



TOPIC HIGHLIGHT

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Blood transfusion for the treatment of acute anaemia in inflammatory bowel disease and other digestive diseases

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Abstract

Allogeneic blood transfusion (ABT) is frequently used as the first therapeutic option for the treatment of acute anaemia in patients with inflammatory bowel disease (IBD), especially when it developed due to gastrointestinal or perioperative blood loss, but is not risk-free. Adverse effects of ABT include, but are not limited to, acute hemolytic reaction (wrong blood or wrong patient), febrile non-hemolytic transfusional reaction, bacterial contamination, transfusion-related acute lung injury, transfusion associated circulatory overload, transfusion-related immuno-modulation, and transmission of almost all infectious diseases (bacteria, virus, protozoa and prion), which might result in increased risk of morbidity and mortality. Unfortunately, the main physiological goal of ABT, i.e. to increase oxygen consumption by the hypoxic tissues, has not been well documented. In contrast, the ABT is usually misused only to increase the haemoglobin level within a fixed protocol [mostly two by two packed red blood cell (PRC) units] independently of the patient's tolerance to normovolemic anaemia or his clinical response to the transfusion of PRC units according to a "one-by-one" administration schedule. Evidence-based clinical guidelines may promote best transfusion practices by implementing restrictive transfusion

protocols, thus reducing variability and minimizing the avoidable risks of transfusion, and the use of autologous blood and pharmacologic alternatives. In this regard, preoperative autologous blood donation (PABD) consistently diminished the frequency of ABT, although its contribution to ABT avoidance is reduced when performed under a transfusion protocol. In addition, interpretation of utility of PABD in surgical IBD patients is hampered by scarcity of published data. However, the role of autologous red blood cells as drug carriers is promising. Finally, it must be stressed that a combination of methods used within well-constructed protocols will offer better prospects for blood conservation in selected IBD patients undergoing elective surgery.

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Key words: Anaemia; Blood transfusion; Autologous blood transfusion; Inflammatory bowel diseases; Risk assessment

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INTRODUCTION

In surgical, medical and critically ill patients, allogeneic blood transfusion (ABT) is frequently used as the first therapeutic option for the treatment of acute anaemia, especially when it developed due to traumatic or acute blood loss or when the patient's compensatory mechanisms have a limited capacity of response^[1-4]. As a result, a high proportion of patients receive at least one ABT unit during their hospital stays.

However, many reports show variation in transfusion practice for comparable groups of patients between hospitals, and even between different departments

within a hospital. Variations in rates of transfusion may be due to many factors, but still differing opinions on the threshold level of haemoglobin (Hb) and the implementation of transfusion alternatives are the most important ones. The first may reflect uncertainty about the benefits and risks of ABT, and the second different perceptions of the value of stimulation of erythropoiesis and minimising blood loss and subsequent transfusion^[5].

Of note, the main physiological goal of ABT, i.e. to increase oxygen consumption by the hypoxic tissues, has not been well documented^[6-8]. In contrast, the ABT is usually misused only to increase the Hb level within a fixed protocol [mostly two by two packed red blood cell (PRC) units] independently of the patient's tolerance to normovolemic anaemia or his clinical response to the transfusion of each PRC unit according to a "one-by-one" administration schedule.

Unfortunately, good clinical studies and outcome data establishing the benefits and risks of ABT for a patient in different clinical settings are not available^[9]. To the best of our knowledge, there are very few situations or pathological entities where ABT and/or liberal transfusion criteria have shown to benefit our patients (drepanocytosis, thalassemic or low-weight premature infants)^[10,11]. Thus, to promote best transfusion practices and reduce variability, minimizing the avoidable risks of transfusion, and to help clinicians in choosing the appropriate treatment options, a number of clinical guidelines have been issued by different medical societies^[12-17]. In this article, we review the indications, benefits and risks of blood transfusion of the different blood components available, both allogeneic and autologous, with special emphasis on patients suffering from inflammatory bowel disease (IBD), either ulcerative colitis (UC) or Crohn's disease (CD).

INDICATIONS FOR ABT

Transfusion of PRC is indicated in order to achieve a fast increase in the supply of oxygen to the tissues, when the concentration of Hb is low and/or the oxygen carrying capacity is reduced, in the presence of inadequate physiological mechanisms of compensation. Tissue oxygenation depends on various factors: (1) the concentration of Hb; (2) the saturation of Hb, which, in turn, depends on the O₂ tension and the affinity of the Hb for O₂; (3) the O₂ requirements, that is, the volume of oxygen needed by the tissues to carry out their aerobic function. But, there are a number of clinical factors that affect the physiological mechanisms of adaptation to anaemia: (1) a reduced increase in cardiac output: hypovolaemia, coronary artery disease, disorders of heart valves, congestive heart disease, negative inotropic drugs; (2) decreased capacity to increase the extraction of O₂: acute respiratory distress syndrome (ARDS), sepsis, systemic inflammatory response syndrome (SIRS), traumatic ischemia-reperfusion syndrome; three, altered gas exchange: chronic obstructive pulmonary disease (COPD), ARDS; and

four, increased consumption of O₂: fever, pain, stress, sepsis, SIRS or hyperventilation syndromes^[17].

When there is an indication to correct anaemia, but the situation is not urgent, strategies other than transfusion are preferred, such as the use of haematopoietic drugs (iron, vitamin B12, folic acid, recombinant erythropoietin) (see another chapter).

Non-surgical IBD patients

Nowadays the administration of oral or IV iron supplements, with or without erythropoiesis-stimulating agents, but not ABT, is the standard therapy for the anaemia of the medical IBD patient (see corresponding article in this issue). According to the recommendations of the Guidelines on the Diagnosis and Management of Iron Deficiency and Anemia in Inflammatory Bowel Diseases (Statement 3A), the goals of anaemia treatment are to increase Hb, and iron studies above the lower threshold of normal, to prevent a further fall in Hb, to avoid the use of ABT, to relieve symptoms related to anaemia, and to improve the quality of life (Grade D)^[18]. Nevertheless, some IBD patients are still being transfused, mostly because of acute gastrointestinal haemorrhage, although the Guidelines do not provided any recommendations in this regard. In our modest opinion, these ABT are some times administered without strict criteria, just to raise a low Hb figure ("cosmetic" transfusion) or to treat a hypovolemic situation, but not to correct transitorily hypoxic symptoms or signs.

Fortunately, severe acute gastrointestinal haemorrhage is uncommon in IBD, although among children 0-5 years of age patients presented with more rectal bleeding than patients aged 6-17 years, despite the later having a more complicated disease course^[19].

Belaiche *et al*^[20] reviewed 34 cases of acute gastrointestinal haemorrhage in CD patients (defined as acute rectal bleeding originating in diseased bowel and requiring an ABT of at least 2 U of PCR within 24 h). When the bleeding source was identified, the bleeding lesion was an ulcer in 95% of cases, most often in the left colon. The treatment was surgical (20.6%), endoscopic (20.6%), or medical (58.8%), and there were no deaths. The authors concluded that given the potential efficacy of endoscopic or medical treatment, as well as the absence of mortality, a conservative approach may be suggested as first-line therapy in the majority of patients.

Similarly, Pardi *et al*^[21] characterized the clinical features and course of such haemorrhage in patients at their institution from 1989 to 1996. Thirty-one patients had acute lower gastrointestinal bleeding from IBD (three UC, 28 CD), representing approximately 1% of admissions for IBD. Again, the bleeding lesion presented with an ileocolonic or colonic localization in most cases (68%), and surgery was required in less than half of cases. However, in both patient series, recurrent haemorrhage was not rare, and for these cases surgery may be the most appropriate treatment.

More recently, Kostka *et al*^[22] characterized the clinical features and course of 11 separate episodes of severe haemorrhage in six of 156 patients with CD (3.8%),

treated between 1985 and 2003 at their institution. Emergency surgery was necessary to stop the primary or recurrent haemorrhage in four patients. The authors concluded that, although a conservative approach may be first-line therapy, surgery is inevitable in patients suffering from massive bleeding and in patients with recurrent bleeding. Similar conclusions were reached by Veroux *et al*^[23] in a previous series of five CD patients with severe gastrointestinal bleeding.

In a recent review of five years, Campos *et al*^[24] reported 301 episodes of massive transfusion occurred at a university hospital, and found that 51 out of these 301 episodes were due to upper gastrointestinal haemorrhage (17%), with a mortality rate of 52%. It is recommended that the Transfusion Services have a special protocol to manage severe bleeding emergency, however the blood component administration schedules are neither clear nor uniform. In the last few years, there has been a general review of the blood component schedule during massive transfusion^[25]. Nowadays, data from several large observational studies show that early beginning of plasma and platelet administration, including the use of the so-called “transfusion packs”, could improve mortality of patients with severe bleeding^[26].

Surgical IBD patients

As for acute gastrointestinal haemorrhage, other emergency complications of IBD are rare, but may be life-threatening, require surgery, and result in permanent end organ damage. The most common non-bleeding complications associated with UC are fulminant colitis and toxic megacolon, and often result in a total proctocolectomy. The most common non-bleeding complications associated with CD are abscesses and intestinal obstruction, and usually also require surgical intervention and intestinal resection^[27].

Despite pharmacological advancements, the management of IBD has become increasingly complicated. In a study of 2892 adults with CD and 5895 with UC who received care between 1998 and 2005, Herrinton *et al*^[28] found: a shift in gastroenterology-related visits from the gastroenterology division to primary care; an increased use of IBD-related drugs; a 36% decline in the prevalence of prolonged steroid exposure for CD patients, with a 27% increase for UC patients; a 30% decline in the hospitalization rates for CD and UC patients; and a 50% decline in the surgery rate for UC, but no significant change for CD. In this regard, it is worth noting that in UC patients, surgery remains an important part of the overall treatment plan, especially for prophylactic total colectomy in certain patients at high risk for colorectal cancer^[29].

As for other patients undergoing major surgery, in the surgical IBD patient, intraoperative and postoperative management of potential or actual blood loss should include (ASA)^[16].

Monitoring the amount of blood loss: A periodic visual assessment of the surgical field and communication with

the surgical team should be done to assess the presence of excessive microvascular bleeding (i.e. coagulopathy).

Monitoring for the presence of inadequate perfusion and oxygenation of vital organs: By using conventional (e.g. blood pressure, heart rate, oxygen saturation, urine output, electrocardiography) and/or special monitoring systems (e.g. echocardiography, mixed venous oxygen saturation, blood gasses, National Institute of Radiological Sciences).

Monitoring for transfusion indications: Measure Hb or haematocrit when there is substantial blood loss or there is any indication of organ ischemia. However, as the haematocrit value is subjected to a variety of bias, especially in hypovolemic anaemic patients, Hb concentration should be preferred^[30]. In this regard, it's worth noting that in most of the available hematological analyzers the “haematocrit” is an indirectly calculated parameter.

Transfusion of allogeneic red blood cells (RBCs): Maintain adequate intravascular volume and blood pressure with crystalloids or colloids until the criteria for ABT are met (see below). Adequate quantities of RBCs should be transfused to maintain organ perfusion (PCR units should be transfused one-by-one, and anaemia symptoms reassessed after each transfusion). When appropriate, pre-deposited autologous blood donation and other means to decrease blood loss (e.g. deliberate hypotension, antifibrinolytics) may be beneficial (see below).

Hb transfusion triggers

The only indication for the transfusion of PRC is to correct or prevent tissue hypoxia; thus, the parameter “of choice” for making decisions should be intracellular pO₂. However, this parameter is not useful for clinical purposes and it is, therefore, necessary to rely on “surrogate” parameters, such as Hb and the haematocrit. The indication for and the degree of urgency of PRC transfusions cannot, however, be defined only on the basis of the values of Hb or the Htc, but must be based on a complete evaluation of the patient's clinical condition and the possible presence of mechanisms compensating for the anaemia (see above)^[17].

According to ASA guideline on blood transfusion^[16], PRC should usually be administered when the Hb level is less than 6 g/dL, whereas they are usually unnecessary when the level is more than 10 g/dL. These conclusions may be altered in the presence of anticipated blood loss. The determination of whether intermediate Hb concentrations (i.e. 6-10 g/dL) justify or require PRC transfusion should be individualised. This indication should be based on any ongoing indication of organ ischaemia, potential or actual ongoing bleeding (rate and magnitude), the patient's intravascular volume status, and the patient's risk factors for complications of inadequate oxygenation. These risk factors include a low cardiopulmonary reserve and high oxygen consumption^[16,17].

Table 1 Transfusion haemoglobin threshold according to patient's age and characteristics and type of anaemia

Haemoglobin threshold (g/dL)	Patients characteristics and type of anaemia
< 5	Patients with chronic anaemia and without risk factors ¹
< 6	Patients with symptomatic ² chronic anaemia and without risk factors
< 7	Acute anaemia in younger patients Asymptomatic chronic anaemia in patients with risk factors
< 8	Acute anaemia in surgical and critically ill patients
< 9	Acute anaemia in surgical patients older than 65 yr
< 10	Acute anaemia in patients with organ dysfunction ³
< 10	Patients with massive transfusion
> 10	Do not transfuse

¹Risk factors; ²Symptomatic anaemia; ³Organ dysfunction.

These indications are in agreement with those proposed by most international clinical guidelines and documents issued by several medical societies, such as the American Consensus Conference on perioperative red blood cell transfusion (Hb < 8 g/dL)^[12], British Haematological Society (Hb < 8 g/dL)^[13], the Scottish Guideline on Perioperative Blood Transfusion (Hb < 7 g/dL)^[4], or the Spanish Society for Blood Transfusion (Hb < 7 g/dL and Hb < 5 g/dL in chronic anemia)^[15]. Recently, the Italian Transfusion Society^[17] proposed the same recommendations as ASA^[16], but giving a Grade of recommendation 1A. A tentative table of Hb transfusion thresholds as a function patient's age and characteristics and type of anaemia is given in Table 1.

Transfusion yield

As a rough guide, in adults one unit of PRC increases the Hb concentration by 1 g/dL and the haematocrit by about 3%. In children, the transfusion of 5 mL/kg increases the Hb concentration by about 1 g/dL. In the case of a lower than expected transfusion yield, conditions causing the loss, sequestration or destruction of RBCs should be looked for. Such conditions include: occult bleeding, repeated blood sampling (particularly in children), fever, hypersplenism, primary and secondary immunological causes, mechanical or other type of hemolysis^[17].

BENEFITS OF ABT

The experience with Jehovah's Witness patients suggests that, overall, postoperative anaemia is well tolerated if Hb > 7 g/dL, but it increases the risk of mortality when Hb falls below 5 g/dL, this effect being magnified by blood loss and cardiac disease (Hb < 10 g/dL), and indirectly suggests that ABT is life-saving in this context^[9]. Also, ABT may be life-saving in children with severe anaemia and signs of respiratory distress and, possibly, in very low birth weight infants^[9]. In contrast, for critically ill patients, severe anaemia (Hb < 8 g/dL) increases the risk of mortality by 1.54, whereas the transfusion of 1-2, 3-4, or more than 4 U increases this risk by 1.48, 2.68, and

Table 2 Theoretical reasons supporting the restrictive or the liberal use of allogeneic red cells in normovolemic patients

Rationale supporting the liberal use of red cells
Augmenting O ₂ delivery may improve patient survival and functional recovery
Increased risk of coronary ischaemia due to increased demand
Reduces respiratory work
Age, disease severity and drugs may interfere adaptation to anaemia
Improved safety margin if further blood loss
Increased safety of donor blood products
Rationale supporting the restrictive use of red cells
Moderate anaemia has not proved to increase mortality
Red cell transfusions impair microcirculatory flow
Progressive loss of red cell functionality during storage
Pathologic supply dependency is rare
Risk of pathogen transmission
Immunodepression causing increased infections and tumor relapse following transfusion
Risk of TRALI and TACO
Blood products are increasingly scarce and expensive

TRALI: Transfusion-related acute lung injury; TACO: Transfusion associated circulatory overload.

4.01, respectively^[31]. However, ABT may be life-saving in extremely ill patients with cardiovascular disease^[11]. Theoretical reasons for using a "liberal" or "restrictive" transfusion protocol are given in Table 2.

On reviewing the literature, it can not be concluded that ABT is beneficial for less sick patients and those without cardiovascular disease when Hb is above 7 g/dL^[11,32]. On the other hand, the effects of anaemia below 7 g/dL and the subsequent beneficial effects of ABT, if any, can also not be determined from published studies since patients either refuse to receive ABT for religious reasons or are transfused systematically, except in the case of chronically anaemic patients like those with thalassemia or drepanocytosis^[10].

As for patients with cardiovascular diseases, there appears to be some evidence that ABT, in small amounts, can reverse ischaemic changes and restore normal myocardial function. However, the randomized controlled trials conducted so far have offered contradictory results regarding the safety of restrictive transfusion triggers in older patients. Whilst four of them reported that a restrictive transfusion protocol resulted in the transfusion of appreciably fewer units of RBC, with no differences between groups regarding postoperative morbidity or mortality^[11,32-34], the last one which was designed to find differences in postoperative quality of life, found that in elderly patients undergoing surgery for hip fracture repair a restrictive transfusion threshold (Hb < 8 g/dL) may result in a higher incidence of postoperative cardiovascular complications (10% *vs* 2%, *P* = 0.05) and 30 d mortality (8% *vs* 0%, *P* = 0.02) when compared with a liberal transfusion threshold (Hb < 10 g/dL)^[35]. The Transfusion Trigger Trial for Functional Outcome in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair^[36], which has been planned to be a 2600 patient, multicentre clinical trial, will most probably address the question of whether patients with cardiovascular disease

or cardiovascular risk factors undergoing surgical repair of hip fracture benefit from a higher or lower transfusion trigger^[15]. While data from randomized trials are available, patients with suspected or proven myocardial ischaemia must be closely monitored and ABT should be given unit-by-unit until cardiac function is normalized, rather than to adopt a fixed transfusion trigger for all such patients^[15].

Packed red cell transfusion to a predetermined Hb in view of optimizing oxygen transport is definitely not supported by a large trial in critically ill patients [Transfusion Requirements In Critical Care (TRICC) trial]^[11]. In fact, in the study by Hébert *et al*^[11], patients submitted to a restrictive transfusion strategy seem to have better outcomes than those submitted to a liberal transfusion strategy, especially those who are younger (< 55 years old) or less ill (APACHE score < 20). However, the analysis by Deans *et al*^[37] suggests that the results of the TRICC trial were strongly influenced by non-comparable subgroups with different practice misalignments in each arm of the study. The excess risk incurred by each of these subgroups makes the comparison of mortality rates between the two treatment arms in the overall study difficult to interpret. Furthermore, as publications before this trial indicated that clinicians used higher transfusion thresholds in patients with ischaemic heart disease compared with younger, healthier patients, neither arm fully represented or was compared with current practices, and it remains unclear if the use of an absolute transfusion threshold is superior to adjusting therapy based on individual patient characteristics or implementing consensus guidelines for transfusion practices^[37].

The rationale behind ABT is to restore oxygen delivery and provide a reserve should further blood loss occurs. After PRC transfusion, an increase in Hb levels is readily observed, but controversial results were found when evaluating the influence of stored PRCs on tissue oxygenation, assessed by surrogate markers of oxygenation, such as gastric pH and CO₂^[7,8]. Very recently, Leal-Noval *et al*^[6] and Smith *et al*^[38] studied the effect of ABT on cerebral oxygenation in patients with severe traumatic brain injury and found erythrocyte transfusion to be associated with a variable and prolonged increment of cerebral tissue oxygenation. However, no relationship was observed between brain tissue partial pressure of oxygen (PtiO₂), cerebral perfusion pressure and Hb concentration. In addition, 3 h after transfusion, all patients with basal PtiO₂ < 15 mmHg showed an increment in PtiO₂, *vs* 74.5% of patients with PtiO₂ ≥ 15 mmHg, *P* < 0.01^[6]. Moreover, in a subsequent study, this group demonstrated that an increment in PtiO₂ was only observed in patients receiving blood stored for less than 19 d^[39]. Thus, low baseline PtiO₂ levels could define those patients who benefit the most from ABT.

However, ABT providing Hb of 10-11 g/dL might be required for patients with COPD, as it may reduce minute ventilation and the work of breathing, for patients bleeding to improve haemostasis in massive transfusion^[25,26], and for surgical patients with sickle cell disease, reducing HbS levels by direct transfusion

or by RBC exchange (partial or total) to avoid sickling crisis^[10,14].

In conclusion, while ABTs save lives, they save far fewer lives than we have been taught to believe. As ABT will never be a risk free therapy (see below), each and every unit transfused unnecessarily is, potentially, a noxious unit. In other words, each ABT which is not strictly indicated is severely contraindicated!

RISKS OF ABT

Nowadays, due to a careful donor selection and the introduction of highly sophisticated tests for pathogen detection, ABT is safer but more scarce and expensive than ever, and is still not risk-free. Transfusion therapy with PRCs can cause adverse reactions, which are classified on the basis of their etiopathogenesis and the time of occurrence with respect to the transfusion. Adverse effects of ABT (Table 3) include a broad panoply including, but not limited to, incorrect blood transfusion ("wrong blood"), acute or delayed haemolytic transfusion reaction, allergic reaction (from urticaria to anaphylactic reaction), bacterial contamination, transfusion-related acute lung injury (TRALI), transfusion associated circulatory overload (TACO), transfusion-related immuno-modulation (TRIM), and transmission of infectious diseases (viruses, protozoas and prions)^[40], which result in increased risk of morbidity and mortality. As the risks of ABT-transmitted viruses were reduced to exceedingly low levels in the US and Europe, TRALI, haemolytic transfusion reactions (HTRs), and transfusion-associated sepsis (bacterial contamination) emerged as the leading causes of ABT-related deaths^[41]. Since 2004, preventive measures for TRALI and bacterial contamination have been implemented, but their implementation remains incomplete^[41]. Infectious causes of ABT-related deaths currently account for less than 15% of all transfusion-related mortality, but the possibility remains that a new transfusion-transmitted agent causing a fatal infectious disease may emerge in the future^[40,41]. These, together with the possible advantages of implementing restrictive transfusion protocols, strongly indicate that transfusion practice in surgery and intensive care should be (and must be) modified, especially in terms of the level of pretransfusion Hb ("restrictive" *vs* "liberal" use of ABT; "acceptable Hb" *vs* "optimal Hb") (Table 2). Briefly, we will describe several of the most important adverse reaction to transfusion.

Transfusion reaction: According to Serious Hazards of Transfusion report 1994-2004, 1832 out of 2628 reported incidents corresponded to episodes of incorrect blood component transfused (IBCT) (wrong blood product or wrong patient)^[42]. Thus, the incidence of reported IBCT is about 1:20 000-25 000 and the consequences can be disastrous. In Spain^[43], 246 "near-miss administration errors" and 134 of IBCT were reported during 2007. Of those, 49 led to HTRs (33 due to ABO incompatibility), with at least three deaths reported and confirmed^[4]. In a Spanish region (Catalunya) the incidences were estimated as 1:11 000 of IBCT, 1:77 000 of "ABO-mistakes" and 1:310 950 of death secondary to transfusion^[44]. As for

Table 3 Risks or hazards of allogeneic blood transfusion

Acute transfusion reactions
Immunologic reactions
Acute haemolytic reaction (or THRs)
Febrile non-haemolytic reaction
Allergic reactions: Urticaria and anaphylaxis
Acute non-cardiogenic pulmonary edema: TRALI
Alloimmunization with acute platelet destruction
Non-immunologic reactions
Bacterial contamination
TACO
Hypotensive reaction
Non-immunologic haemolysis
Others: Hypocalcemia, hyperkalemia (cardiac arrest), hypothermia, hyperglycemia, <i>etc</i>
Delayed transfusion reactions
Immunologic reactions
Delayed haemolytic reaction
Alloimmunization against blood cell antigens (also platelets and leukocytes)
Graft <i>vs</i> host disease
Transfusion-related immunomodulation
Post-transfusion purpura
Non-immunologic reaction
Transfusion-transmitted infection: viruses (Hepatitis A, B, C, E, VIH 1-2, West Nile virus, HTLV I - II, Citomegalovirus, Virus Herpes viridae, TTV, SEN-1, SARS, <i>etc</i>), protozoa (malaria, babe biosis, Chagas disease, <i>etc</i>), prion (new variant Creutzfeldt Jacob disease)
Post-transfusion hemosiderosis (iron overload)

TRALI: Transfusion-related acute lung injury; TACO: Transfusion associated circulatory overload.

the surgical patient, general anaesthesia may mask the symptoms of both HTRs and non-HTRs. Signs of HTRs include hypotension, tachycardia, haemoglobinuria and microvascular bleeding, but these may be erroneously attributed to other causes in the anaesthetized patient. The most common signs of a non-haemolytic transfusion reaction in awake patients include fever, chills, or urticaria. However, these signs may not be detectable during anaesthesia. Thus, checking for signs and symptoms of a THR should periodically be done in the anaesthetized patient, including urine output and colour and peak airway pressure^[16].

Bacterial contamination: Bacterial contamination of blood products, most frequently platelets, is one of the leading causes of death from ABT^[40,41] (seven deaths in UK from 1996 to 2004)^[42]. The increased risk of bacterial overgrowth is related to a storage temperature of > 20-24°C. Many blood banks are now culturing their platelet concentrates, or inactivating them, although this leads to a decreased functionality. If a patient develops a fever within 6 h of receiving platelets, sepsis from contaminated platelets may be a possibility. Between 2001 and 2003, an average of 11.7 years in the United States were reported to the Food and Drug Administration, whereas 7.5 per year were reported in 2004 and 2005 - a decrease attributable in part to the mandating of bacterial screening of platelets beginning in 2004^[40]. In Spain, during 2007 at least 17 cases, with one death, have been reported and confirmed^[43].

TRALI: TRALI is a well-characterized and serious adverse consequence of blood product transfusion; its overall occurrence is almost certainly more common than the quoted estimate of one case in 4000 U of blood transfused (as TRALI is generally unrecognized or misdiagnosed, its actual incidence is unknown)^[45]. TRALI is non-cardiogenic pulmonary edema resulting from immune reactivity of certain leukocyte antibodies a few hours after transfusion. Signs and symptoms will appear 1-2 h after transfusion and are in maximum force within 6 h. Hypoxia, fever, dyspnea, and even fluid in the endotracheal tube may occur. There is no specific therapy other than stopping transfusion and instituting critical care supportive measures. Most patients recover in 96 h, although TRALI is one of the top three most common causes of transfusion related deaths^[45]. In Spain, 32 cases have been reported and confirmed during 2007, with at least two deaths^[43]. The estimated rate was 1/32 000 (at Catalunya), but the authors suspected a great underreporting^[44]. For example, during preparation of this manuscript one of the authors diagnosed one highly probable case of TRALI during a plasma exchange, but no physician at the intensive care unit knew what TRALI meant.

TACO: TACO is a cause of hydrostatic pulmonary oedema with clinical and radiologic manifestations similar to those of TRALI. In fact, the distinction between TRALI and TACO after transfusion is difficult, in part because the two conditions may coexist^[44,46]. During 2007, in Spain at least 39 cases had been reported and confirmed, with at least one death confirmed^[43].

TRIM: TRIM is associated with increased risk of postoperative infection^[2,3,47-49]. The combined data from three studies including over 1700 patients undergoing elective cardiac surgery with cardiopulmonary bypass showed that (1) transfusion of RBC concentrates was independently associated with increased rates of postoperative pneumonia, mediastinitis and sepsis; (2) these effects were dose-dependent and storage-time-dependent; and (3) other blood components might be also involved^[50-52]. As for patients undergoing elective surgery for gastrointestinal cancer resection or urgent surgery for hip fracture repair, similar data have been reported^[4,49,53].

Infectious diseases: Another major adverse effect of transfusion therapy is the transmission of infectious agents^[40,41]. For the past 20 years, transfusion induced hepatitis and acquired immunodeficiency syndrome (AIDS) have been dominant concerns regarding ABT. These infectious risks are now very rare. One of the major reasons for the decrease in blood borne infections has been the use of nucleic acid technology (NAT). The human immunodeficiency virus (HIV), C hepatitis virus (CHV), and West Nile virus can now be detected by this technology. To date, malaria, Chagas disease, severe acute respiratory syndrome (SARS), and variant Creutzfeldt-Jakob disease (vCJD) cannot be detected^[16]. The possible safety intervention that might further

reduce the risk of transfusion-transmitted infection is not static, as new agents continue to emerge, old ones change their properties and epidemiologic patterns, and new information and technology become available to change our understanding of that risk^[40,41]. During 2007 in Spain, twenty five cases of possible hepatitis B or C were reported, but none of them were confirmed^[43]. Between 2005-2007 five cases of Chagas disease were diagnosed, although four of them retrospectively after a “look back”^[43].

PREOPERATIVE AUTOLOGOUS BLOOD DONATION (PABD)

PABD consists of obtaining the patient's own blood prior to surgery in order to administer it if necessary afterwards^[1,54]. Extraction frequency, type of blood component or bag for conservation, and volume of blood extracted are established by each Local Blood Bank on an individual basis^[1,54-56]. In the elective surgical setting, PABD is a convenient, predictable, safe and widely practised form of transfusion support^[4]. However, PABD cannot be made available to all patients (minimal Hb ≥ 11 g/dL), and it is contraindicated in the presence of several infectious, cardiac, oncologic or neurologic pathologies. Hospital admission and operative dates must be guaranteed, as donated blood has a limited storage life of 35 d (up to 42 d in additive SAG-mannitol solution). In addition, it used to carry some of the risks of ABT, especially IBCT, although in the European Union there are regulations aimed to reduce these risks (e.g. personalized unit identification, separate conservation and transport, de-referral for allogeneic use, *etc*), and these can often present logistical difficulties^[1,54,55]. Nonetheless, PABD avoids immunological and viral hazards of ABT. In spite these benefits, PABD use is decreasing worldwide^[56].

In accordance with the conclusion of the Spanish Consensus Statement on Alternatives to Allogeneic Blood Transfusion (Seville's Document)^[55]: PABD would be indicated in elective surgery if the risk of ABT > 20%-30%, and in patients with difficulties receiving ABT; PABD can be used safely in children and elderly populations^[54,57]; the administration of rHuEPO in patients with moderate anaemia, facilitates PABD^[57]; PABD contribution to ABT reduction is decreased when a transfusion protocol is adopted; PABD may have problems of over-collection and over-transfusion (in fact, PABD increases the total number of transfusion episodes). It is not without infectious risks; PABD erythrocytes undergo “storage lesion”. PABD has been classically associated with higher rates of “clerical errors”, and ABT may still be required (break-through transfusion).

In this regard, it is well known that surgery in IBD is frequently associated with a need for perioperative blood transfusions, but PABD is often limited by IBD-associated anaemia, although it is reversible by intravenous iron and rHuEPO. Consequently there is a paucity of studies on the use of PABD in surgical IBD patients

(and none in the use of perioperative cell salvage or acute normovolemic haemodilution). Mittermaier *et al*^[58] tested the feasibility of PABD (2-4 U; 350-450 mL blood per unit; 1 U/wk) in six patients (five CD, one UC) with indications for elective bowel resection IBD. Patients received 200 mg of iron sucrose IV after each donation, plus concomitant rHuEPO if there was preexisting anaemia or C-reactive protein > 2 mg/dL. Four patients received PABD transfusions intra- or postoperatively, and no patient needed ABT. No serious adverse events were observed during blood donations, perioperatively, and during the one year follow-up period. Thus, when appropriately indicated and supplemented with IV iron and rHuEPO, PABD seems to be safe and useful for surgical IBD patients. Since 2003, we have treated 2668 PABD patients in our hospital, only three of them with IBD (two CU and one EC) scheduled to prostatectomy, coxarthrosis and avascular femoral necrosis surgeries, donating two units each patient. The first patient required two doses of β -epoetin 30 000 IU plus iron sucrose iv 400 mg, and the second was transfused with two PABD units plus two ABT units.

Recently, PABD has been used, not as an alternative to ABT, but as a carrier of drugs, owing to the ability of the RBC membrane to be opened and resealed under appropriate conditions. In an uncontrolled pilot study, Annese *et al*^[59] investigated efficacy and safety of dexamethasone-encapsulated erythrocytes in 10 steroid-dependent adults IBD patients (five UC, five CD). Fifty milliliters of blood were drawn from each subject; dexamethasone 21-phosphate (Dex 21-P) was encapsulated into erythrocytes by means of specially designed equipment, and drug-loaded erythrocytes were infused into the original donors (5.5 ± 2.4 mg Dex 21-P). The procedure was repeated after 4 and 8 wk, and patients were instructed to withdraw corticosteroids. After the third infusion, all patients were in clinical remission. After a mean follow-up of 12 ± 3 mo, six patients relapsed, and the remaining four patients remained in remission. Pre-existing steroid-related adverse effects disappeared during the follow-up. The authors concluded that Dex 21-P loaded autologous RBC is a feasible technique, which is safe, maintains patients in clinical remission and allows steroid withdrawal.

More recently, infusions of autologous RBCs loaded with Dex 21-P, performed every 4 wk for 24 mo, to 18 consecutive paediatric patients with steroid-dependent CD resulted in a reduction of the CD activity index, 78% of patients discontinued steroids and endoscopic findings showed remission in 44% of patients, whereas none of the patients experienced serious side effects^[60]. Therefore, infusions of autologous RBCs loaded with Dex 21-P seem to be safe and useful for maintaining long-term remission in paediatric patients with moderately active CD. However, large randomized controlled trials are needed to confirm these promising results.

CONCLUSION

ABT used to be the first therapeutic option for the treatment of acute anaemia in IBD patients, especially

when it developed due to gastrointestinal or perioperative blood loss, but was not risk-free. Adverse effects of ABT include, but are not limited to, IBCT (wrong blood), THRs, bacterial contamination, TRALI, TACO, TRIM and transmission of infectious diseases, which might result in increased risk of morbidity and mortality. Evidence-based clinical guidelines may promote best transfusion practices and reduce variability, minimizing the avoidable risks of transfusion, and help clinicians in choosing the most appropriate treatment for the patient-ABT, PABD or pharmacologic alternatives. The acceptance of normovolemic anaemia is indeed one of the most effective measures to reduce ABT requirements. Thus, the adoption of restrictive transfusion criteria (lower threshold level of Hb) must be the first measure to implement in order to reduce both the number of transfused units and transfused patients. Obviously, the second measure must be the pharmacological treatment of anaemia. PABD consistently reduces the frequency of ABT, with a small incidence of adverse effects, although its contribution to ABT avoidance is reduced when performed under a transfusion protocol. In addition, interpretation of utility of PABD in surgical IBD patients is hampered by scarcity of published data. However, the role of autologous RBCs as drug carriers is promising. Finally, for selected patients, a combination of methods used within well-constructed protocols will offer better prospects for blood conservation in IBD patients undergoing elective surgery.

REFERENCES

- Muñoz M, García-Erce JA, Campos A, Fernando Barrios L. [Legal framework for the use of autologous blood and other alternatives to allogeneic transfusion] *Med Clin (Barc)* 2007; **128**: 256-262
- Muñoz M, Leal-Noval SR, García-Erce JA, Naveira E. [Prevalence and treatment of anemia in critically ill patients] *Med Intensiva* 2007; **31**: 388-398
- Muñoz M, García-Erce JA, Leal-Noval SR. Perioperative transfusion in anaemic patients undergoing coronary artery bypass. *Lancet* 2002; **360**: 1427; author reply 1427-1428
- Muñoz M, Llaou JV, Leal SR, García-Erce JA, Culebras JM. Transfusión sanguínea perioperatoria en el paciente neoplásico (II). Alternativas para la reducción de los riesgos transfusionales. *Cir Esp* 2002; **72**: 337-348
- Scottish Intercollegiate Guidelines Network. (2004) Perioperative blood transfusion for elective surgery. A national clinical guideline. Available from: URL: <http://www.sign.ac.uk>
- Leal-Noval SR, Rincón-Ferrari MD, Marin-Niebla A, Cayuela A, Arellano-Orden V, Marín-Caballeros A, Amaya-Villar R, Ferrándiz-Millón C, Murillo-Cabeza F. Transfusion of erythrocyte concentrates produces a variable increment on cerebral oxygenation in patients with severe traumatic brain injury: a preliminary study. *Intensive Care Med* 2006; **32**: 1733-1740
- Marik PE, Sibbald WJ. Effect of stored-blood transfusion on oxygen delivery in patients with sepsis. *JAMA* 1993; **269**: 3024-3029
- Fernandes CJ Jr, Akamine N, De Marco FV, De Souza JA, Lagudis S, Knobel E. Red blood cell transfusion does not increase oxygen consumption in critically ill septic patients. *Crit Care* 2001; **5**: 362-367
- Hardy JF, Bélisle S. The benefits of allogeneic blood transfusion. What evidence do we have? In: NATA Textbook. Transfusion Medicine and alternatives to blood transfusion. Paris: R & J Éditions Médicales, 2000: 48-59
- Lee MT, Piomelli S, Granger S, Miller ST, Harkness S, Brambilla DJ, Adams RJ. Stroke Prevention Trial in Sickle Cell Anemia (STOP): extended follow-up and final results. *Blood* 2006; **108**: 847-852
- Hébert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, Tweeddale M, Schweitzer I, Yetisir E. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med* 1999; **340**: 409-417
- Consensus conference. Perioperative red blood cell transfusion. *JAMA* 1988; **260**: 2700-2703
- Murphy MF, Wallington TB, Kelsey P, Boulton F, Bruce M, Cohen H, Duguid J, Knowles SM, Poole G, Williamson LM. Guidelines for the clinical use of red cell transfusions. *Br J Haematol* 2001; **113**: 24-31
- Ortiz P, Mingo A, Lozano M, Vesga MA, Grifols JR, Castrillo A, Algora M, Romón I, Cárdenas JM. [Guide for transfusion of blood components] *Med Clin (Barc)* 2005; **125**: 389-396
- Habler O. Indications for perioperative blood transfusion in orthopedic surgery. *Transfus Altern Transfus Med* 2006; **8**: 17-28
- Practice guidelines for perioperative blood transfusion and adjuvant therapies: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Transfusion and Adjuvant Therapies. *Anesthesiology* 2006; **105**: 198-208
- Liumbruno G, Bennardello F, Lattanzio A, Piccoli P, Rossetti G. Recommendations for the transfusion of red blood cells. *Blood Transfus* 2009; **7**: 49-64
- Gasche C, Berstad A, Befrits R, Beglinger C, Dignass A, Erichsen K, Gomollon F, Hjortswang H, Koutroubakis I, Kulnigg S, Oldenburg B, Rampton D, Schroeder O, Stein J, Travis S, Van Assche G. Guidelines on the diagnosis and management of iron deficiency and anemia in inflammatory bowel diseases. *Inflamm Bowel Dis* 2007; **13**: 1545-1553
- Gupta N, Bostrom AG, Kirschner BS, Cohen SA, Abramson O, Ferry GD, Gold BD, Winter HS, Baldassano RN, Smith T, Heyman MB. Presentation and disease course in early-compared to later-onset pediatric Crohn's disease. *Am J Gastroenterol* 2008; **103**: 2092-2098
- Belaiche J, Louis E, D'Haens G, Cabooter M, Naegels S, De Vos M, Fontaine F, Schurmans P, Baert F, De Reuck M, Fiasse R, Holvoet J, Schmit A, Van Outryve M. Acute lower gastrointestinal bleeding in Crohn's disease: characteristics of a unique series of 34 patients. Belgian IBD Research Group. *Am J Gastroenterol* 1999; **94**: 2177-2181
- Pardi DS, Loftus EV Jr, Tremaine WJ, Sandborn WJ, Alexander GL, Balm RK, Gostout CJ. Acute major gastrointestinal hemorrhage in inflammatory bowel disease. *Gastrointest Endosc* 1999; **49**: 153-157
- Kostka R, Lukás M. Massive, life-threatening bleeding in Crohn's disease. *Acta Chir Belg* 2005; **105**: 168-174
- Veroux M, Angriman I, Ruffolo C, Barollo M, Buffone A, Madia C, Caglià P, Fiamingo P, D'Amico D. Severe gastrointestinal bleeding in Crohn's disease. *Ann Ital Chir* 2003; **74**: 213-215; discussion 216
- Campos A, Muñoz M, García-Erce JA, Ramírez G. [Incidence and mortality of massive transfusion in a university hospital: study of the period 2001-2005] *Med Clin (Barc)* 2007; **129**: 366-371
- Johansson PI, Hansen MB, Sørensen H. Transfusion practice in massively bleeding patients: time for a change? *Vox Sang* 2005; **89**: 92-96
- Johansson PI, Stensballe J, Rosenberg I, Hilslov TL, Jørgensen L, Secher NH. Proactive administration of platelets and plasma for patients with a ruptured abdominal aortic aneurysm: evaluating a change in transfusion practice. *Transfusion* 2007; **47**: 593-598

- 27 **Cheung O**, Regueiro MD. Inflammatory bowel disease emergencies. *Gastroenterol Clin North Am* 2003; **32**: 1269-1288
- 28 **Herrinton LJ**, Liu L, Fireman B, Lewis JD, Allison JE, Flowers N, Hutfless S, Velayos FS, Abramson O, Altschuler A, Perry GS. Time trends in therapies and outcomes for adult inflammatory bowel disease, Northern California, 1998-2005. *Gastroenterology* 2009; **137**: 502-511
- 29 **Scherer JR**. Inflammatory bowel disease: complications and extraintestinal manifestations. *Drugs Today (Barc)* 2009; **45**: 227-241
- 30 **Valeri CR**, Dennis RC, Ragno G, Macgregor H, Menzoian JO, Khuri SF. Limitations of the hematocrit level to assess the need for red blood cell transfusion in hypovolemic anemic patients. *Transfusion* 2006; **46**: 365-371
- 31 **Corwin HL**, Gettinger A, Pearl RG, Fink MP, Levy MM, Abraham E, MacIntyre NR, Shabot MM, Duh MS, Shapiro MJ. The CRIT Study: Anemia and blood transfusion in the critically ill--current clinical practice in the United States. *Crit Care Med* 2004; **32**: 39-52
- 32 **Grover M**, Talwalkar S, Casbard A, Boralessa H, Contreras M, Boralessa H, Brett S, Goldhill DR, Soni N. Silent myocardial ischaemia and haemoglobin concentration: a randomized controlled trial of transfusion strategy in lower limb arthroplasty. *Vox Sang* 2006; **90**: 105-112
- 33 **Carson JL**, Poses RM, Spence RK, Bonavita G. Severity of anaemia and operative mortality and morbidity. *Lancet* 1988; **1**: 727-729
- 34 **Bracey AW**, Radovancevic R, Riggs SA, Houston S, Cozart H, Vaughn WK, Radovancevic B, McAllister HA Jr, Cooley DA. Lowering the hemoglobin threshold for transfusion in coronary artery bypass procedures: effect on patient outcome. *Transfusion* 1999; **39**: 1070-1077
- 35 **Foss NB**, Kristensen MT, Jensen PS, Palm H, Krashenninnikoff M, Kehlet H. The effects of liberal versus restrictive transfusion thresholds on ambulation after hip fracture surgery. *Transfusion* 2009; **49**: 227-234
- 36 **Carson JL**, Terrin ML, Magaziner J, Chaitman BR, Apple FS, Heck DA, Sanders D. Transfusion trigger trial for functional outcomes in cardiovascular patients undergoing surgical hip fracture repair (FOCUS). *Transfusion* 2006; **46**: 2192-2206
- 37 **Deans KJ**, Minneci PC, Suffredini AF, Danner RL, Hoffman WD, Ciu X, Klein HG, Schechter AN, Banks SM, Eichacker PQ, Natanson C. Randomization in clinical trials of titrated therapies: unintended consequences of using fixed treatment protocols. *Crit Care Med* 2007; **35**: 1509-1516
- 38 **Smith MJ**, Stiefel MF, Magge S, Frangos S, Bloom S, Gracias V, Le Roux PD. Packed red blood cell transfusion increases local cerebral oxygenation. *Crit Care Med* 2005; **33**: 1104-1108
- 39 **Leal-Noval SR**, Muñoz-Gómez M, Arellano-Orden V, Marín-Caballos A, Amaya-Villar R, Marín A, Puppò-Moreno A, Ferrándiz-Millón C, Flores-Cordero JM, Murillo-Cabezas F. Impact of age of transfused blood on cerebral oxygenation in male patients with severe traumatic brain injury. *Crit Care Med* 2008; **36**: 1290-1296
- 40 **Blajchman MA**, Vamvakas EC. The continuing risk of transfusion-transmitted infections. *N Engl J Med* 2006; **355**: 1303-1305
- 41 **Vamvakas EC**, Blajchman MA. Transfusion-related mortality: the ongoing risks of allogeneic blood transfusion and the available strategies for their prevention. *Blood* 2009; **113**: 3406-3417
- 42 **Serious Hazards of Transfusion (SHOT)**. Annual reports 1996-2004. National Blood Service, London
- 43 **Unidad de Hemovigilancia**. Área de Hemoterapia. Informe Hemovigilancia Año 2007. Available from: URL: http://www.msc.es/profesionales/saludPublica/medicinaTransfusional/hemovigilancia/docs/informe_2007.pdf
- 44 **Muñiz-Díaz E**. L'a hemovigilància a Catalunya. Informe 2007. Banc de Sang i Teixits. Available from: URL: http://www.bancsang.net/media/pdf/Hemovigilancia_2007.pdf
- 45 **Shander A**, Popovsky MA. Understanding the consequences of transfusion-related acute lung injury. *Chest* 2005; **128**: 598S-604S
- 46 **Gajic O**, Gropper MA, Hubmayr RD. Pulmonary edema after transfusion: how to differentiate transfusion-associated circulatory overload from transfusion-related acute lung injury. *Crit Care Med* 2006; **34**: S109-S113
- 47 **Vamvakas EC**, Blajchman MA. Deleterious clinical effects of transfusion-associated immunomodulation: fact or fiction? *Blood* 2001; **97**: 1180-1195
- 48 **Vamvakas EC**. Possible mechanisms of allogeneic blood transfusion-associated postoperative infection. *Transfus Med Rev* 2002; **16**: 144-160
- 49 **Izuel Rami M**, García Erce JA, Gómez-Barrera M, Cuenca Espírruez J, Abad Sazatornil R, Rabanaque Hernández MJ. [Relationship between allogeneic blood transfusion, iron deficiency and nosocomial infection in patients with hip fracture] *Med Clin (Barc)* 2008; **131**: 647-652
- 50 **Leal-Noval SR**, Marquez-Vácaro JA, García-Curiel A, Camacho-Laraña P, Rincón-Ferrari MD, Ordoñez-Fernández A, Flores-Cordero JM, Loscertales-Abril J. Nosocomial pneumonia in patients undergoing heart surgery. *Crit Care Med* 2000; **28**: 935-940
- 51 **Leal-Noval SR**, Rincón-Ferrari MD, García-Curiel A, Herruzo-Avilés A, Camacho-Laraña P, Garnacho-Montero J, Amaya-Villar R. Transfusion of blood components and postoperative infection in patients undergoing cardiac surgery. *Chest* 2001; **119**: 1461-1468
- 52 **Leal-Noval SR**, Jara-López I, García-Garmendia JL, Marín-Niebla A, Herruzo-Avilés A, Camacho-Laraña P, Loscertales J. Influence of erythrocyte concentrate storage time on postsurgical morbidity in cardiac surgery patients. *Anesthesiology* 2003; **98**: 815-822
- 53 **Leal SR**, Jara I, Román MJ. [Transfusion of packed red cells and postsurgical infection in critical patients] *Med Clin (Barc)* 2000; **115**: 625-629
- 54 **García Erce JA**, Muñoz Gómez M. [Leucodepletion and autologous blood transfusion] *Med Clin (Barc)* 2002; **119**: 138-139
- 55 **Leal R**, Alberca I, Asuero MS, Bóveda JL, Carpio N, Contreras E, Fernández-Mondéjar E, Forteza A, García-Erce JA, García de Lorenzo A, Gomar C, Gómez A, Llaur JV, López-Fernández MF, Moral V, Muñoz M, Páramo JA, Torradabellà P, Quintana M, Sánchez C. [The <<Seville>> Consensus Document on Alternatives to Allogenic Blood Transfusion.] *Med Clin (Barc)* 2006; **127**: 3-20
- 56 **García-Erce JA**, Cuenca J, Leal-Noval SR, Muñoz M. Preoperative autologous blood donation in Spain (1994-2004). *Vox Sang* 2007; **93**: 89-90
- 57 **García-Erce JA**, Solano VM, Sáez M, Muñoz M. Recombinant human erythropoietin facilitates autologous blood donation in children undergoing corrective spinal surgery. *Transfusion* 2005; **45**: 820-821; author reply 821-822
- 58 **Mittermaier C**, Kurz M, Roskopf K, Hoecker P, Moeschl P, Gangl A, Gasche C. Autologous blood donation for surgery in inflammatory bowel disease--a report of six cases. *Z Gastroenterol* 1999; **37**: 1169-1173
- 59 **Annese V**, Latiano A, Rossi L, Lombardi G, Dallapiccola B, Serafini S, Damonte G, Andriulli A, Magnani M. Erythrocytes-mediated delivery of dexamethasone in steroid-dependent IBD patients-a pilot uncontrolled study. *Am J Gastroenterol* 2005; **100**: 1370-1375
- 60 **Castro M**, Rossi L, Papadatou B, Bracci F, Knafelz D, Ambrosini MI, Calce A, Serafini S, Isacchi G, D'Orio F, Mambrini G, Magnani M. Long-term treatment with autologous red blood cells loaded with dexamethasone 21-phosphate in pediatric patients affected by steroid-dependent Crohn disease. *J Pediatr Gastroenterol Nutr* 2007; **44**: 423-426