

# Sepsis-induced T-cell suppression in pediatric sepsis

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## Abstract

Sepsis contributes to significant mortality and morbidity in children. Despite rigorous resuscitation effort, adequate antibiotics and advanced medical support, a significant proportion still face mortality due to multiple organ failure. Re-

cent hypothesis suggests host's immune response pathology in the form of compensatory anti-inflammatory response syndrome (CARS). This review aims to elucidate the pathophysiology of immune paralysis, both affecting innate and acquired immunity.

**Key words:** Immunoparalysis, sepsis, compensatory anti-inflammatory response syndrome, HLA-DR, TNF- $\alpha$ .

## Introduction

Severe sepsis is the most common cause of death in children worldwide. The Sepsis Prevalence, Outcomes, and Therapies (SPROUT) Study reported that the prevalence of pediatric severe sepsis in the world is 8.2% with mortality 25%. (1)

Nowadays, some children survive the acute first three days of sepsis only to face delayed death as a consequence of late organ dysfunctions. (2) In the Intensive Care Unit (ICU), despite adequate antibiotics and resuscitation effort, some patients die from multiple organ failure beyond three days rather than shock in the first three days. (3) This arises a question whether other factors such as host immune response may influence the patient outcome. Currently, it is known that in addition to excessive in-

flammation, concurrent compensatory anti-inflammatory response syndrome (CARS) also occurs. (4) Transient CARS may benefit the host to prevent perpetual inflammation, however, continued CARS can be harmful to the host. This response is so-called immunoparalysis or immune paralysis associated with organ failure. (2,5)

Children with sepsis-induced immune suppression have impaired infection clearance, prolonged reduction of adaptive and innate immune system function, and lymphoid organ depletion. (6) This pathology can be examined by reduction of monocyte human leukocyte antigen D related (HLA-DR) expression to <30% or <200 pg/ml ex vivo lipopolysaccharides (LPS)-induced tumor necrosis factor alpha (TNF- $\alpha$ ) production beyond three days in children with multiple organ dysfunction. (7,8)

Genetic and environmental factors contribute to the occurrence of immune paralysis associated with multiple organ failure syndromes and impede the inflammation resolution. (2) This requires specific targeted pathobiology treatment and causative treatment to restore the host immune system. This review aims to explain immune paralysis, especially sepsis-induced T-cell suppression in pediatric sepsis.

## Sepsis

In the last decades, sepsis was defined as a systemic inflammatory response syndrome (SIRS). (9) However, the definition is controversial due to its broad

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inclusion criteria that often includes milder state. Therefore, in 2016 the European Society of Intensive Care Medicine (ESICM) and the Society of Critical Care Medicine (SCCM) made a consensus on sepsis and septic shock definition (Sepsis-3). Sepsis was then defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection, while septic shock is a part of sepsis which includes circulatory and metabolic/cellular abnormalities that are sufficient enough to increase mortality significantly. (10)

The Sepsis-3 definition emphasizes on life-threatening organ dysfunction. This definition is consistent with the cellular defect that underlies the physiological and biochemical abnormalities in the organ-specific tissue. The involvement of organ dysfunction has a more complex pathobiological process compared with SIRS and infection only. Sequential Organ Failure Assessment (SOFA) score  $\geq 2$  can be used to assess organ dysfunction. Currently, SOFA score of the Sepsis-3 definition has been validated and adapted for pediatric patients. (10)

### **Sepsis pathophysiology**

General consensus defined sepsis in pediatric as systemic inflammatory response syndrome which occurs during infection. (9) Several researchers were conducted using agents that suppress inflammation in septic patients. However, the results failed to demonstrate positive effect. These failures raise a question whether death in septic patients is a result of overwhelming inflammation conditions or something else. (11)

Furthermore, many septic patients died despite adequate antibiotics therapy and microbial clearance. (12) Hence, these facts suggest that besides pathogen virulence, host response also plays an important role in sepsis pathophysiology.

The current concept on sepsis pathophysiology addresses intricate interplay of host pro-inflammatory and anti-inflammatory processes. (13) Bone et al. suggests that the early inflammatory response can give way to following CARS. (14) Nevertheless, in a septic patient, a complex mechanism with variable host response occurs, in which both pro-inflammatory and anti-inflammatory responses contribute to secondary infection and organ failure. These, on the other hand, also help to eradicate the infection and enhance tissue restoration. (13) The host response is different for each individual depending on the host factors (genetic, age, race, sex, nutritional status, comorbidities, and treatments) and the pathogen factors (virulence and load) and it probably changes over the clinical course. (12)

Interaction between pattern recognition receptors

(PRRs) such as toll-like receptors (TLRs), C-type lectin receptor (CLRs), retinoic acid-inducible gene 1-like receptor (RLRs), and nucleotide-binding oligomerization domain-like receptors (NLRs) in host cells with pathogen-associated molecular patterns (PAMPs) from microbial components elicits the inflammation response. (12) As a result, excessive activation of complement, leukocyte, and coagulation occurs and causes necrotic cell death and collateral tissue damage. Subsequently, damage-associated molecular patterns (DAMPs) are released from the dead cell and perpetuate inflammation by acting on the PRRs. (12,13)

While in contrast, anti-inflammatory response acts by several mechanisms to attenuate the disadvantageous effect of the exaggerated pro-inflammatory response. The neural pathway suppresses inflammation by acting through the afferent vagus nerve and hypothalamus-pituitary-adrenal axis. Vagus nerve activates the coeliac ganglion, which results in norepinephrine release in spleen and acetylcholine secretion by immune cells, thus inhibiting the release of pro-inflammatory mediators. (12) Hypothalamus-pituitary-adrenal axis acts on the adrenal gland resulting in the release of catecholamine mediators, which inhibits the release of pro-inflammatory mediators. (12)

Death in the first three days in sepsis is usually caused by an excessive proinflammatory response such as refractory shock, hypermetabolism, and acidosis. (13) The initial acute inflammatory response varies individually depending on genetic factors, pathogen load and virulence, as well as host comorbidities. (13) Therapeutic failure in those patients is likely due to inadequate resuscitation and antibiotic treatment, or delayed treatment. (15)

Patients who survive three days after adequate pathogen clearance and supportive therapy yet remain critically ill may have immunosuppressive state indicated by impaired immune cells function and inhibition of pro-inflammatory genes transcription. Evidence of immunosuppression state is marked by reduced TNF- $\alpha$  release and HLA-DR expression on immune cells. (16) Despite adequate sepsis therapy, primary infection control cannot eliminate the pathogen. Moreover, in this phase patients may acquire secondary hospital-acquired infections, typically by opportunistic and drug-resistant pathogens. (17)

### **Immune paralysis**

Immune paralysis or immunoparalysis is a condition in which the host has an impaired ability to eliminate the infection. This condition can be caused by several factors. Several internal and external factors may cause immune paralysis

**(Figure 1).** Internal host factors include genetics, nutritional status, and disease (primary immunodeficiency, leukemia, traumatic injury, sepsis, and *Staphylococcus aureus* infection), while external factors include treatment-related or iatrogenic immune paralysis.

Genetic factors significantly affect cytokines production thus predispose immune paralysis. Family studies in monozygotic twins reported that heritability of interleukin (IL) 10 and TNF- $\alpha$  production were 0.75 and 0.60, respectively. (18) A study in pediatric patients undergoing cardiopulmonary bypass also suggested that IL-10 gene regulation may be affected by epigenetic alteration. (19)

Immune paralysis also tends to occur in some diseases or pathogens. Primary immunodeficiency patients are more likely to have immune paralysis due to immune system dysfunction. (20) Leukemic patients also have abnormal leukocytes count and its subset, thus tend to have immune paralysis. (21) Severe trauma is also associated with immunosuppressive conditions in critically injured children. (22) Pathogens such as *Staphylococcus aureus* can cause early innate immune suppression. (23) Chronic inflammation can also cause suppression of natural killer (NK) cells and T cells by activation of several signaling pathways. (24) Apoptosis of lymphocytes increases the release of anti-inflammatory cytokines and decreases pro-inflammatory cytokines by predominantly stimulating the CD4 T cells into T-helper 2 cells thus allowing negative feedback to the cellular immunity.

Malnourished patients also tend to have specific immune paralysis depending on their nutritional deficiency. (25) Protein calorie malnutrition (PCM) causes dysfunction of cellular immune response particularly T cells, atrophy of the lymphoid and thymus organs, alteration of immunoglobulin (Ig) A and complements serum levels, diminution of host mucosal immune regulatory response, impairment of cytokine response, and a decrease in Leptin and insulin-like growth factor (IGF) 1. (25)

Deficiency in protein and calorie can cause various disorders of the immune system because it is usually accompanied by other deficiencies in vitamins and minerals such as iron, copper, zinc, selenium, magnesium, and antioxidant vitamins. (25) Iron deficiency causes impairment in phagocytic activity, oxidative burst of neutrophils, lower IgG levels, and IL-6 levels. (26) Copper deficiency causes neutropenia, lymphopenia, and reduced IL-2 levels, while zinc deficiency can cause lymphopenia, altered T-cell subsets, and thymus gland atrophy. (25) Selenium is an essential part of host antioxidant, which influences leukocytes and NK cells activities. Low

selenium level correlates with progression of viral infection. (27) Vitamin A deficiency causes disruption of mucosal barrier function, reduces the activity of macrophages, neutrophils, and NK cells, and also impairs T-cells responses. (28)

Combination of malnutrition and infection further diminishes the host immune system, thus alters the immune cell population and inflammatory mediators. Immune paralysis increases the vulnerability to infection, reactivation of viral infection, as well as the development of opportunistic and nosocomial infections. (25)

External factors also play a role in the development of immune paralysis. Some of the known treatment-related factors such as chemotherapy, immunosuppressant, and overuse of corticosteroids may induce immune paralysis. Some chemotherapeutic agents can cause immune system suppression by killing the host immune cells. (29) Immunosuppressive agents such as tacrolimus and cyclosporine inhibit calcineurin, resulting in reduced IL-2, IL-3, IL-4, TNF- $\alpha$ , interferon (IFN)  $\gamma$ , and granulocyte-macrophage colony-stimulating factor (GM-CSF) transcriptional activation. Inhibition of those transcriptional processes ultimately reduces T lymphocytes proliferation. (30) Corticosteroid impairs proinflammatory signaling by inhibiting IL-1 transcription, enhancing IL-10 transcription, and diminishing the stability of IL-1, IL-2, IL-6, IL-8, TNF- $\alpha$ , and GM-CSF messenger ribonucleic acid (RNA) in post-translational phase. Steroids also promote lymphocyte apoptosis and cause lymphopenia. (31)

Other treatment-related factors may cause immune paralysis but are less prominent and established. Sedatives, analgesics, vasoactive drugs, certain antibiotic types, insulin, and furosemide can affect leukocyte function with overall immunosuppressive effect. The drug mechanism remains hypothetical and poorly understood. (7) Transfusion-related factors can also cause immune paralysis through inhibition of host proinflammatory cytokine production capacity. (7)

### **Diagnosis**

Immune paralysis can affect both innate (phagocytes and complements system) and adaptive (B cells and T cells) immune systems. Some immune paralysis may occur in combination and associated with primary immunodeficiency, thus detailed clinical and laboratory examination should be conducted. There are two examples of examinations for innate immune paralysis measurement, namely the detection of monocyte HLA-DR expression and *ex vivo* LPS-induced TNF- $\alpha$  production. Using those examinations, immune paralysis is defined by the

reduction of HLA-DR expression to <30%, or <200 pg/ml ex vivo LPS-induced TNF- $\alpha$  production beyond three days in children with multiple organ dysfunction. (7,8)

HLA-DR expression on monocytes can be measured by flow cytometry. Normally, monocytes express high amount of HLA-DR, however in the setting of immune paralysis, HLA-DR molecule is internalized. (32) Other method involves quantification of ex vivo LPS-induced TNF- $\alpha$  production. This examination does not reflect the amount of TNF- $\alpha$  in the plasma, but the host ability to produce TNF- $\alpha$  when stimulated by LPS. (5,7)

The adaptive immune paralysis diagnostic test can be measured by the presence of lymphopenia with absolute lymphocyte count <1000 cells/mm<sup>3</sup> or reduction of ex vivo phytohemagglutinin (PHA)-induced IFN- $\gamma$  by lymphocyte, similar to TNF- $\alpha$  measurement in the innate immune response. (33) Other specific tests adaptive immune test may evaluate cell ligands or receptors, immunoglobulins, immunophenotyping, advanced flow cytometry, functional testing, and genetic analysis. For example, programmed death (PD)-1 on lymphocytes and its ligands on antigen presenting cell (APC) expression is upregulated in critical patients with immune paralysis. (16)

**Figure 2A** shows normal immune response to pathogen contributes to effective pathogen elimination and negative feedback to cellular immunity, hence inflammation is resolved, while **Figure 2B** shows that in immunoparalysis, there is a decreased in total leukocytes count, decreased HLA-DR expression by APCs, decreased pro-inflammatory cytokines IFN- $\gamma$  and upregulated IL-10 (hence favour CD4 Th2 against CD4 Th1 differentiation), also decreased TNF- $\alpha$  secretion by macrophage. Decreased Th1 differentiation leads to ineffective pathogen elimination. Despite pathogen persistence, regulatory response is activated (dominant Th2 pathway).

### Treatment

Treatment of immune paralysis, especially sepsis-induced T-cell suppression includes GM-CSF, IFN- $\gamma$ , and immunosuppressant tapering. (2) Recombinant human GM-CSF has been used to treat patients with immune paralysis. GM-CSF administration reverses the immune paralysis by augmenting myeloid-derived cell functions, inducing proliferation and differentiation of myeloid-derived cells. (2) GM-CSF should only be given in children with reduced HLA-DR expression or TNF- $\alpha$  production capacity. Children who received GM-CSF were associated with significant reduction of nosocomial infection and restoration of HLA-DR expression or

TNF- $\alpha$  production capacity. (8)

Immunosuppressant tapering can be given in cases of immunosuppressant-related immune paralysis. (34) The administration of IFN- $\gamma$  can also reverse the immune paralysis in vivo. IFN- $\gamma$  increases HLA-DR expression, augments TNF- $\alpha$  production capacity, and attenuates IL-10 levels. (35) Nakos et al. reported that inhaled IFN- $\gamma$  restored alveolar macrophage HLA-DR expression, influencing the inflammatory reaction, decreasing the incidence of ventilator-associated pneumonia. (35)

Immune paralysis therapy in the adaptive immune system is still under development stage. Experimental studies in animals have shown that anti programmed death ligand-1 (PD-L1) and recombinant human IL-7 can increase survival. (36)

### Immune paralysis in pediatric sepsis

Sepsis is one of several factors which induces immune paralysis, but unfortunately, septic patients are more prone to die in the state of sepsis-induced immune paralysis. (37) Hall et al. found that children with multiple organ dysfunction syndromes who had HLA-DR expression <30% for more than 3 days had increased likelihood for mortality and nosocomial infection development. (8) Another study from Hall et al. in children with multiple organ dysfunction syndromes, which mostly triggered by septic shock, reported that non-survivors demonstrated lower ex vivo LPS-induced TNF- $\alpha$  production compared to survivors. (38)

Adaptive immune system suppression also happens in septic patients. Muszynski et al. reported that in children with septic shock, lower lymphocyte counts and decreased the capability of lymphocyte to produce IFN- $\gamma$  after ex vivo stimulation with PHA associated with infectious complication. (33) A novel study from septic adult showed that T regulatory cells are resistant from apoptosis in sepsis, resulting in T regulatory cell predominant state that may perpetuate immune paralysis, but this has not yet been seen in pediatric sepsis. (39)

As mentioned above, the compensatory anti-inflammation response in septic children leads to increase vulnerability to infection, notably the development of opportunistic and nosocomial infection. However, the exact pathophysiology and etiology of immune paralysis in sepsis still poorly understood.

Recently, Cheng et al. investigated the metabolic activities alteration in the white blood cells in patient with sepsis. (40) The incapability of white blood cells to respond to bacterial or fungal infection appeared to be caused by reduction in the cells' total metabolic activity, both glycolysis and oxidative metabolism. The patients were then treated with

recombinant IFN- $\gamma$  resulting in restoration of white blood cell metabolic activity. This phenomenon suggests that cellular metabolic activity plays a role in immune paralysis pathophysiology and might be a potential therapeutic target in sepsis. (40) Immune paralysis in septic patients has been linked to increased risk of infection, infection complications, longer length of stay, and lower survival rate. (8,33)

### **Diagnosing and treating immune paralysis in pediatric sepsis**

In clinical setting, early identification of pediatric sepsis is mandatory. Upon diagnosis of sepsis, pediatric septic patients should get adequate pathogen elimination, resuscitation, and other supportive therapies according to the sepsis guidelines and patient diagnosis. Should the patient's clinical profile show no improvement, become worsened, or develop more organ dysfunction after three days with adequate treatment, we should suspect the development of immune paralysis. Immune paralysis examination should be examined immediately in order to give the therapy earlier. Innate immune system paralysis can be examined by quantification of monocyte HLA-DR expression or *ex vivo* LPS-induced TNF- $\alpha$  production, while adaptive immune system paralysis can be examined by lymphocyte count and *ex vivo* PHA-induced IFN- $\gamma$  production. (7,33) Also, we should assess other factors that can contribute to immune paralysis in the patient such as immunosuppressant, chemotherapy, and so on as mentioned above. If immune paralysis is proven and there is an ongoing or impending infection, GM-CSF or IFN- $\gamma$  can be administered to restore the patient immune system functions. (7)

### **Conclusion**

The immune system response in pediatric sepsis

with multiple organ failure is highly dynamic, SIRS and CARS often coexist. Early identification and management of pediatric septic patients according to sepsis guidelines can increase survival. We should suspect the development of immune paralysis if after three days with adequate clinical therapy, the patient does not improve or worsen. We can identify the presence of innate immune system paralysis by detecting a reduction of monocyte HLA-DR expression or *ex vivo* LPS-induced TNF- $\alpha$  production, while adaptive immune system paralysis can be detected with lymphopenia and reduction of *ex vivo* PHA-induced IFN- $\gamma$  production. GM-CSF or IFN- $\gamma$  can be given if the patient is proven to be immune paralysis. More studies should be conducted with better methodology and a novel therapeutic approach to immune system paralysis to increase the survival of pediatric sepsis with immune system paralysis.

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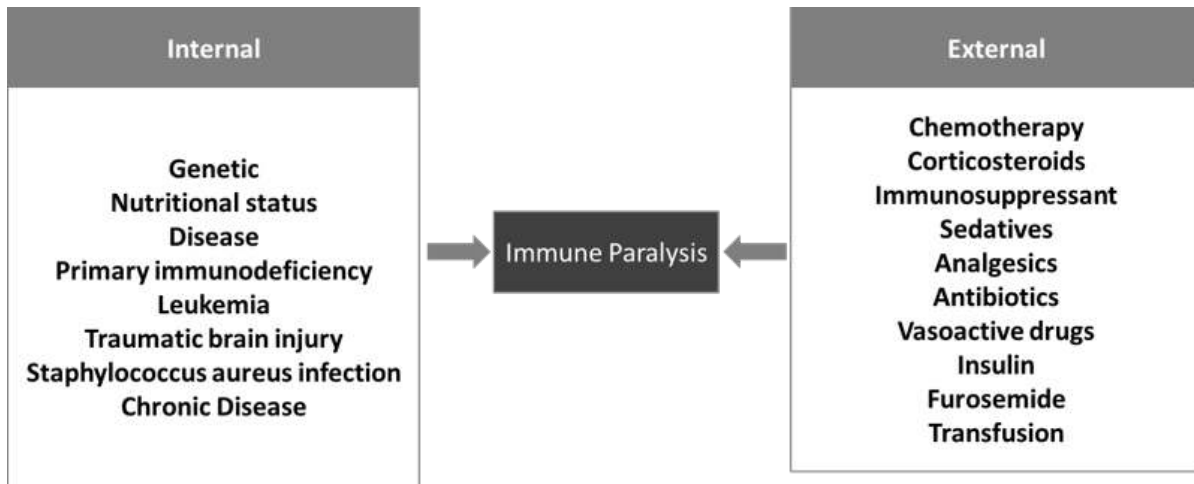
### **Competing interests**

The author has no conflicts of interest to declare.

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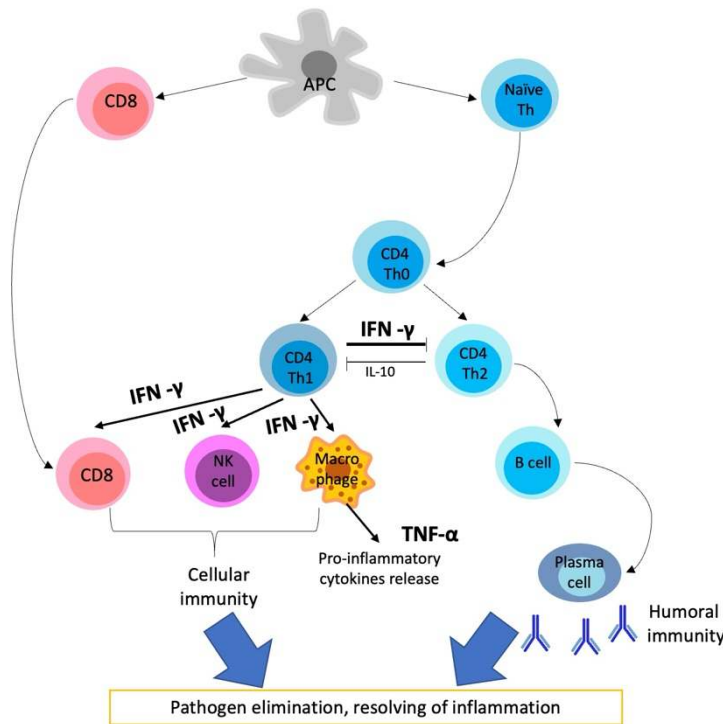
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**Figure 1.** Internal and external factors associated with immune paralysis



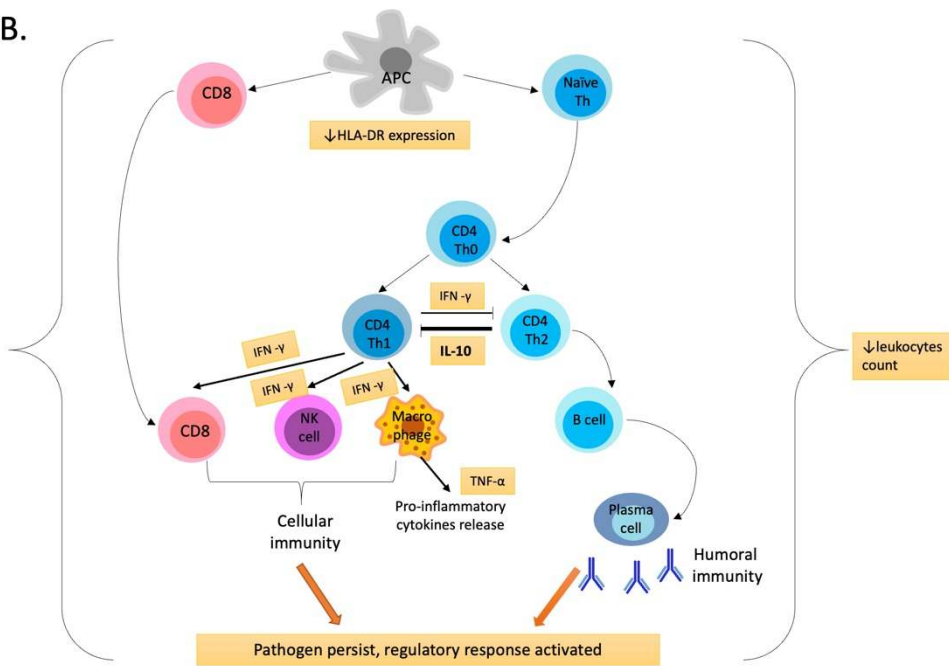
**Figure 2.** Deranged immune response towards pathogen in immunoparalysis

A.



Legend: APC=antigen presenting cell; Th=T helper; IFN=interferon; IL=interleukin; TNF=tumor necrosis factor; NK=natural killer.

B.



Legend: APC=antigen presenting cell; Th=T helper; HLA-DR=human leukocyte antigen D related; IFN=interferon; IL=interleukin; TNF=tumor necrosis factor; NK=natural killer.

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