefully assess the mental ability of elderly patients before starting OAT.

### **Duration of anticoagulant treatment**

A higher frequency of bleeding early in the course of OAT has been reported in many studies<sup>2,3,5,15</sup> but not in all.<sup>36,37</sup> In the ISCOAT study<sup>5</sup> more than one third of all the bleeding episodes occurred within the first 90 days of each anticoagulant course, the incidence of bleeding stabilizing thereafter. The rate of hemorrhagic events during the first 90 days of treatment was as high as 11% patient/years, decreasing considerably thereafter (6.3% patient/years).

Several factors may contribute to the increased risk of bleeding in the early period of anticoagulant courses. First, anticoagulant therapy can unmask a cryptic lesion; second, the dosage adjustment of therapy may be less well controlled at the start of treatment. As clearly pointed out by Landefeld and Goldman<sup>3</sup> studies which examine non-inception cohort patients and/or include patients who have resumed OAT for a second course after an interval period are likely to underestimate the true risk of bleeding by either missing early events or excluding from any second course patients who had bled in the first course.

### **Quality of anticoagulation control**

The quality of monitoring anticoagulated patients is certainly an important factor affecting the risk of bleeding complications. It is a general experience, and one confirmed by certain studies,<sup>38,39</sup> that the rate of bleeding is lower when patients are monitored by dedicated anticoagulation clinics. In the dedicated clinics the special training and experience of medical/paramedical staff, proper education of the patients, the use of computer programs and various other factors all

help to ensure optimization of anticoagulant therapy. Proper monitoring of OAT calls not just for commitment from the doctors and nursing staff but also for involvement of the patients and this is only possible by offering well-thought-out health education. Only by doing this will it be possible to optimize anticoagulant therapy with the aim of preventing the onset of new thrombi or the spread of pre-existing ones, with the minimum number of complications, especially hemorrhagic ones.

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## Recombinant FVII in orthotopic liver transplantation: a way to reduce blood loss and transfusion requirements?

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End stage liver disease is almost always associated with impaired hemostasis leading to a bleeding tendency. Major causes of the altered hemostasis in this clinical setting are the imbalance between activators and inhibitors and between coagulation and fibrinolysis: lower levels of coagulation factors and natural coagulation inhibitors, hyperfibrinolysis and thrombocytopenia are among the most important haemostatic defects of the end stage liver disease.<sup>1</sup> In cirrhotic patients intraoperative hemorrhage is not infrequent during major surgery and particularly during orthotopic liver transplantation (OLT), nowadays the treatment of choice for end stage liver disease, one year survival rate largely exceeding 80% in most part of the transplant centers both in Europe and USA.

Among the major problems encountered during this complex and demanding surgical procedure, excessive blood loss and the need for massive transfusion of blood and blood products still rank first.<sup>2</sup> Increased blood loss and larger transfusion requirements have been correlated with increased morbidity (longer ICU stay, higher incidence of pulmonary and infectious complications, higher rate of acute renal failure) and lower survival rate.<sup>3</sup> Main causes of massive blood loss are technical surgical problems and impaired hemostasis.<sup>2,3</sup>

Innovative preservation solutions, refinements in surgical and anesthetic techniques, better comprehension of the major pathophysiological changes during the various phases of surgery, appropriate supplementation of blood and blood products and pharmacological manipulation of the hemostatic defects (mainly the use of antifibrinolytic drugs and the judicious use of protamine in case of redundant heparin effect) have concurred in reducing blood losses and transfusion needs.<sup>2,4,5</sup> The pharmacologic approach to improve impaired hemostasis, however, could increase the risk of thrombosis, a serious complication in the perioperative period of liver transplantation. Particularly at risk is the hepatic artery thrombosis, the most common and feared vascular complication following OLT, with an incidence of 5%, and most part of the cases occurring early after transplantation.<sup>6</sup> Then, any measure to improve hemostasis has to be balanced against the risk of thrombosis.

Recently, recombinant blood coagulation factor VIIa (rFVIIa, NovoSeven, NovoNordisk) became available to treat patients with hemophilia, with inhibitors of coagulation factors IX or X.<sup>7,8</sup> In patients with liver cirrhosis, correction of a prolonged prothrombin time was observed after administration of rFVII.<sup>9</sup> rFVIIa has also been used to treat other causes of severe bleeding: among them trauma victims, cirrhotic patients scheduled for major surgery,<sup>9</sup> candidates to liver transplantation,<sup>10</sup> liver transplantation in children with fulminant hepatic failure,<sup>11</sup> major surgery in thrombocytopenic patients.

FVIIa binds to tissue factor exposed by the activated subendothelial tissue inducing thrombin generation.<sup>12</sup> Still under debate is the possible additional role of the exposed tissue factor on activated platelets.<sup>13</sup> In OLT, expression of tissue factor is present within the hepatic sinusoids as a result of ischemia/reperfusion injury and at the sites of vascular anastomosis.<sup>14</sup> The necessity of subendothelial tissue factor leads to a localized effect of rFVIIa, without systemic activation of coagulation.<sup>10</sup> In this peculiar setting, of particular interest is the absence of demonstration of an increased risk of thrombosis as a side effect of rFVIIa. This is of the utmost importance because of the risk of hepatic artery thrombosis, spontaneously occurring even in the absence of rFVIIa or any other prohemostatic drug.

The largest published clinical experience was performed by Hendricks *et al.*<sup>10</sup> in a pilot study in adult patients undergoing OLT. rFVIIa was administered at a dosage of 80 µg/kg at the start of operation. Perioperative transfusion requirements were compared in study patients with matched controls. Blood loss and transfusion requirements (autologous and compatible red blood cell units) were significantly lower (-67%) in the study group when compared with controls. One patient, however, had hepatic artery thrombosis, successfully treated with local infusion of urokinase and intravenous infusion of heparin. Graft function remained intact thereafter. Another preliminary study during OLT has very recently been published in abstract: the scheduled dosage was lower (20 µg/kg; Hart, *personal communication*). The results were a significant reduction in blood loss and transfusion requirements and no thrombotic event or drug related adverse event.<sup>16</sup>

The effects of rFVII on coagulation measured by thromboelastography (TEG) during OLT were recently studied by the Groningen group.<sup>15</sup> r, k, and significant incline of the  $\alpha$  angle were observed after rFVII infusion,

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whereas maximal amplitude did not change significantly. The reported data suggested the influence of rFVIIa on the speed of clot formation and the quality of its viscoelastic properties, detected by TEG only and not by conventional coagulation tests.

These promising data have to be confirmed in prospective placebo controlled trials.

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## Therapeutic controversies in disseminated intravascular coagulation

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The subcommittee of the *International Society of Thrombosis and Hemostasis* has defined disseminated intravascular coagulation (DIC) as *an acquired clinical syndrome characterized by the intravascular activation of coagulation without a specific localization and arising from different causes. It can originate from and cause damage to the microvasculature which, if sufficiently severe, can produce organ dysfunction.*<sup>1</sup> DIC is associated with many clinical conditions and may complicate the clinical course and the prognosis of the underlying disease.<sup>1,2</sup> The clinical picture is characterized by hemorrhages and/or thrombosis; organ failure may complicate the outcome.<sup>2</sup> The bleeding may be diffuse, may involve the skin and the mucous membranes, and is either spontaneous or induced by minor trauma (e.g. venipuncture); if thrombosis is present, signs and symptoms are related to the involved organ (*overt DIC*). DIC may be asymptomatic and revealed only by laboratory data indicative of clotting activation (*compensated DIC*).<sup>1</sup> The clinically useful laboratory parameters are: increased D-dimer or fibrin-fibrinogen degradation products (FDP), absolute or relative thrombocytopenia and hypofibrinogenemia, decreased antithrombin (AT) and protein C (PC), and presence of schistocytes in the peripheral blood smear.<sup>1,4</sup> The laboratory data must be interpreted in the context of the clinical picture. The clinical conditions associated with DIC are reported in Table 1.

Ongoing studies are elucidating the links between hemostasis and inflammation.<sup>5-9</sup> This relationship was already the object of investigations in the sixties. Dr. Oscar Ratnoff, in his seminal studies, envisioned the Hageman factor and the contact phase of blood coagulation as the crossroads of coagulation, fibrinolysis and inflammation. Dr. Nossel, in the text-book *Human Blood Coagulation Haemostasis and Thrombosis* edited by Rosemary Biggs (1976), referred to the experimental studies of Dr. Ratnoff stating: «*The above mentioned experiments, as their counterparts in the hemostatic and thrombotic processes, are as yet in their infancy and it is to be hoped that future work will quantitatively delineate the role of the Hageman factor in in vivo clotting and inflammation*».<sup>10</sup>

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In recent years the anti-inflammatory properties of AT and PC, the physiologic inhibitors of coagulation, were recognized.<sup>11-16</sup> This review will focus on the rationale of their use in clinical trials and on the interpretation of the results.

Thrombin, the final active enzyme of the coagulation cascade has dual properties: it converts fibrinogen to fibrin and activates its own inhibitor PC (activated protein C/APC). Thrombin is also a pro-inflammatory agent. Factor X (FX) is the pivot of the coagulation cascade. It is physiologically activated to FXa by either the intrinsic or the extrinsic pathway and in turn activates prothrombin (FII) to thrombin. Factor VIII (FVIII) and factor V (FV) are the cofactors involved in the intrinsic pathway. Factor VII (FVII) and tissue factor (TF) are the components of the extrinsic pathway and activate FX to FXa either directly or through the activation of FIX to FIXa.

Thrombin intervenes in inflammation by binding to the cell-membrane of different cells (endothelium, platelets, granulocytes and monocytes) through specific receptors (proteases activated receptors/PAR). Activated cells release several types of molecules (endothelium derived adhesion molecules/EDLAM, platelet activating factor/PAF), up-regulate expression of P selectins and induce the adhesion of leukocytes to the endothelium with release of pro-inflammatory cytokines and oxygen radicals.<sup>11-21</sup>

The physiologic inhibitors of coagulation, antithrombin (AT) and APC, have different mechanisms of action, but have in common a broad effect on the coagulation cascade. APC inhibits FVIIIa and FVa, the plasminogen activator inhibitor 1 (PAI 1) and the thrombin activatable fibrinolysis inhibitor (TAFI).<sup>22</sup> Therefore APC inhibits thrombin formation and activates fibrinolysis. AT is a serine protease inhibitor. Its efficacy is increased by its co-factors, heparin and glucosaminoglycans (GAGs) present in the endothelium. AT targets the serine proteases generated during blood coagulation (thrombin, factors Xa, IXa, XIa, XIIa, kallikrein and plasmin) by an irreversible bond between the serine residue in the active site of the proteases and its own arginine-serine site.<sup>23</sup>

AT and APC downgrade inflammation indirectly by their inhibitory effect on thrombin formation but experimental data suggest that they have also anti-inflammatory properties independent from coagulation downgrading the transcription process of inflammatory molecules.<sup>22,24-26</sup> Furthermore AT binding with the endothelial cells releases prostaglandin I<sub>2</sub> (PGI<sub>2</sub>) which in turn inhibits the activation of the leukocytes and their adhe-

**Table 1. Clinical conditions associated to DIC.**

• Sepsis/severe infection
• Trauma, organ destruction
• Solid tumours
• Obstetrical calamities
• Vascular abnormalities (Kasabach-Merrit syndrome)
• Severe hepatic failure
• Severe toxic or immunologic reactions (snake bite, drugs, transfusion reactions, transplant rejection)

sion to endothelial cells.<sup>27,28</sup> AT, therefore, has a vascular protective effect by reducing vascular permeability and the thrombogenicity of the injured wall surfaces.<sup>28</sup> The anti-inflammatory effect is inhibited by heparin, probably because this drug prevents the interaction of AT with the glucosaminoglycans (GAGs) of the endothelial cells.<sup>24,28-30</sup> The main characteristics of AT and PC are reported in Table 2.

The goal of therapy in DIC is dual: identification of the underlying disorders and correction of the hemostatic dysfunction with prevention of multi-organ failure. The appropriate management of DIC is still debated but the management of the underlying disease is pivotal. Fresh-frozen plasma, specific coagulation factor concentrates and platelet concentrates have been used to correct the hemostatic defect. The therapeutic decision should be based on the clinical status of the patient and not only on the laboratory tests. Replacement therapy is indicated in patients with active bleeding or with a high risk of bleeding.<sup>3,31-33</sup> The risk of further activation of coagulation with these therapeutic measures was suggested but is unproven.<sup>33</sup>

There are no controlled trials proving that heparin reduces morbidity and mortality in patients with DIC.<sup>34,35</sup> Some information is provided by the retrospective analysis of patients in the placebo arm of two randomized controlled trials using AT (KyberSept) or APC (PROWESS) in the treatment of severe sepsis: the mortality of the patients treated with heparin was significantly lower than that of the untreated patients (32.9 vs 41.9%;  $p < 0.001$ ).<sup>36</sup>

AT and APC concentrates are another option.<sup>37-41</sup> Two phase III randomized studies in severe sepsis were reported and will be discussed. Sepsis is a clinical condition in which DIC is prevalent and current evidence demonstrates the early presence of hematologic parameters indicative of increased clotting and decreased fibrinolysis.<sup>42-45</sup> Severe sepsis is one

**Table 2. Different characteristics of antithrombin and protein C.**

	AT	PC
Half life	2.5 days – 18 h (DIC)	20 minutes
Activating factors	no	thrombin thrombomodulin
Cofactors	heparin	protein S and C4-binding protein
Mechanism of action	anticoagulant anti-inflammatory	anticoagulant anti-inflammatory fibrinolytic
Heparin interaction	increase anticoagulant effect decrease anti-inflammatory effect	no

of the most serious complications and a frequent cause of death.<sup>45,46</sup> The mortality, in spite of the improvement in anti-microbial therapy and supportive measures over the last 30 years, is still 35-45%; no single therapeutic agent has significantly reduced the overall mortality.<sup>47-51</sup> In the USA the incidence was reported to be 500,000 cases per year with an hospital mortality rate of 28.6%, being higher for patients with pre-existing disease and failure of more than one organ. The mortality rate increases with age, being 10% in children and 38.4% in patients over 85 years old.<sup>44,52,53</sup> DIC has an important role in the onset and course of the multi-organ dysfunction syndrome (MODS): thrombin is generated and depletion of the coagulation factors and physiologic inhibitors (mainly AT and PC), thrombocytopenia and deposition of fibrin in the microvascular bed ensue.<sup>42,45,54,55</sup> In the early phase of sepsis the fibrinolytic system is activated with generation of plasmin but, as sepsis progresses to severe sepsis and septic shock, it is inhibited by the increased release of the plasminogen activator inhibitor 1 (PAI 1) induced by TNF- $\alpha$ , endotoxin, IL-1, IL-6 and thrombin.<sup>56-59</sup> In patients with septic shock a high level of PAI 1 at the onset of fever in neutropenic patients is a negative factor for survival.<sup>60</sup> The inhibition of fibrinolysis contributes to the persistence of fibrin in the microvascular bed and to the progression to MODS.<sup>61</sup> AT and PC are constantly decreased in patients with sepsis or septic shock and a low plasma concentration are prognostic of poor outcome and survival.<sup>5,41,62-69</sup>

Early clinical studies addressing the use of AT in DIC referred mainly to the modifications of the laboratory parameters. These studies included a small number of patients with diseases of different etiology and often in very critical conditions. Normalization of the laboratory data was a common observation but the effect on survival was inconsis-

**Table 3. Main differences between KyberSept and PROWESS study.**

	<i>KyberSept</i>	<i>PROWESS</i>
Number of centres	219 mainly in Europe	164 mainly in USA and Canada
Coordinating center consultation	Optional	Mandatory
Severity score	SAPS II	APACHE II
Follow-up	28/56/90 days	28 days
Dose	Fixed (total 30,000 U in 4 days)	Body weight adjusted 24 µg/kg/h per 4 days
Eligibility criteria	within 6 hours	less than 24 hours
Changes in the product	no	yes
Protocol amendment	no	yes

tent.<sup>70-82</sup> In 1995 Vinazzer reported the results of a retrospective analysis of 170 patients with traumatic shock treated with heparin or AT (85 patients in each group). A significant reduction of mortality from 31% to 13% was observed in the patients treated with AT versus patients treated with heparin alone ( $p < 0.005$ ). This difference was more significant in the subgroup of patients in phase IV shock (defined as fully developed consumption coagulopathy).<sup>83</sup>

The results of two large, randomized, double-blind, placebo-controlled, international Phase III studies evaluating the efficacy and safety of AT (KyberSept)<sup>84</sup> and APC (PROWESS)<sup>85</sup> in severe sepsis were recently published.

In the KyberSept trial, 2,314 adult patients with severe sepsis were randomized to receive either AT at a fixed loading dose of 6,000 U followed by a continuous infusion of 6,000 U per day for 4 days or placebo (1% albumin solution). In the PROWESS study 1,690 patients with systemic inflammation and organ failure were enrolled and assigned to receive i.v. infusion of drotrecogin- $\alpha$  activated (24 µg/kg of body weight per hour) or placebo for a total duration of 96 hours. The main end point of the two studies was all cause mortality 28 days after start of treatment. The main differences between the two studies are reported in Table 3. The conclusions were different: no difference in the overall 28-day mortality was observed in the KyberSept study (AT 38.9% vs placebo 38.7%) with a trend toward a reduced mortality in the patients who did not receive heparin (AT 43.6% vs placebo 37.8%;  $p = 0.08$ ). In the PROWESS, the absolute reduction of the risk of death was 6.1% ( $p = 0.005$ ). The incidence of severe bleeding was higher in the APC group than in the placebo one (3.5% vs 2.0%;

$p = 0.06$ ). In the discussion that followed on the possible explanations of the different results of the two studies several points were raised.

1. Are the different outcomes related to different mechanisms of action?  
AT and APC have different mechanisms but have in common a broad-spectrum effect on hemostasis and inflammation. The fibrinolytic effect of APC may be important. The significance of these differences, if any, is poorly understood at present.
2. Are the groups of patients enrolled in the studies different?
  - i) the control groups in the two studies had different mortality rates at 28 days: 38.7% in the AT vs 30.8% in the APC, pointing to a difference in the patients enrolled;<sup>86</sup>
  - ii) two different score systems were used to grade the severity of the sepsis: the *Simplified Acute Physiology Score* (SAPS) in the KyberSept study and *Acute Physiology and Chronic Health Evaluation* (APACHE II) in the PROWESS;
  - iii) the pre-defined window of eligibility was different in the two studies. In the KyberSept study all the clinical criteria had to be present within 6 hours. In the PROWESS the pre-defined window was 24 hours and the duration of the organ dysfunction less than 24 hours; patients with long-standing organ dysfunction were not eligible. The PROWESS study was amended, introducing strict inclusion criteria; bone marrow or solid organ transplantation, metastatic cancer, acute pancreatitis were excluded.<sup>87</sup> The inclusion criteria were different but both studies were intended to enroll patients in a stage of sepsis likely to be reversible.
  - iv) consultation with the co-ordinating center, available throughout the 24 hours, was mandatory in the PROWESS but optional in the KyberSept study.
3. Was AT administered in adequate doses?  
Experimental studies in animals have indicated that the administration of AT is protective provided that high plasma levels are obtained (200-250%).<sup>88</sup> In the KyberSept trial AT was not administered at a weight-adjusted dose but rather at a fixed dose. This modality may have prevented an optimal plasma level from being obtained.
4. The known interaction between heparin and AT with a decrease of the anti-inflammatory effect should not be overlooked.<sup>18</sup>

All these points highlight how difficult it is for the clinician to interpret these data.<sup>89</sup> A *post-hoc* analysis of different subgroups, carried out by the *Food and Drug Administration* (FDA) showed that treatment with APC would benefit patients older than 50 years with more than one organ dysfunction, in

**Table 4. Antithrombin replacement therapy in severe sepsis: early randomized trials.**

	<i>Fourrier F<sup>91</sup></i>	<i>Baudo F<sup>92</sup></i>	<i>Eisele B<sup>93</sup></i>
Number of centers	2	3	7
Number of patients	35	120	42
Patients per center/year	8	10	–
Type of patients	Septic shock	Severe sepsis	Severe sepsis
Shock %	100	46	–
Treatment (days)	4	5	5
AT total dose (U)	30,000	22,000	18,000
Mortality placebo %	50	54	41
Mortality AT %	28*	28 <sup>°</sup>	25*

\* not significant; °  $p = 0.04$ ; §post-hoc analysis.

**Table 5. Mortality % in patients with severe sepsis and septic shock: meta-analysis.**

<i>Meta-analysis</i>	<i>Number of patients</i>	<i>Mortality %</i>		<i>OR</i>	<i>p</i>
		<i>AT</i>	<i>Placebo</i>		
Eisele B <sup>93</sup>	122	35	45	0.29	–
Calori G <sup>94</sup>	130	48	60	0.43	0.029

shock and with an APACHE score over 25.<sup>90</sup> The FDA approved the use of APC for the treatment of adult patients with severe sepsis and a high risk of death. A phase III study in this subgroup of patients will be carried out on request of the FDA.

Three placebo-controlled, randomized studies have evaluated the effect of AT in sepsis (Table 4).<sup>91–93</sup> The difference in the overall survival was not significant. Each study enrolled a small number of patients. The *post-hoc* analysis of one study was consistent with a beneficial effect in the subgroup more seriously affected.<sup>92</sup> Two meta-analyses of these studies were also carried out (Table 5). Both pointed to the AT treatment having a beneficial effect on survival.<sup>93,94</sup> These older studies do not prove the point but raise the question of whether AT should be re-evaluated in a phase III study designed with pre-set criteria of eligibility.

A concentrate of non-activated PC was successfully used in patients with life-threatening sepsis secondary to meningococcal infection.<sup>95,96</sup> Its use may be extended to other indications.

DIC is a multifactorial syndrome affecting extremely heterogeneous populations. Many factors contribute to the outcome, clinical trials are

difficult to perform, the results difficult to measure and the interpretation of the results is not straightforward. The appropriate management of the underlying disease, if possible, is the main therapeutic intervention. There is no sound evidence for the efficacy of heparin; but it may be used on an individual basis. Fresh-frozen plasma or platelet concentrates may be indicated as replacement therapy in patients at high risk of bleeding or with active bleeding. The use of APC should not be considered as standard until the results of the new phase III study is available.<sup>97,98</sup>

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## Idiopathic thrombocytopenic purpura: an old disease revisited in the era of evidence-based medicine

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In 1735 P. G. Werlhof<sup>1</sup> first described under the name of *Morbus Maculosus Hemorrhagicus* a new disorder which is now identified as idiopathic thrombocytopenic purpura (ITP). This condition, often also known as immune thrombocytopenic purpura, is a primary, acquired disease of adults and children, characterized by a transient, self-limited (acute form) or persistent (chronic form) decrease of platelet count (less than  $150 \times 10^9/L$ ), caused by autoantibody-mediated platelet destruction.<sup>2</sup> In some cases, a defective platelet production has also been demonstrated.<sup>3,4</sup>

The study of its pathophysiology started 50 years ago with the historical experiments of Harrington,<sup>5</sup> showing that a humoral factor in the patient's plasma transfused into a normal subject was able to cause a drop in platelet count. Despite this long history, the diagnosis remains one of exclusion and the clinical management of ITP is still largely based on anecdotal evidence, descriptions of series of patients and a very few controlled studies, mostly concerning initial treatment of children. As a consequence, many guidelines, such as those of the *American Society of Hematology* (ASH)<sup>6</sup> and of the *British Committee for Standards in Haematology* (BCSH), have been produced largely based on expert opinion.<sup>7</sup>

### Pathogenesis

Autoantibodies are certainly involved in the pathogenesis of ITP as anticipated by the pioneering work of Harrington<sup>1</sup> and the identification by Shulman<sup>8</sup> of the causative agent in the plasma of patients as a 7S IgG (immunoglobulin G) fraction. When Dixon developed his assay for the measurement of platelet-associated Ig, high values of platelet-associated autoantibodies were found in ITP patients.<sup>9</sup> Later, Van Leeuwen, working with platelets congenitally lacking membrane glycoprotein (GP) IIb/IIIa (obtained from a patient with Glanzman thrombasthenia), demonstrated that most autoantibodies were directed against this platelet GP complex.<sup>10</sup> Recent techniques are available to measure antibodies, both platelet-associated and free in the plasma, with specificity for GP IIb/IIIa and Ib/IX, IV and V.<sup>2,11</sup>

Very recent molecular studies are evidencing that inherited polymorphisms of platelet-membrane GP

genes may be associated with alteration of their antigenicity, regulating their expression level and modulating their functional expression.<sup>12</sup> In addition, an association of ITP with some HLA polymorphisms, such as HLA-DRw2 and DRB1\*0410 alleles has been described in certain ethnic populations,<sup>13</sup> suggesting a crucial role of the antigen-presenting cell to T-lymphocytes, which in turn regulate the antibody production by B-lymphocytes. However, despite the many recent progresses, the initiating events of ITP still remain unsettled.

### Epidemiology

No firm data are available on the incidence and prevalence of ITP. An incidence ranging from 1 to 12 cases/100,000/year, including both children and adults, can be extrapolated from case series.<sup>14-17</sup> A recent study estimated the incidence of ITP through an exhaustive direct examination of all in- and out-patients in a well-defined health care region of a Danish county during a 22 year period, purporting to capture all symptomatic and also asymptomatic cases seen by general practitioners.<sup>18</sup> An annual standardized incidence rate of 2.64 (CI 2.29-2.98) per 100,000 persons (platelet count less than  $100 \times 10^9/L$ ) and 2.25 (CI 1.92-2.57) per 100,000 persons (platelet count less than  $50 \times 10^9/L$ ) was calculated, with a female/male ratio of 1.7 and an increasing annual incidence rate with age up to 4.6 per 100,000 in subjects aged 60 years or more. These accurate estimations largely confirm the results of previous studies.<sup>19,20</sup>

### Natural history

In children, ITP manifests typically with an acute, abrupt onset, often following a viral illness. The platelet count at presentation is less than  $50 \times 10^9/L$  in most patients.<sup>21,22</sup> The majority of these children (80%) do not require specific treatment, and will reach a spontaneous remission within 6 months.<sup>6,23</sup> Some 10%-20% of cases develop a chronic form<sup>24,25</sup> persisting after six months, with a later remission, during the next years in one third of cases.<sup>24,26-29</sup> The incidence of intracranial hemorrhage is estimated to be about 0.5-1%, with a fatal evolution in 50% of these cases, but only limited observational data are available.<sup>6,27,30,31</sup>

In adults, ITP often has an insidious onset, with a mean platelet count between  $30 \times 10^9/L$  and  $130 \times 10^9/L$  at diagnosis and a typical evolution into a chronic form, lasting more than 6 months,<sup>32-34</sup> and indeed often lifelong. Less than 10% of cases present with an overt

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hemorrhagic picture and a platelet count less than  $5-10 \times 10^9/L$  requiring hospitalization and immediate treatment.<sup>35,36</sup> Very few cases, less than 5 %, are unresponsive to first line treatments including splenectomy,<sup>37</sup> whereas about 10-15%<sup>38</sup> of chronic cases develop a disease which is refractory to second-line therapy. The clinical relevance of refractory ITP was recently evaluated by a meta-analysis<sup>39</sup> which pooled 17 studies including 1,817 refractory patients with a platelet count less than  $30 \times 10^9/L$ . A total of 49 fatal hemorrhages were recorded, with an annual incidence rate of 0.0162 and 0.0389 per patient (not age-adjusted). In 9/17 studies, reporting age at the time of event, the risk of hemorrhage increased from 0.4% per year in patients younger than 40 to 13% per year in patients older than 60, confirming the results of a previous study.<sup>36</sup> The mortality rate at 5 years was 2.2% in young patients and 47.8% in older patients. In another retrospective study on a cohort of 138 patients,<sup>37</sup> the relative risk of mortality from hemorrhage in refractory ITP patients was significantly higher than that observed in the general population, the RR being 4.2 (1.7-10). Interestingly, 5% of 138 patients were still under treatment 2 years after diagnosis to maintain a platelet count  $> 30 \times 10^9/L$ , with an ITP-related hospital admission rate 5 time higher than that of mild, untreated thrombocytopenic patients. Sadly, a large proportion of deaths (14%) were due to bacterial infections favored by the various immunosuppressive treatments<sup>37</sup> or to fulminant sepsis in splenectomized patients (1-2%).<sup>40,41</sup>

### Diagnosis

The diagnosis of ITP requires the exclusion of any recognizable underlying disease at presentation. The concomitant presence of isolated lupus anticoagulant, antiphospholipids antibodies, antinuclear antibodies or Coombs' test positivity does not cause any change in the management. Testing for anti-platelet antibodies with the various available techniques is not necessary. They lack sufficient sensitivity and specificity and have no prognostic value. About half of patients manifest some mucocutaneous bleeding, without systemic symptoms. The finding of thrombocytopenia should always be confirmed by direct microscopic examination of a peripheral blood smear, to exclude pseudo-thrombocytopenia or inherited disorders with giant platelets such as Bernard-Soulier syndrome.

The guidelines of the ASH<sup>6</sup> and BCSH<sup>7</sup> are concordant in advising a diagnosis of ITP based on history, physical examination, blood count and peripheral blood film examination (Table 1), to exclude secondary causes of thrombocytopenia. Further investigations (Table 2) are not required in typical cases. Bone marrow examination is recommended

**Table 1. Aspects that need to be investigated in a patient with suspected ITP.**

History
– Family history of thrombocytopenia
– Previous viral illness
– Drug or alcohol intake
– Systemic symptoms such as fever or weight loss
– History of hemorrhage
– Risk factors for bleeding, such as hypertension, gastrointestinal disease, surgery
– Pregnancy (exclude gestational thrombocytopenia)
Physical examination
– Spleen, liver, lymph nodes
– Skin rash, arthralgias, evidence of thrombosis
– Type and localization of mucocutaneous bleeding
Peripheral blood smear examination
– Pseudo-thrombocytopenia
– Red cell shape abnormalities
– Evidence for myelodysplasia, e.g. Pelger-Huet anomaly, immature white blood cells
Bone marrow examination (see text)

in adults with atypical features at diagnosis or those over the age of 60, after a relapse following complete remission and before splenectomy. However, consensus on this policy is far from unanimous and we continue to retain bone marrow a valuable investigation in most cases. In children, marrow examination is required in the presence of atypical features and recommended before therapy with corticosteroids or in case of no response to immune globulin administration.

### Treatment

Many recent reviews<sup>42-45</sup> and guidelines<sup>6,7</sup> have addressed the management of ITP and the reader is invited to refer to them for detailed analysis of the different aspects. Specific references will here be provided only where appropriate to focus on particular aspects.

### Hospitalization and emergency treatment

Hospitalization is rarely mandatory, apart from in cases with active severe or life-threatening bleeding. In these cases, in addition to emergency treatment, immediate transfusion with platelet concentrates is appropriate. In other cases, including children and adults with extensive purpura, subconjunctival hemorrhage or mucosal hemorrhagic bullae of the oral cavity, patients with overt bleeding (hematuria, epistaxis, etc.) or women with menorrhagia, hospitalization is appropriate and may be required on a prudential basis, especially if the platelet count is less than  $20-30 \times 10^9/L$ . These

**Table 2. Laboratory tests suggested to complete the clinical assessment in a patient with suspected or confirmed ITP.**

- 
- Anti-platelet antibodies. Testing not required: low sensitivity and specificity. Their assay may be of some value in case of associated bone marrow failure and ITP, in refractory forms or drug-dependent thrombocytopenia.
  - Platelet survival time: not required.
  - Coagulation profile: necessary during pregnancy.
  - Reticulated platelets: increase in ITP in comparison with in other causes of thrombocytopenia, but their assay is not yet validated in a clinical set.
  - Autoimmune markers, if autoimmune disease is suspected.
  - *Helicobacter pylori* infection: in case of a refractory form
  - Urinalysis, liver function tests, hemolysis markers and arterial hypertension monitoring during pregnancy to exclude obstetric causes of thrombocytopenia.
- 

cases are at higher risk of acute intracerebral bleeding (1-5%)<sup>46,47</sup> than are less symptomatic patients, those younger than 60 years or those with a higher platelet count (less than 1%).<sup>36</sup> The fatality rate is around 50% when intracerebral hemorrhage occurs.

Emergency treatment includes intravenous methylprednisolone (1 g/day for 3 days in adults or 30 mg/kg/day in children). Administration of high dose intravenous immune globulins (IVIg) (1 g/kg/day for 2 days in adults or 1 g/kg/day for 1 day in children) is also recommended.<sup>43</sup>

### **Initial treatment**

Clinical criteria for selecting patients in whom initial treatment could be safely deferred have not been properly investigated. In general, in adult patients, even if asymptomatic, treatment is advised when the platelet count is less than  $20-30 \times 10^9/L$ , or when significant mucous-cutaneous bleeding is present, regardless of the platelet count. Other cases in which initial treatment is appropriate include patients at higher risk of hemorrhage, such as those with hypertension, peptic ulcer, recent surgery, head trauma and a platelet count less than  $50 \times 10^9/L$ . These criteria could be relaxed in children, who have a high percentage of spontaneous remission within a few weeks. Indeed in the young the aim of therapy is mainly to increase the platelet count in risky situations, i.e. in the presence of severe bleeding symptoms or an extremely reduced platelet count (less than  $10 \times 10^9/L$ ). In order to allow the children to maintain their life-style we prefer to treat them with a short course of corticosteroids when the platelet count is less than  $20-30 \times 10^9/L$ .

Initial therapy includes oral corticosteroids, IVIg

and splenectomy. Up to 80% of adults will respond to prednisone 1 mg/kg/day for 2-4 weeks. Tapering of prednisone should be prolonged over several weeks. However, most patients frequently relapse within 6 months when the dose is tapered.<sup>7,32,48</sup> Two randomized trials showed no difference between low (0.25-0.5 mg/kg/day) and high (1-2 mg/kg/day) doses.<sup>49,50</sup> Long-term remission is seen in only 10-20% of cases.<sup>32,37,48</sup> In children, the dosage of oral corticosteroids is usually higher than in adults (1.5-2 mg/kg/day for 3 weeks<sup>51</sup> or 4 mg/kg/day for 1 week) with tapering in 2 weeks.

IVIg are very effective in the treatment of ITP, inducing a substantial increase or normalization of platelet count in almost all untreated patients. However the response is invariably transient, lasting for no more than 2 to 4 weeks.<sup>52,53</sup> IVIg are indicated only in patients with very low platelet count and severe bleeding. A single randomized study showed no difference between a dose of 400 mg/kg/day for 5 days and 1 g/kg/day for 1 day.<sup>54</sup> Another randomized clinical trial found no difference between the use of corticosteroids and IVIg (as single agents or in association) in preventing evolution into chronic ITP.<sup>33</sup> Their use is not always devoid of significant side effects including renal impairment or failure.<sup>55,56</sup> In children, IVIg infusion is appropriate as first-line therapy in case of severe bleeding and/or a platelet count less than  $10 \times 10^9/L$  or in cases of bleeding and a platelet count less than  $20 \times 10^9/L$ . Limited evidence suggests that repeated IVIg infusions in children might be useful in order to postpone or possibly avoid splenectomy. In non-splenectomized Rhesus (D)-positive patients anti-D IgG treatment at a dose of 75  $\mu g/kg/day$  is similarly effective and less expensive than IVIg is not without problems such as intravascular hemolysis.<sup>57</sup>

In two-thirds of adult patients with ITP, splenectomy will be curative<sup>6,7,42,43</sup> with a complete and sustained remission without additional therapy. This intervention is indicated in the case of no response after first line therapy with oral corticosteroids (6 weeks after diagnosis in asymptomatic patients with platelet count less than  $10 \times 10^9/L$ ; 3 months after diagnosis in symptomatic or asymptomatic patients with a platelet count less than  $30 \times 10^9/L$ ) or when a response is obtained only with long-term corticosteroid treatment at a dosage higher than 0.15-0.20 mg/kg/day.<sup>43,44</sup> Our policy is to try to postpone splenectomy until at least six months after diagnosis, since late remissions may occur. Splenectomy is rarely indicated in children. It seems appropriate in cases of chronic severe ITP (platelet count less than  $10 \times 10^9/L$  or major bleeding) unresponsive to corticosteroids or IVIg 12-24 months after diagnosis or in the presence of life-threatening hemorrhage.<sup>7</sup> Patients should be given prophylactic vaccination with pneumococcal, meningococcal C and *Haemo-*

*philus influenzae* vaccines, preferably 2 weeks prior to splenectomy<sup>58</sup> and advised on the conduct to be observed in the case of fever. They should also be provided with broad spectrum antibiotics for immediate treatment of any suspected infection.

During pregnancy, asymptomatic women with a platelet count exceeding  $20\text{--}30 \times 10^9/\text{L}$  do not need treatment during the first and second trimesters. During the third trimester, specific treatment is warranted, to maintain a peripheral platelet count above  $50 \times 10^9/\text{L}$ . IVIg are indicated as first line therapy in the case of severe thrombocytopenia (platelet count less than  $10 \times 10^9/\text{L}$ ) during the third trimester, or in the case of failure to respond to oral corticosteroids treatment. It is appropriate to plan splenectomy during the second trimester in women with platelet counts less than  $10 \times 10^9/\text{L}$  who are refractory to moderate doses of corticosteroids and IVIg.

### **Second-line therapy**

Second-line treatments are reserved for patients with refractory ITP, defined as the persistence of thrombocytopenia after initial therapy including splenectomy, with the need of active treatment to maintain a safe platelet count.<sup>59</sup> The identification of a safe platelet count should take into account the patient's life style and preferences but is usually defined as a platelet count not associated with significant bleeding symptoms including purpura and a count higher than  $10 \times 10^9/\text{L}$ .<sup>38</sup> In refractory patients, the need to obtain a hemostatic level of platelets is counterbalanced by the risk of severe side-effects of the drugs.<sup>6,37,38</sup> Indeed, the morbidity and mortality in these patients is often more associated with iatrogenic side effects including fatal infections in immune-suppressed patients. This is particularly the case in older patients and the risk of overtreatment must be seriously considered.<sup>38</sup> In the series of 138 patients described by Portiejlie,<sup>37</sup> of the four deaths occurring during the first two years, one was due to hemorrhage and three to infections.

The first-line therapy (corticosteroids and IVIg) should be reconsidered, reducing corticosteroids to the lowest effective dose, taking into account their chronic use. High-dose steroids, such as 40 mg of dexamethasone daily for 4 days, repeated every 28 days for six cycles, has been proposed<sup>60</sup> but initially reported favorable results were not confirmed. Ultimately most patients become refractory to IVIg and cannot tolerate prolonged administration of corticosteroids. Vinca alkaloids (vincristine, 1 mg, occasionally 2 mg, single dose) are effective in producing a short-sustained platelet increase in up 50% of splenectomized patients and might be the agents of choice in cases requiring rapid correction of the platelet count.<sup>7</sup> Immunosuppressive treatments with cyclophosphamide (1–2 mg/kg /day)

and azathioprine (150 mg/day) produce a sustained response in about 25% of cases, but are associated with a significant risk of developing a secondary neoplasia.<sup>43</sup> These treatments should be reserved for the management of acute bleeding or for prophylaxis of risky situations. Cyclosporin A, alone or with prednisolone (3–5 mg/kg /day), has been shown to increase the platelet count in 55% of patients, but with significant side effects in up to 30% of patients.<sup>61,62</sup> Danazol,<sup>63,64</sup> an attenuated androgen, should be tried in male patients or in females aged more than 50, at a dose of 200 mg 2–4 times daily. At least two months of treatment are required to assess the response. A variety of diverse drugs including interferon,<sup>65</sup> dapson,<sup>66</sup> ascorbic acid,<sup>67</sup> colchicine,<sup>68</sup> and protein A immunoadsorption.<sup>69</sup> have been used in small case series with minor and transient response. Most of these disappointing results discouraged the planning of controlled trials with these agents.

In patients with *Helicobacter pylori* infection, microbial eradication with antibiotic therapy was associated with a substantial increase in platelet count in some series of patients with refractory ITP,<sup>70–73</sup> with a median remission of 8.3 months.<sup>71</sup>

### **Innovative and experimental therapy**

In recent years, autologous peripheral blood stem cell transplant (PBSCT) has been used as salvage therapy in severe unresponsive autoimmune diseases, including ITP.<sup>74</sup> The risk of early and late toxicity with an high transplant-related mortality and the lack of clear evidence of long-term effectiveness suggest that this option should be considered only in the setting of controlled clinical trials.

In a small group of refractory ITP patients, mycophenolate mofetil, a drug licensed for prophylaxis of acute rejection of solid organ transplants, has been shown to induce sustained remission (5/6).<sup>75</sup> Its use is attractive since this agent is devoid of nephrotoxicity and is able to inhibit both T- and B-lymphocytes. Larger studies are needed to confirm its value.

An emerging role for biological treatment based on chimeric humanized monoclonal antibodies against membrane receptors of specific lymphocyte subsets is apparent from recent literature and ongoing trials. Anti-CD20 antibody was used at a dosage of  $375 \text{ mg}/\text{m}^2$  weekly for 4 weeks (as for the treatment of lymphomas) in a single study<sup>76</sup> in 25 ITP patients. A total of 13/25 (52%) patients showed a complete or partial response, maintained for 6 months in 7 of them (28%). No increase of infection was recorded. Similar results were obtained in other studies.<sup>77,78</sup>

Campath-1H, an anti CD52 humanized antibody against B- and T-lymphocytes, was used by Lim<sup>79</sup> in 6 patients with refractory ITP; four of them showed a response which lasted more than 4–9

months in three of them. Willis<sup>80</sup> treated 21 patients with a variety of cytopenias at a dosage of 10 mg/day for 10 days. A response was obtained in 15 and maintained in 6 patients but at the expense of significant side effects. Finally, anti-CD25 antibody, against IL-2 receptor, impairing the activated T-lymphocyte, is being tested in an ongoing clinical trial at the *Warren G. Magnuson Clinical Center* of Bethesda (USA), in ITP patients not responding to corticosteroids treatment. So far no successful results have been obtained with the use subcutaneous human recombinant thrombopoietin, which was associated in some cases with *de novo* production of autoantibodies against the natural hormone<sup>80</sup> with a potential to worsen the thrombocytopenia.

### Conclusions

Because of the lack of controlled clinical trials on which to establish recommendations for decision-making, the management of ITP remains largely guided by expert opinion based on retrospective analyses of limited series of patients, often producing unconfirmed results. Local practices may vary and expose patients to the risks of over or undertreatment, a situation which demands rapid correction. Considering the very low incidence of mortality and major morbidity of this condition, prospective trials will require the enrollment of thousands of patient to demonstrate the superiority of a particular agent or management protocol. Accordingly, the definition of appropriate surrogate endpoints agreed on by the scientific community would be a major step forward. Further pathophysiologic studies are needed to produce a better understanding of the mechanisms of this disease and its initiating mechanisms and to offer highly specific and sensitive confirmatory laboratory tests.

In the light of these considerations, the co-operative prospective data register made available by the *Intercontinental Childhood ITP Study Group*, which has enrolled 2,073 children with newly diagnosed ITP in three years<sup>24</sup> represents an admirable effort to put the problems of ITP in the right direction. We hope that this initiative will stimulate similar initiatives to investigate pathophysiology, diagnosis, clinical course, short- and long-term efficacy and safety of therapy also in adult patients with ITP.

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## Thrombotic microangiopathies: thrombotic thrombocytopenic purpura and the hemolytic uremic syndrome

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**T**hrombotic thrombocytopenic purpura (TTP) and the hemolytic uremic syndrome (HUS) are diseases with features in common such as thrombocytopenia, hemolytic anemia and thrombotic occlusions in terminal arterioles and capillaries, which form on areas of damaged vascular endothelium and are mainly composed of platelets. The triggers of TTP are varied (including pregnancy, infections, cancer and drugs) and are likely to act by damaging or activating, directly or indirectly, vascular endothelial cells. The most frequent triggers of HUS, at least in infants, are infectious agents in the gastrointestinal tract. Characteristic clinical features are the presence of focal neurologic symptoms in TTP and renal impairment in HUS, often associated with diarrhea and fever in the form that affects infants. In clinical practice these differences are seldom clear-cut, particularly in adults. It is also known that in some cases clinical features may shift from one syndrome to another. Hence in individual cases the differential diagnosis between TTP and HUS is often so uncertain that it has been proposed that the syndromes should be grouped under the comprehensive term of thrombotic microangiopathies.

It has been recognized for several years that von Willebrand factor has a role in the pathogenesis of thrombotic microangiopathies. von Willebrand factor is a large multimeric glycoprotein contained in plasma, platelets and vascular endothelial cells. It mediates the adhesion of platelets to sites of vascular lesions and, as the carrier protein for coagulation factor VIII, is required for normal factor VIII survival in the circulation. By using immunohistochemical techniques Asada *et al.*<sup>1</sup> showed that, in TTP, intravascular thrombi and subendothelial hyaline deposits react positively for von Willebrand factor antigen and negatively for fibrinogen (the opposite of thrombi in disseminated intravascular coagulation); Moake *et al.*<sup>2</sup> found abnormally large (ultralarge) multimeric forms of von Willebrand factor in the plasma of patients with chronic relapsing TTP. Ultralarge multimers are the most biologically active forms in platelet-vessel wall interactions and directly induce platelet aggregation in conditions of high shear stress.<sup>3</sup> This abnormality cannot be taken as diagnostic marker

for thrombotic microangiopathies because, particularly in the acute phase of these syndromes, ultralarge and large von Willebrand factor multimers are often lacking after they have bound avidly to activated platelets and been cleared from plasma.<sup>4,5</sup>

The mechanism of the relation between ultralarge von Willebrand factor multimers and thrombotic microangiopathies remained elusive until Furlan *et al.*<sup>6</sup> and Tsai<sup>7</sup> independently demonstrated that the link is a plasma metalloprotease that physiologically cleaves von Willebrand factor at the peptide bond between amino acid residues 842 Thr and 843 Met in the A2 domain of the von Willebrand factor subunit.<sup>8</sup> The protease degrades ultralarge multimers, normally stored in the Weibel-Palade bodies of vascular endothelial cells from which they are secreted lumenally into plasma and ablumenally into the subendothelium.

In the late 1990s Furlan *et al.*<sup>9-10</sup> and Tsai and Lian<sup>12</sup> made the intriguing observation that the protease is deficient in patients with TTP but measurable in normal amounts in those with HUS. The chronic relapsing form of TTP, characterized by recurrent episodes of thrombocytopenia with or without signs of ischemic organ damage, is due to the complete deficiency of the metalloprotease,<sup>9</sup> often inherited as an autosomal recessive trait. On the other hand, in the more common acute idiopathic form of TTP, which is usually not familial and occurs sporadically, and in ticlopidine and clopidogrel-associated TTP the level of the protease is low because is inactivated or removed by a specific autoantibody.<sup>10-12</sup>

According to Furlan and Tsai, HUS, the clinical manifestation of which are not easily distinguishable from those of TTP unless the prototypic renal symptoms are present, can now be clearly distinguished by the presence of normal levels of the metalloprotease and by the absence of inhibitory antibodies.<sup>11,12</sup>

These findings are important because they would allow these two disorders to be reliably differentiated for the first time, with potentially important clinical implications. In TTP the therapeutic efficacy of plasma exchange and its greater efficacy over plasma infusion has been demonstrated by a randomized clinical trial.<sup>13</sup> However, the possibility of distinguishing cases due to an inherited deficiency of the protease from those due to its inactivation by an autoantibody might help to choose the infusion of plasma only for the former cases, leaving the more dangerous and cumbersome procedure of plasma exchange to immunomediated cases. No randomized clinical trial has yet demonstrated the

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efficacy of plasma exchange or infusion in HUS, even though this treatment is currently recommended and is claimed to be effective.<sup>14-16</sup> The availability of the protease assay might help to establish these recommendations more objectively, because cases diagnosed as HUS, particularly those occurring in adults, might be misdiagnosed cases of TTP, and *vice versa*.

How specific is the aforementioned decrease of the protease in thrombotic microangiopathies? The paradigm that low protease means TTP and normal protease means HUS has already been challenged. Van der Plas *et al.*,<sup>17</sup> for instance, have shown that plasma levels are normal in TTP associated with bone marrow transplantation. In a case of familial HUS reported by te Loo *et al.* the protease was unmeasurable.<sup>18</sup> In a large series of patients with HUS and TTP we obtained data that challenge the views that the protease is always normal in HUS.<sup>19</sup> Although mean protease levels were lower in TTP than in HUS, there were HUS patients who had unmeasurable protease levels, like many patients with TTP.<sup>19</sup> Other clinical studies provide additional evidence that low levels of protease activity are not specific to TTP.<sup>20,21</sup>

Whether or not low plasma levels of the protease are at least a specific beacon of thrombotic microangiopathies or also occur in other physiologic and pathologic conditions was not known until recently. Using a novel protease assay based on the binding affinity to human collagen type III which is lower with protease-cleaved von Willebrand factor,<sup>22</sup> we have evaluated the plasma changes of the protease in physiologic states and in pathologic conditions associated with organ failure or acute phase reactions, conditions often present in patients with thrombotic microangiopathies.<sup>23</sup> The protease was lower in healthy individuals aged more than 65 years than in those of younger ages, was low in newborns (but became normal within 6 months) and decreased in the last two trimesters of pregnancy compared with the level in the first trimester. The protease was also low in patients with cirrhosis, uremia, and acute inflammation and fell in the post-operative period.<sup>23</sup> Hence, low plasma levels of the protease are not a specific beacon of thrombotic microangiopathies, because the protease is low in several other physiologic and pathologic conditions.

The limited knowledge on the biochemical and metabolic behavior of the protease means that the interpretation of the low plasma levels found in so many physiologic and pathologic conditions is currently uncertain. It is not clear whether low plasma levels are due to decreased synthesis or increased turnover or to other mechanisms, although mixing experiments have ruled out inactivation by autoantibodies as a mechanism.<sup>23</sup> In

**Table 1. Changes of the von Willebrand factor cleaving protease activity in various clinical conditions.**

TTP		Aging	↓
Acute sporadic or chronic relapsing	↓↓↓↓	Newborns	↓↓↓
Transplantation associated	normal	Pregnancy	↓↓
Ticlopidine –or clopidogrel associated	↓↓↓	Cirrhosis Uremia	↓↓↓ ↓↓
Cancer-associated	↓↓↓	Inflammation	↓↓↓
HUS			
Acute sporadic or chronic relapsing	normal or ↓↓↓↓	Post-operative period	↓↓↓

severe liver failure decreased synthesis is a plausible mechanism. In patients with uremia the moderately reduced protease levels were not related to serum creatinine taken as an index of renal function. In patients undergoing major abdominal surgery the protease fell consistently in the post-operative period.<sup>22</sup> The protein seems to be influenced by high levels of estrogens, because plasma levels decrease progressively from the first trimester of pregnancy, albeit moderately.<sup>23</sup> The low values found in full-term newborns can perhaps be explained as another phenotypic expression of the immaturity of the newborn liver, as indicated by the protease reaching normal levels within 6 months of birth.<sup>23</sup>

In conclusion, low protease values may not be a specific beacon for TTP (Table 1). There are cases of HUS in which the protease is unmeasurable, although this pattern is seen more frequently in TTP. In both microangiopathies the protease is sometimes measurable, albeit at reduced levels. However, similarly reduced values are found in clinical conditions other than thrombotic microangiopathies, such as liver and renal disease and inflammatory states. These data challenge the views that low protease levels are specific for a diagnosis of thrombotic microangiopathies.

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