

## Etiology and Pathogenesis of Burn Anemia. The Role of the Blood Transfusion in the Treatment of Patients with Burns

**T.G. Spiridonova\*, E.A. Zhirkova**

Department of Acute Thermal Trauma  
N.V. Sklifosovsky Research Institute for Emergency Medicine of the Moscow Healthcare Department  
Bolshaya Sukharevskaya Square, 3, Moscow 129090, Russian Federation

\* **Contacts:** Tamara G. Spiridonova, Scientific Consultant of the Department of Acute Thermal Trauma, N.V. Sklifosovsky Research Institute for Emergency Medicine. Email: SpiridonovaTG@sklif.mos.ru

**ABSTRACT** The presented data of domestic and foreign literature reveal the etiology and pathogenesis of burn anemia caused by the development of systemic inflammatory response (SIR) and blood loss. Manifestations of SIR are characterized by a decrease in the areas of erythropoiesis, inadequate reaction to endogenous and exogenous erythropoietin, a decrease in serum iron, the death of erythrocytes as a result of endogenous intoxication, the development of DIC syndrome, thermal and non-immune hemolysis of erythrocytes, and severe metabolic disturbances. Developing burn anemia progresses as a result of hemorrhage with multiple dressings and operations, as well as bleeding in patients with erosive and ulcerative lesions of the gastrointestinal tract. Domestic and foreign experience with blood transfusions in the past century indicates the need for blood transfusions during the development of moderate severity of anemia (hemoglobin less than 90 g/l), burn patients, which will increase the effectiveness of treatment, reduce the time of hospital stay and expenses.

**Keywords:** systemic inflammatory response, critical condition, blood loss, burn anemia, blood transfusion

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### Affiliations

Spiridonova Tamara Geogiyevna, Scientific Consultant of the Department of Acute Thermal Trauma, N.V. Sklifosovsky Research Institute for Emergency Medicine of the Moscow Health Department, ORCID: 000-0001-7070-8512.

Zhirkova Elena Aleksandrovna, Researcher of the Department of Acute Thermal Trauma, N.V. Sklifosovsky Research Institute for Emergency Medicine of the Moscow Health Department, ORCID: 0000-0002-9862-0229.

CPV — circulating plasma volume

DIC — disseminated intravascular coagulation

EUL — erosive and ulcerative lesions

MOF — multiple organ failure

SIR — systemic inflammatory response

## BACKGROUND

Since the middle of the last century, the etiology and pathogenesis of anemia in burn patients has been the subject of a considerable number of works in the Russian and English literature [1–6].

Burn anemia is a typical clinical manifestation of a burn disease after the shock is managed, until the skin is completely restored. Moreover, burn anemia accompanies not only the acute period of burn disease, but can persist for a long time even after discharge from the hospital, both in adults and children [7–9].

Considering the various causes of anemia for burns, the authors propose to divide them into 2 groups: due to the critical state of the body and due to blood loss, which may help develop targeted methods of prevention and treatment. At the same time, the authors indicate that burn anemia during the period of critical condition determines indications for 52% of all blood transfusions in patients with a total lesion area of more than 20% of the body surface [10, 11].

## BURN ANEMIA ASSOCIATED WITH CRITICAL CONDITION

Anemia of a critical condition has a complex multifactorial genesis [10, 12]. The systemic inflammatory response syndrom (SIRS) is the basis of the critical condition for burn disease [13, 14], which was first described in the early 90s of the last century in severe surgical patients [15, 16]. Historically, the syndrome of SIR was clinically isolated much later (1991) than the syndrome of multiple organ failure was described. In 1975, A. Baue published his observations that patients in intensive care units die of a new syndrome of progressive failure of several organs [17]. By a strange coincidence, numerous studies and the development of various grade scales for assessing the critical condition of patients excluded the burn ones from the analysis. At the same time, the authors pointed out that the MOF in burn patients excluded from the analysis manifested the same way as in other surgical patients [18, 19]. Today, many authors argue that burn disease should be considered a model of SIRS [20–22]. There is an opinion that SIRS develops in 30% of burn patients with an area 30% of the body surface or more [23], however, our observations have shown that SIRS can develop even with the area of burn injury up to 10% of the body surface [24].

The initial part of SIRS in burn patients is acute hypovolemic burn shock. Its feature is a dramatic generalized increase in the permeability of the microvascular system with loss of plasma proteins, resulting in

hemoconcentration and hiding the signs of anemia [24, 25]. However, it has been proven that thermal injury causes significant changes in red blood system, leading to a decrease in the number of circulating erythrocytes and the development of anemia. Back in the middle of the last century, the empirical use of erythrocytes labeled with radioactive phosphorus and chromium, shown that in the stage of burn shock with a lesion area of 20% of the body surface, the volume of circulating erythrocytes decreases by 11–40% [26–28]. The destruction of red blood cells in the first hours after a burn reaches 30–46% and is manifested by abrupt hemolysis, microcytosis, anisocytosis, poikilocytosis, hemoglobinuria, the appearance of erythrocyte shadows, their sequestration and deposition in burned tissues as a result of capillary stasis [4, 29, 30]. An early and dramatic decrease in the number of erythrocytes in the blood during burn shock is usually not detected due to a concomitant decrease in circulating plasma volume (CPV). Hemoconcentration, as was shown in the experiment, arises from the first minutes after the burn has been received [31]. Only the shock is managed and the CPV restores on day 3–4, the true number of red blood cells in the blood is detected.

The authors call anemia of early terms of a burn disease *non-immune hemolytic anemia* describing the morphological anomalies of red blood cells (spherocytes, schistocytes) [30]. The same indicates the content of a large amount of hemoglobin in the blood plasma, which was discovered in the middle of the last century [25, 32]. A study of the total amount of heme pigments in the plasma of patients showed that on the 1<sup>st</sup> day after extensive burns their number was 737.4 mg%, 130.8 mg% on day 2, and 32.7 mg% on day 3–5. At a later date, the concentration of heme pigments in the blood plasma did not exceed normal values [33]. Intravascular hemolysis of erythrocytes is one of the mechanisms of multiorgan disorders in critical conditions, including burn injury [34].

Against the background of SIRS, burn patients have a more significant and longer immune inflammatory reaction than patients with trauma. This is manifested by higher levels of interleukins (IL) IL-6 and IL-8 in the blood plasma in the first week and reflects the severity of burn damage [35]. The most important pathogenetically caused manifestation of SIRS in burn patients are changes in the hematopoietic system: expansion or reduction of zones of granulopoiesis and reduction in the rate of erythropoiesis, as was shown in the autopsy material and in the experiment [36–39]. The depression of erythropoiesis as one of the causes of anemia developing in burns has been noted since the middle of the last century [5, 40, 41]. Later it was found that elevated levels of pro-inflammatory cytokines, such as tumor necrosis factor, interferon and interferon- $\gamma$ , IL-6, inhibit the formation of erythroid cells in the red marrow [42–45]. The reduction in the formation of erythroid colonies persists until the 40<sup>th</sup> day after the burn injury, sustaining anemia for a long time [36].

The human body responds to a decrease in erythropoiesis by increasing the blood level of endogenous erythropoietin. Erythropoietin is secreted by peritubular kidney cells in response to low oxygen levels in the hemoglobin of red blood cells [46] and binds to the receptor on the progenitor cells of erythroid cells, stimulating their proliferation and differentiation [47]. Recent studies have shown that the titers of endogenous erythropoietin of the blood serum in patients with extensive burns increased from day 1 (2 times), reaching a maximum on day 14 (14.7 times) and remained above the reference value by day 60 (1.44 times). At the same time, the values of peripheral erythrone indicators (hemoglobin, erythrocytes, daily erythrocyte production, erythrocyte life expectancy) were low after the patient's shock, indicating anemia, which persisted for a long time [4, 48]. Against the background of high titers of erythropoietin, microcytes and macrocytes prevailed in the blood, and the proportion of medium-active erythrocytes decreased twice or more, not reaching normal values by day 60 [48]. Thus, elevated concentrations of endogenous erythropoietin do not contribute to the correction of anemia in burn patients.

The administration of high doses of exogenous erythropoietin to burn patients also does not lead to an increase in the number of erythroid colonies [2], as in patients with chronic kidney disease, which allows to reduce the volume of blood transfusion in them [49, 50]. A study of the effect of exogenous erythropoietin in high doses in red blood samples of burn patients (hemoglobin, hematocrit, red blood cell count) showed that exogenous erythropoietin only increased the number of reticulocytes, not affecting hemoglobin and hematocrit and not reducing the need for blood transfusion [51, 52]. The same pattern is typical for patients in critical conditions with another disease [53, 54].

An essential element for normal erythropoiesis is serum iron. It is believed that the lack of response to high titers of erythropoietin is caused by a deficiency of serum iron, which was detected in severely burn patients within 60 days from the moment of injury, while the level of ferritin was significantly increased in the same period. The accumulation of iron in ferritin and the fall in the level of serum iron are associated with a protective reaction of the body, isolating iron from bacteria, since it is an important product of their vital activity [48].

Another mechanism of the pathogenesis of anemia in a burn disease is a wave-like DIC that causes a large number of red blood cells to die [55, 56]. DIC syndrome is initiated at first by burn shock, and then by extensive necrectomy, autodermoplasty, sepsis, when a significant number of red blood cells are lost as a result of generalized formation of microthrombus.

The acute period of a burn disease, caused by SIRS, is accompanied by accumulation of various types of pathological substances which impair homeostasis, form and support endogenous intoxication. Among the numerous substances with toxic effects, great importance is given to medium molecular peptides [57, 58], lipid peroxidation products [48, 59], anti-erythrocytic autoantibodies [60], medium and small circulating immune complexes [61]. All toxic products affect the erythron system both directly and indirectly.

Another important mechanism for the development of anemia in burn patients is metabolic disturbances in SIRS, characterized by a dramatic increase in basal metabolism and the development of protein-energy deficiency, which the organism compensates by the breakdown of its own proteins, carbohydrates and lipids [62]. First of all, plasma proteins and skeletal muscle proteins are consumed, and then organ proteins. The heavier the burn injury is, the higher is the breakdown of proteins. The highest catabolism is observed during the first weeks after a burn injury, with albumin being consumed predominantly, which quickly forms hypoalbuminemia and dysproteinemia. Protein-energy deficiency increases with hyperthermia, which is one of the permanent signs of SIRS and has been accompanied by an acute period of burn disease for a long time [63]. It has been shown that a decrease in the level of nutrition in patients with burns leads to the pathological morphology of erythrocytes and a decrease in their number [3].

Thus, burn anemia of a critical condition is a syndrome caused by the pathogenetic mechanisms of SIR. It requires repeated blood transfusions [64] and can manifest itself even in patients with extensive superficial burns who do not need surgical treatment.

#### **BLOOD LOSS IN THE PATHOGENESIS OF BURN ANEMIA**

In patients with deep burns, anemia of a critical condition is inevitably supplemented by anemia associated with acute blood loss during the process of dressings and surgical treatment of burn wounds. Prior to the use of early surgical necrectomy, purulent melting of necrotic tissue led to severe burn disease, frequent development of purulent-septic complications, multiorgan disorders, as well as burn cachexia, which was distinguished in old classifications as a regular stage of burn disease [65, 66].

The current active surgical tactics of treatment of burn patients implies the earliest possible removal of necrotic tissues by means of necrectomy operation and restoration of the skin by autodermoplasty, which makes it possible to achieve significant success in treating burn patients, including elderly and senile patients [67, 68].

The necrectomy is always accompanied by blood loss, which aggravates burn anemia. Subfascial removal of necrosis with the underlying tissues is characterized by the least blood loss, but this operation is crippling from the esthetic point of view. Tangential and radical excision of necrotic tissue is accompanied by significant blood loss, which limits the area of necrectomy. In the necrectomy with simultaneous autodermoplasty, the total blood loss (necrotomy and skin flap collection) can be up to 1 ml per 1 cm<sup>2</sup>. It is obvious that surgical intervention contributes to the progression of burn anemia and requires blood transfusion, at least in the immediate postoperative period [66, 69, 70].

Thorough hemostasis is very important in the process of necrectomy. During operations on the limbs, the use of a tourniquet significantly reduces blood loss (from 1.26 to 0.72 ml per 1 cm<sup>2</sup>) [71, 72]. Operational blood loss can be reduced by topical administration of thrombin, warm saline, and infiltration of vasoconstrictor drugs, which reduce the volume of perioperative blood transfusion [73, 74].

Speaking of acute blood loss in patients with burns, we should say about acute erosive and ulcerative lesions (EULs) of the gastrointestinal tract with erosive and ulcerative bleeding. The first publications about acute ulceration of the gastrointestinal mucosa appeared in the middle of the XIX century [75, 76]. Acute erosive and ulcerative bleeding plays an important role in the genesis of burn anemia, and massive bleeding may be fatal [77–79].

We performed preventive dynamic esophagogastroduodenoscopy and revealed that EULs due to destructive changes in the gastrointestinal mucosa in burn patients with SIR wykly found in 96.8% of patients, and in 3.2% there were isolated acute ulcers. EULs developed, starting from the shock stage, throughout the acute period of a burn disease and even its relapses, and was characterized by different shape, size, quantity and location. In 64.5% of patients with EULs, there were signs of bleeding. In the overwhelming majority of cases, erosive and even ulcerative bleeding was capillary and, at the time of inspection, it was recent. The development of bleeding coincided with a high score of SIRS (3–4 points in 82.5% of cases) [80]. One of the causes of acute gastroduodenal bleeding in burn patients was severe endogenous intoxication [81]. Massive spurting ulcerative bleeding (Forrest IA) [82] required emergency hemostasis, hemotransfusion, and often triggered the development of MOF and death. First of all, plasma proteins are consumed. Thus, burn anemia has a complex multifactorial pathogenesis, due to the critical condition of burn patients and acute blood loss accompanying surgical treatment of deep burns or due to EULs.

#### **RETROSPECTIVE, MODERN AND PROSPECTIVE TACTICS OF TREATMENT FOR BURN ANEMIA**

Combustionologists of the middle of the last century used whole blood (less often its components) in the treatment of severely burn people [66, 83, 84]. Domestic authors recommended blood transfusions if the victim had a hemoglobin level below 110–120 g/l, and the number of erythrocytes is less than 3,500,000–4,000,000 per ml<sup>3</sup>. Victims with deep burns on the area from 10 to 20% of the body surface received up to 8–10 litres of blood, and when the area of a deep burn is more than 20% of the body surface — up to 14–16 litres for the entire period of treatment [6].

The authors noted the effectiveness blood transfusions daily or every 2–3 days of 250.0–500.0 ml, paying attention to the fact that with rare transfusions of erythrocytes, irreversible changes in the body occur even with limited burn lesions. Only transfusion of whole blood to severe burn patients allowed to manage severe anemia,

hypo- and dysproteinemia, intoxication, purulent-septic complications successfully and achieve accelerated cleansing of wounds from non-viable tissues [85, 86]. Direct blood transfusions used at that time were more effective than blood transfusions [87]. On a large clinical material, combustiologists of the last century were convinced that without performing blood transfusions, it is impossible to prevent anemia in severely burn people by any other therapeutic means [88, 89].

In Russia, until the 90s of the twentieth century, transfusion therapy using fresh citrate blood, plasma, albumin was widely used, which made it possible to maintain hemodynamic parameters, hemoglobin level, red blood cell count, protein composition of blood at the level of reference values, thereby contributing to the successful course of the wound process. Blood transfusions in complex treatment ensured timely cleansing of wounds from necrosis with minimal blood loss, development of granulation tissue and performance of the first stage of autodermoplasty on average by the end of the 3<sup>rd</sup> week after the injury, which prevented the development of septic complications [6, 85, 90]. The concept of active surgical tactics in the domestic literature implied the quickest possible closure of a burn wound, with the direct dependence of the patient's condition and the readiness of the granulating wound for the plastic surgery on the hemoglobin level and blood proteins [70, 91]. However, in the 21<sup>st</sup> century there are foreign authors claiming that anemia does not affect wound healing [92].

Until the end of the 20<sup>th</sup> century-the beginning of the 21<sup>st</sup> century, blood transfusions in burn patients were widely used throughout the world, and the greater the burn area was, the greater was the volume of blood transfusion the patient received. Today, there are no standards for the volume of transfused red blood cells, however, the results given by different authors show a direct correlation between the area of the burn lesion and the volume of red blood cells transfused. So, when the burn area is more than 10% of the body surface on average, 8.94–19.7 units of blood were transfused (from 0 to 201 units) [93, 94]. In patients with a lesion area equal to or more than 20% of the body surface, 13.7±1.1 units were transfused, 17 units if the lesion area was 30% of the body surface, more than 30 units of erythrocytes if the lesion area was more than 50% of the body surface, and 117 units for lesions over 90% of the body surface [94, 95].

This dependence was confirmed in a retrospective study of 1999–2004, and it was shown that even for patients with a burn with a total area of up to 10% of the body surface, the transfusion of 4±0.6 units was required. As the burn area increased, the number of patients whose condition required blood transfusion also increased (with a burn of less than 10% of the body surface – 5.7% of patients; 11-20% – 21% of patients; 21-30% – 39% of patients; more than 30% – 62% of patients) [96]. In addition to the total lesion area, the volume of blood transfusions was greater in patients with heart disease and acute respiratory distress syndrome, as well as in elderly patients [97].

Studying the level of alloimmunization to erythrocyte antigens in patients with multiple blood transfusions in various diseases revealed the lowest probability of its development (1.8%) in patients with burn disease, lymphoproliferative syndromes and acute myeloid leukemia [98].

In the end of the 20<sup>th</sup> century and the beginning of the 21<sup>st</sup> century, many studies appeared indicating direct transmission of infectious diseases through blood transfusion, such as HIV (1 case per 2,000,000 transfusions), hepatitis B (1 per 250,000) and hepatitis C (1 per 1,500,000 – 2,000,000) [99, 100]. The experiment found that bacterial translocation from the intestine and bacterial survival increase with burn injury in combination with blood transfusion [101]. A correlation between blood transfusion and infectious complications has been established [93, 95, 102].

The most serious fatal complication is incompatible blood transfusion. At the same time, the error rate with incompatibility by ABO can reach 1 case per 1,800,000 units [103].

Apparently, this sad experience of complications and errors has led to the fact that since the 90s of the last century there has been a tendency in the world to minimize blood transfusion therapy in various pathologies, including burn disease. Indications for blood transfusion are set selectively depending on the area of the burn, the presence of inhalation injury and comorbidities, studies are being conducted to determine the trigger indicator for red blood cell transfusion [97, 104, 105].

In 2004, the Council on Blood and Transfusions in New York issued recommendations on the transfusion of erythrocytes for adults (2<sup>nd</sup> edition), which were based on a multicenter study conducted in the United States [106]. Recommendations included indications for red blood cell transfusion in acute hemorrhage (surgery, trauma, bleeding), perioperative blood loss, chronic anemia, and special situations, where a special group of burn trauma was given indications for blood transfusion. For critical burn patients and/or with cardiopulmonary problems, it is recommended to transfuse erythrocytes if the hemoglobin level is 100 g/l and lower.

In Russia, multicenter studies have not been conducted, and blood transfusion therapy is used in accordance with the regulatory documents, where burn patients are not a separate group, taking into account the multi-component genesis of anemia and the need for regular blood transfusions. The Order of the Ministry of Health of the Russian Federation No. 363 dated November 25, 2002 “On Approval of the Instructions on the Use of Blood Components” permits transfusion of oxygen carriers if hemoglobin levels are lower than 80 g/l. The Order of the Ministry of Health of Russia No. 183n dated April 2, 2013 “On Approval of the Rules for the Clinical Use of Donor Blood and (or) Its Components” repeats the previous one, determining the indication for red blood cell transfusion if the hemoglobin level is lower than 70–80 g/l.

In order to study the effect of anemia on the course of burn disease in patients with deep burns of 20% of the

body surface, we performed the comparative analysis at the Department of Acute Thermal Lesions of the N.V. Sklifosovsky Research Institute for Emergency Medicine of two comparable groups of patients who received 480 ml of blood on 1% of a deep burn in 1968–1976 (Group 1), and 112 ml (only after the hemoglobin concentration fell below 80 g/l) in the late 90s - early 2000 (Group 2). It turned out that in patients of the Group 1, granulating wounds were prepared for the first autodermaplasty much earlier, while the hemoglobin level corresponded to the reference values, unlike the Group 2 of patients [107].

It should be noted that at present, when active surgical tactics imply early surgical necrectomy, the development of anemia becomes a contraindication for surgical treatment of burn patients at an early date, which significantly extends the treatment and contributes to the development of complications, including pneumonia and sepsis. Since the pathogenesis of anemia in the burn patients indicates the inevitability of its development, the rejection of blood transfusions can be regarded as an iatrogenic complication [108].

According to the classification of anemia existing in Russia, the degree of severity is divided into 3 groups: mild for hemoglobin level above 90 g/l, moderate for hemoglobin within 90–70 g/l and severe for hemoglobin level less than 70 g/l, while reference hemoglobin values are at least 130 g/l for men and 120 g/l for women [109]. Evaluating existing Russian laws, we are forced to perform the transfusion, when the deficit of the total number of erythrocytes is 1/3 from the lower limit of the norm, while, as was shown above, more than half, 2/3 of erythrocytes, are short-living microcytes. Domestic authors claim that the greatest degree of hemoglobin fall is observed on day 14–21 of a burn disease, while 75% of patients have moderate anemia and only 25% have mild anemia [48].

Treatment of severe burn patients with anemia of moderate severity increases the duration of their stay in the hospital, and, consequently, the cost of treatment. We believe that for adequate treatment of victims with severe burn injury, the trigger hemoglobin level indicator for red blood cell transfusion should be 90 g/l or less, which will contribute to timely surgical treatment and prevention of complications.

## CONCLUSION

The pathogenesis of burn anemia is complex and is caused, above all, by the development of a critical condition in burn patients as a result of a systemic inflammatory response. Blood loss during surgery and gastroduodenal bleeding with erosive and ulcerative lesions of the gastrointestinal tract aggravate burn anemia. With the development of anemia of moderate severity (hemoglobin below 90 g/l), the correction should be carried out by components of donor erythrocytes. This will increase the effectiveness of treatment, reduce the incidence of complications and mortality, as well as reduce the cost of treatment.

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