



## Mini Review

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## Phagocytosis alteration preceding staphylococcal infection

Wilma Carvalho Neves Forte\*, Tainá Mosca

Immunology Discipline, Santa Casa de Sao Paulo School of Medical Sciences, São Paulo, SP, Brazil.

### Article Info

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#### \*Correspondence:

Dr. Wilma Carvalho Neves Forte, Immunology Discipline,  
Santa Casa de Sao Paulo School of Medical Sciences, São  
Paulo, SP, Brazil;

Email: wilmanevesforte@yahoo.com.br

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There is a scarcity of studies in relation to chemotaxis and phagocytosis by neutrophils on *Staphylococcus aureus* infections, despite the increase of these infections in the last two decades, especially associated with prosthetic devices and soft tissue infections determined by methicillin-resistant *S. aureus*<sup>1</sup>.

The two main obstacles to transplants are finding compatible HLA (Human Leukocyte Antigen) matched donors and post-transplant infections. The most frequent Gram-positive infections after intestinal transplantation are infections by *Staphylococcus aureus*<sup>2</sup>. *S. aureus* are still among the main etiological agents of hospital infections.

Catalase-positive microorganisms, such as *S. aureus* and *Aspergillus fumigatus*, are primarily fought by neutrophils<sup>3,4</sup>. Thus, studies on the functionality of neutrophils are an attempt to understand infections mainly against such pathogens.

The article "Laboratorial alteration preceding clinical staphylococcal infection clinical manifestations after intestinal transplantation" evaluates the immune response in vitro of a 2-year-old girl who underwent small bowel transplantation owing to a small bowel volvulus<sup>5</sup>. On the first postoperative day, the authors observed a decrease in the ingestion phase of phagocytosis by neutrophils. On the second postoperative day, the patient began to present low fever and, on the third day abdominal pain accompanied by worsening of her physical condition.

After the clinical manifestation and the laboratory abnormality, an exploratory laparotomy was performed, which revealed purulent ascites, with a positive culture for *S. aureus*. The results of the exams were compared to those of 20 healthy, non-transplanted children of the same age group<sup>6</sup>. The other immunological tests were serum immunoglobulin dosages, quantifications of CD19, CD3, CD4, CD8, chemotactic activities, and ingestion and digestion (NBT) of neutrophil and mononuclear phagocytosis. All exams were normal, except for the neutrophil phagocytosis ingestion stage, which revealed the formation of few phagocytic vacuoles.

The authors describe in detail the methods they used, in particular phagocytosis and chemotaxis, which can be repeated by other professionals. Neutrophils were separated by spontaneous sedimentation because this method presents less spontaneous activation of these cells<sup>7</sup>.

For analysis of the phagocytic ingestion phase, Leighton tubes were used and three tests were performed: neutrophils; neutrophils, zymosan particles and homologous serum; and neutrophils,

zymosan particles and autologous serum. The first assay demonstrated cell viability. The second and third tests allowed the complement system to be activated by the zymosan particles; activated C3b and C5b components act as opsonins, coating the particles (Table 1). The results observed in the second and third tests, with no difference between them, demonstrated that the alteration was not in the complement system, concluding an intrinsic problem of the phagocytic cell<sup>5,6,8</sup>.

**Table 1.** Three tests were performed to analyze the ingestion phase of neutrophil phagocytosis.

Assays:	N + Zy	N + Zy + Homologous serum	N + Zy + Autologous serum
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N: neutrophils; Zy: zymosan

Homologous and autologous serum contains complement, which is activated by zymosan particles.

The components C3b and C5b are opsonins, which coat zymosan particles.

The coated zymosan particles undergo phagocytosis by neutrophils.

All neutrophil activities - transendothelial migration, chemotaxis and phagocytosis with its four steps (adhesion, ingestion, digestion and elimination) - are needed to be perfectly functional for efficient defense against *S. aureus*<sup>4</sup>. Any disturbance of neutrophil functionality predisposes to *S. aureus* infections<sup>8,9</sup>. Thus, patients with primary immunodeficiency due to neutrophilic phagocytosis disorders, such as chronic granulomatous disease, or with neutrophil activity impairment have repeated *S. aureus* infections<sup>8</sup>.

The observed change in neutrophil phagocytosis may be a consequence of surgery. Studies showed that the innate immune system is suppressed from the early period of upper abdominal surgery, with suppression of phagocytic activity by the fourth postoperative day<sup>10</sup>.

During major surgery there is a decrease in the production of tumor necrosis factor (TNF- $\alpha$ ) induced by lipopolysaccharide (LPS), with normalization after the first postoperative day. The decrease in TNF results in lower transendothelial migration, a decrease in the activation of defense cells, and a reduction in neutrophilic activity. On the other hand, surgical stress significantly increases the plasma concentration of IL-10, which inhibits the function of phagocytes<sup>11</sup>. There may also be a decrease in the proliferation and secretory function of Th1, an IFN- $\gamma$  synthesizer, which enhances adaptive and innate immunity, especially by increasing the phagocytosis stage<sup>4</sup>.

Intestinal transplantation also causes a series of changes in the adaptive immune response, derived from the surgery itself, such as a decrease in secretory IgA due

to the reduction of intestinal microvilli and tight junction damage<sup>11</sup>.

Immunosuppressive therapy associated with intestinal transplantation induces a reduction in the cell activity of both the innate and acquired responses (the patient had received tacrolimus, basiliximab and methylprednisolone)<sup>12</sup>. Among the immunosuppressants received by the patient, it is known that methylprednisolone decreases the expression of adhesion molecules by neutrophils, impairing their transendothelial migration. Thus, a reduction in macrophage antigen-1 (Mac-1) expression has been observed in patients receiving intravenous methylprednisolone for 5 days, with normal parameters two days after the end of treatment<sup>13</sup>. The Mac-1 glycoprotein binds to the molecule of the endothelium immunoglobulin superfamily, intracellular cell adhesion molecule-1 (ICAM-1). The  $\beta$ 2-integrin leukocyte function-associated antigen-1 (LFA-1) expressed by the neutrophil also binds to endothelial ICAM-1. Such connections are important for neutrophil adhesion to the endothelium and enabling to migrate to the tissues<sup>13</sup>. In addition, a decrease in the phagocytosis of *Exserohilum rostratum* from isolated blood neutrophils has been described in adults treated with methylprednisolone<sup>14</sup>.

Intestinal transplants often cause changes in the local microbiota, resulting in the presence of pathogenic microorganisms; these changes have been related to the development of sepsis<sup>15</sup>.

Thus, changes caused by the transplant surgery itself or due to the use of immunosuppressants may result in infections caused by many microorganisms, such as *S. aureus*.

The diagnosis of intra-abdominal collections is difficult to make, especially in immunocompromised patients<sup>15</sup>. Immunosuppressants mask clinical manifestations of infection, such as fever by reduction of endogenous pyrogens<sup>16-19</sup>. In addition, fever may occur in the first days after major surgeries as a consequence of inflammatory stimuli specific to surgery, with spontaneous resolution. However, post-operative fever may be a sign of complications, especially infection, which can totally change the patient's prognosis. Thus, the fever presented by the patient described in the case report would not necessarily be indicative of infection but the absence of fever would not exclude an infectious condition due to the effects of immunosuppression.

The laboratory abnormality observed in the disturbance of phagocytic neutrophil activity contributed to the hypothesis of infection by *S. aureus*, aiding in the early investigation of infectious disease and accurate evaluation of the patient.

It is possible that laboratory evaluation of chemotaxis

and phagocytosis by neutrophils is important for intestinal transplant recipients in an attempt to aid in the diagnosis and early treatment of infection by *S. aureus*, seeking a better prognosis for such patients.

The reference article allows a view of changes in the immune response on the propensity of intestinal transplant recipients to develop *S. aureus* infections. Further studies are needed to try to detect patients predisposed to infections by *S. aureus* not only after transplantation but also in cases of hospital infections by *S. aureus*. Studies on immunological alterations that can increase the risk of *S. aureus* infection lead to new research field.

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