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Sepsis: A Background Guide

A new drug offers hope in the treatment of a complex and devastating syndrome

Introduction

Every year, more than 750,000 people in the United States develop severe sepsis, a syndrome characterized by an overwhelming systemic response to infection that can rapidly lead to organ failure and ultimately death.[1] Sepsis may cause multiple organs in the body to fail, and can trigger the onset of both abnormal clotting and bleeding. Thirty percent of people with sepsis die from its consequences within the first month; up to 50 percent die within six months.[2, 3, 4]

Formerly known as "blood poisoning,"[5] sepsis can strike anyone, but is most likely to develop from infection associated with events such as pneumonia, trauma, surgery, and burns, or serious illnesses such as cancer and AIDS. In fact, people whose deaths are ascribed to complications of cancer, AIDS, or pneumonia, often actually die as a direct result of sepsis. It is most commonly seen in critically ill hospitalized patients and, in the United States, is the leading cause of death in medical intensive care units.

Until recently, there was no drug therapy specifically approved to treat sepsis; the only recourse was to provide supportive care and antibiotics for the underlying infection. A better understanding of the complex mechanisms of sepsis has led to the development of a breakthrough drug with the potential to save the lives of patients that would otherwise be lost to life-threatening severe sepsis. After decades of research on promising but ultimately ineffective medications, recombinant human activated protein C (drotrecogin alfa [activated], or Xigris®) has emerged as the only drug with proven efficacy in treating life-threatening severe sepsis. Approved by the U.S. Food and Drug Administration in November 2001, Xigris has a proven 29 percent relative risk reduction in patients at a higher risk of death. There are still hurdles to overcome, however, in the understanding of sepsis and its treatment.

What is sepsis?

Sepsis is defined as a range of clinical conditions caused by the body's immune response to infection or trauma. This immune response is characterized by systemic inflammation and disordered coagulation that can lead to organ failure or death. [6]

As a medical term, sepsis refers to the evidence of an infection plus the presence of at least three of these criteria:

- Heart rate greater than 90 beats/minute
- Increased respiratory effort
- High or low white blood cell count
- Fever or low body temperature. [7]

Symptoms of sepsis may include reduced mental alertness, confusion, shaking, chills, fever, nausea, vomiting, and diarrhea in the presence of an infection. The most frequent sites of infection leading to sepsis are the lungs, urinary tract, abdomen, and pelvis, although in up to 30 percent of patients a definite source of infection cannot be identified.[8,9] *The course of the syndrome is unpredictable; some patients quickly deteriorate into septic shock (a severe form of sepsis in which the cardiovascular system begins to fail), while others suffer from varying degrees of organ dysfunction or begin to recover.* [10]

The term "septicemia" is used by many clinicians to describe a situation in which viable bacteria can be cultured from the blood. "Severe sepsis" is a condition in which sepsis is accompanied by associated acute dysfunction in one or more of the organs. "Septic shock" refers to severe cases in which the cardiovascular system begins to fail and blood pressure drops, and vital organs are deprived of adequate blood supply.

How does sepsis occur?

Formerly doctors believed that inflammation – the body's biochemical warfare system against injury and invasion by microbes – was the dominant process underlying sepsis and its damage. Certainly, inflammation is a key player in the disorder. But the failure of anti-inflammatory agents, such as ibuprofen and anti-TNF (tumor necrosis factor), to prevent death in clinical trials of patients with sepsis has forced researchers to search for other pieces of the puzzle. Attention is now focused on two other interlocking processes: coagulation (clotting) and fibrinolysis (pronounced fye-brin-OH-lie-sis), the body's own natural "clot-busting" system. [11]

Inflammation, of course, is familiar to anyone who has ever had a burn, minor cut, or allergic reaction. Swelling and redness signal that the immune system is fighting a perceived invader or injury through a complicated chain of reactions throughout the bloodstream. In sepsis, however, the massive defense reaction can become a dysfunctional one, causing further damage from inflammation itself and from an imbalance in the body's blood clotting mechanisms.

Current diagnosis and treatment

Diagnosing sepsis can be tricky. Its symptoms – fever, rapid pulse, and respiratory difficulty – are very general and mimic many other disorders. Because people with sepsis often experience increases in white blood cells in their blood, a complete blood count (CBC) is a common diagnostic procedure.[12]

The first line of treatment is to identify and eliminate the underlying infection – for example, by draining an abscess (a localized collection of pus), culturing the infected material to identify a microorganism, and prescribing an appropriate antibiotic for that organism. [13] This, however, can be surprisingly difficult; in many sepsis cases, no specific infection is ever identified. [14] Adding to the treatment puzzle is the possibility that certain antibiotics may even worsen sepsis by increasing the breakdown of bacteria and the release of cell-wall fragments of certain bacteria known as endotoxin. In addition to this passive release of endotoxin, some bacteria actively produce poisons while they are still alive. These are known as exotoxins.

Depending on the patient's clinical status, other therapies may be used. These may include:

- using mannitol or furosemide for patients with severely limited urine production;
- administering drugs to raise blood pressure (vasopressors) and agents to improve cardiac function (inotropes) to patients with circulatory dysfunction and heart failure; and
- occasionally, giving heparin to patients with disseminated intravascular coagulation (DIC). [15]

Additionally, patients often require assisted breathing through the use of a mechanical ventilator. [16] Although such measures may be effective in keeping the body functioning, they do not actually fight sepsis and do little to halt the progression of the condition.[17]

Xigris is the only therapy proven to save the lives of adult patients with severe sepsis. In clinical studies, Xigris has been shown to reduce the relative risk of death by 29 percent in patients at high risk of death.[18] While the specific mechanism by which Xigris exerts its clinical effect is not known, Xigris boosts the supply of an important naturally occurring compound in the body, activated protein C, which is very often severely depleted in septic patients. Activated protein C keeps coagulation in check and enhances fibrinolysis. Xigris has anti-inflammatory actions, some of these are mediated by its ability to suppress the production of thrombin – an important molecule in the clotting cascade.[19] Unchecked thrombin production causes inflammatory effects on the lining of blood vessels known as the endothelium.

The Need for Better Diagnosis and Treatment

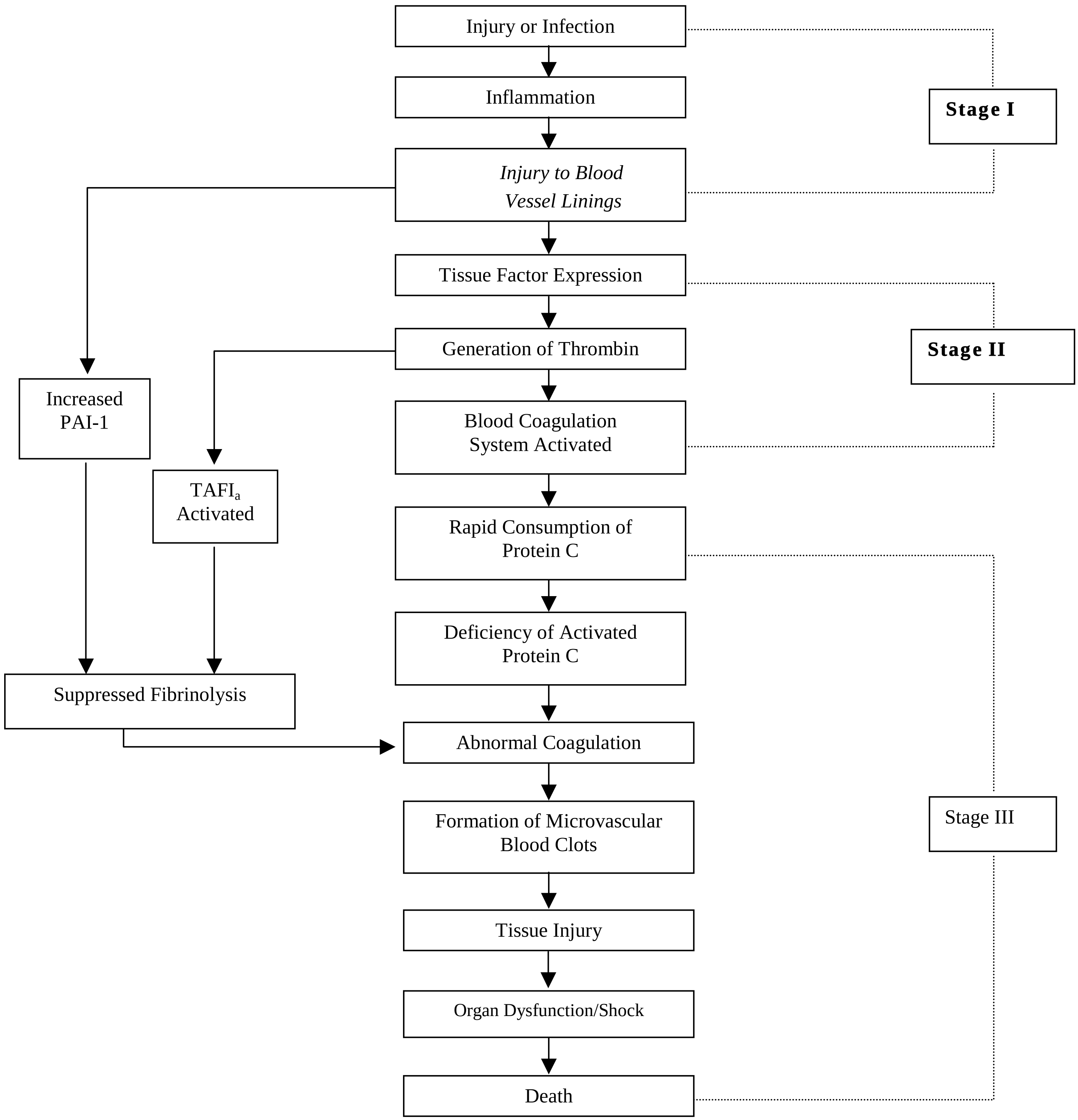
Today, critical care organizations are calling on their members and peer organizations for a concerted effort to help reduce the mortality rate of severe sepsis by 25 percent over the next five years through better diagnosis and treatment. This call-to-action is the debut initiative of the newly formed *Surviving Sepsis Campaign*, which brings together, for the first time, three leading professional organizations in the field of sepsis, the European Society of Intensive Care Medicine, the Society of Critical Care Medicine and the International Sepsis Forum. Launched in October 2002 at the 15th Annual Congress of the European Society of Intensive Care Medicine (ESICM) in Barcelona, Spain, this campaign urges governments and healthcare providers to recognize the growing burden of sepsis and to commit to providing adequate resources to combat it.

For healthcare professionals, the campaign details a five-point action plan designed to improve the management of sepsis and save lives by:

- Developing a clear definition of sepsis to facilitate early diagnosis,
- Ensuring appropriate and timely use of treatments and interventions,
- Developing guidelines for referring patients to sepsis specialists,
- Educating physicians about how to manage the condition, and
- Ensuring that patients continue to receive care after time in the intensive care unit.

A great deal of this effort is focused on not only preventing sepsis but also preventing conditions that predispose patients to the condition. This includes encouraging hospital workers to better manage medical devices and procedures to prevent infection in the first place, and educating physicians about techniques that can lower the likelihood that patients will develop sepsis. Eli Lilly and Company, the manufacturer of Xigris, has provided a grant to support this initiative.

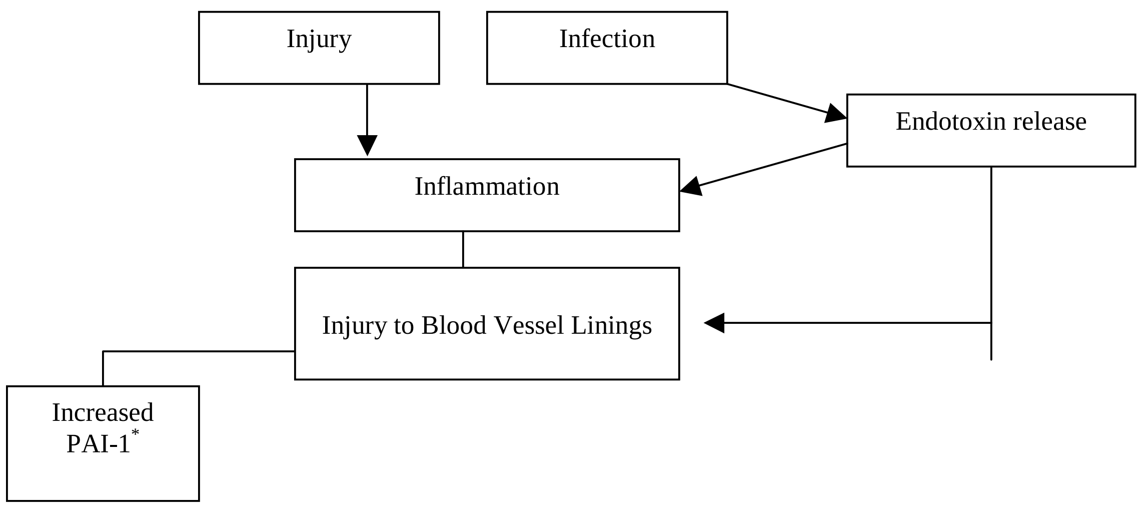
THE COMPLEX PATH OF SEPSIS [20-30]



Stage I: Inflammation

The process known as the systemic inflammatory response syndrome (SIRS) begins when some injury to the body, such as burns, trauma, or infection, triggers the release of substances called immune modulators that affect the inner lining (endothelium) of the blood vessels. When infection is present, the process is further amplified by the release of endotoxin or exotoxins – depending on the organism responsible. This process is then known as Sepsis. These or other toxic stimuli also provoke the release of immune modulators. Many of these modulators are inflammation-producing ("proinflammatory") and clot-activating substances, including cytokines such as tumor necrosis factor (TNF) and various forms of interleukin. These cytokines inflame the linings of blood vessels and activate the blood clotting process, triggering the release of yet another wave of inflammatory modulators.

STAGE I

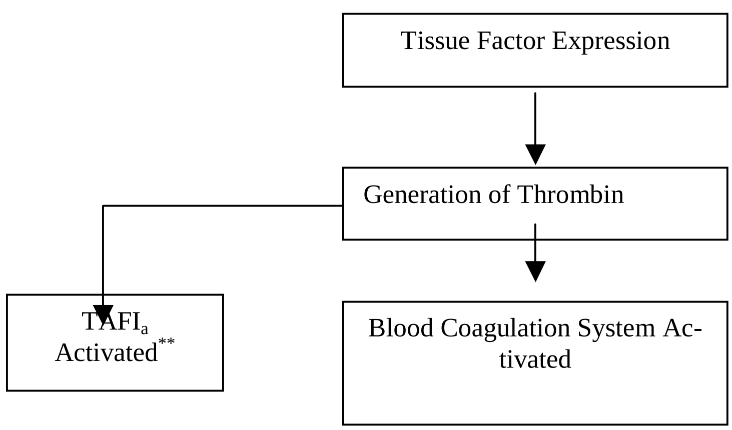


** PAI-1 (plasminogen activator inhibitor type 1, which offsets fibrinolysis)*

Stage II: Coagulation

The clotting of blood is one of the most complex cascades of events in the human body. Inflammation prompts the release of a substance called tissue factor, which in turn generates thrombin, a key stimulus for blood clots to form.[31] Thrombin promotes coagulation by forming fibrin, the protein building block of blood clots. In sepsis, this chain functions abnormally.

STAGE II



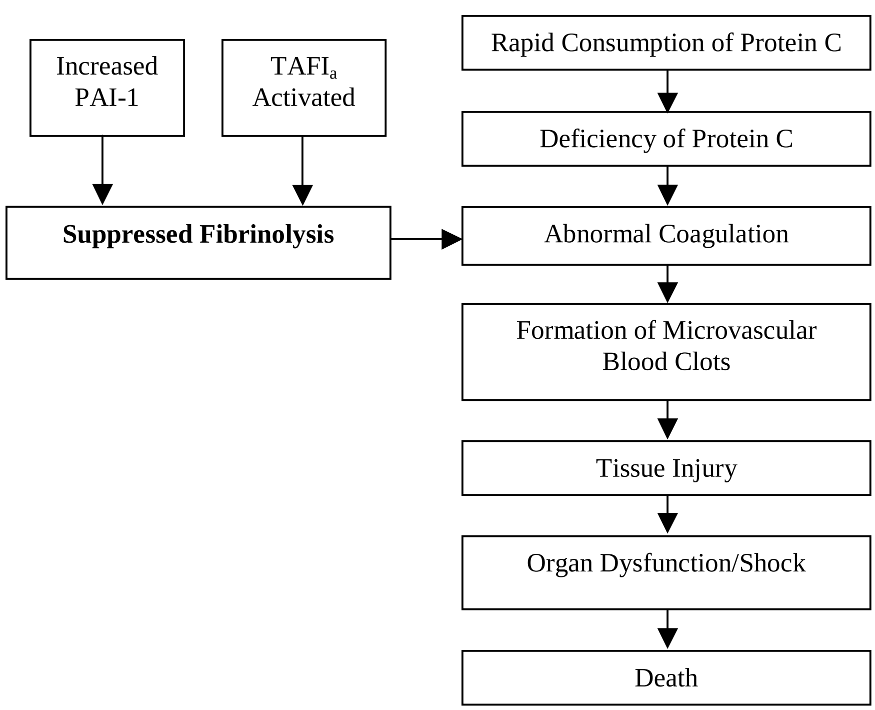
*** thrombin activatable fibrinolysis inhibitor (TAFI$_a$)*

Stage III: Dysfunctional Clot Busting, Tissue Injury, and Death

Ordinarily, the body regulates inflammation and coagulation through a series of biochemical feedback loops.[32] *It keeps blood clot formation from going dangerously out of control by breaking down fibrin in a process called fibrinolysis, sometimes dubbed "clot-busting." But in the vicious cycle of sepsis, fibrinolysis is suppressed. As a result, microscopic blood clots begin to form within vital organs, blocking blood flow and causing tissue damage. There apparently are several biochemical factors at work, including:*

- *Increased levels of plasminogen activator inhibitor type 1 (PAI-1), which offsets fibrinolysis*[33]
- *Increased levels of thrombin activatable fibrinolysis inhibitor ($TAFI_a$)*
- *Reduced levels of protein C (in its endogenous activated form, a major inhibitor of PAI-1).* [34, 35, 36]

STAGE III



The Role of Endogenous Activated Protein C

Protein C is a naturally occurring immune modulator that may help balance many of the major forces behind sepsis, including inflammation, coagulation, and altered fibrinolysis.[37] *In its activated form (endogenous activated protein C, or APC), it rapidly blocks the clotting process, especially in the tiniest blood vessels.*[38] *In sepsis, activated protein C levels are frequently markedly reduced. Part of the explanation may be that the level of thrombomodulin – which is needed for the conversion of protein C to activated protein C is also depressed. Depressed levels of activated protein C have been associated with poorer outcome in patients with sepsis, but as yet, we do not know which of the many effects of activated protein C is the most important factor in this observation.*

A note on terminology

Systemic inflammatory response syndrome, or SIRS, is one term used to describe the cascade of immune reactions. Sepsis can be defined as SIRS in the presence of infection. When sepsis worsens to the point where blood pressure drops and organs can no longer function normally, the condition is called septic shock.[39]

Mounting Costs – In Lives and Dollars

The physical and economic costs of sepsis are enormous. In the United States alone, the annual cost of treating patients with sepsis is $17 billion.[40] Expenditures for each patient are high and largely due to ICU charges, physician and nursing care, mechanical ventilation, and/or drug therapy [41, 42, 43]

It is estimated that more than 1.5 million cases of sepsis are diagnosed each year.[44] The individuals who are most vulnerable to sepsis are infants and children (particularly newborns), the elderly, and people whose immune systems are compromised by medical treatment for cancer, organ transplantation or immune-suppressing diseases such as AIDS. The death rate for sepsis has dipped slightly since the 1960s, probably owing to improved general medical care for affected patients. But a dramatic increase in the numbers of patients with sepsis is expected in coming years.[45, 46] An aging population, combined with improved supportive care for the most medically fragile patients and the widening use of aggressive and invasive medical procedures, will increase the number of people most at risk for sepsis.

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Xigris is indicated for the reduction of mortality in adult patients with severe sepsis (sepsis associated with acute organ dysfunction) who have a high risk of death (e.g., as determined by APACHE II). See complete prescribing information on www.Xigris.com.