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# HISTORY AND DEVELOPMENTS IN THE SEPSIS SYNDROME

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*Sepsis sendromunda tarihçe ve gelişmeler.*

When the eminent physician, William Osler, near the turn of the century, termed "Pneumonia as the captain of the men of death", his focus was on pneumococcal pneumonia, tuberculosis and post-influenzal bacterial pneumonia. By the mid-point of the century following the introduction of penicillin, streptomycin, tetracycline, chloramphenicol and vaccine against *Influenza* virus the situation had changed. Gram negative bacteremia and a syndrome of septic shock, sometimes believed to be endotoxic shock, became increasingly recognized as a major cause of death among people in acute care hospitals.

Prior to 1950 the infections were caused mostly by Gram positive cocci. After the introduction of antibiotics their use caused changes in the flora of treated patients and a rise in infections with aerobic Gram negative bacilli; new and more extensive surgical procedures were performed with antibiotic cover; more patients with immunocompromised status were successfully treated; immunosuppression was induced in others by anticancer treatment; and the age of the population increased. All of these events dramatically increased the occurence of Gram negative bacteremia. The clinical syndrome of bacteremic sepsis consisted of an abrupt change in the condition of a patient manifested by certain symptoms and signs. Of these manifestations fever or hypothermia, tachycardia, tachypnea and one or more manifestations of inadequate organ perfusion has recently been termed the sepsis syndrome to facilitate nearly clinical recognition and treatment.

Three domains of developments can be identified in the evolution and understanding of bacteremia as a cause of the sepsis syndrome. The three areas of increased information are:

1. Recognition of the specific bacterial etiologies and effective antimicrobial regimens.
2. Host disease conditions that identify people at greatest risk of developing bacteremia and fatality from the infection.
3. Information about the pathophysiologic stimuli and host responses that mediate the lethal effects of sepsis.

Increasingly the pathophysiologic responses to sepsis are being elucidated. Among the array of bacterial constituents recognized as antigens or virulence factors for the host, endotoxin, especially the lipid A fraction of the bacterial membrane, when presented to the host can elicit a series of physiologic and pathologic responses through immunologic mechanisms and cytokines, using common pathways that control a number of delicately balanced homeostatic mechanisms. Control of infection at the stage of antigen presentation is best. Immunoglobulins, both natural antibody (or bactericidins) and specific antibodies, acting with complement, by the classical and alternative pathways (through properdin) can interrupt and neutralize the bacterial products at the onset of infection. Unneutralized endotoxin and other bacterial products elicit secretion of cytokines and organ secretory responses that directly and indirectly cascade physiologic to pathologic effects in at least five major systems of plasma reactants involved in maintenance of homeostatis: Complement, coagulation, thrombolysis, kallikrein-bradykinin and prostoglandins. Tumor necrosis factor (TNF) appears to be a modulator of common pathways for the activation of these systems. Organ responses in each system are controlled by specific and nonspecific inhibitors and by production limitations of the reactants. Distortion by product consumption and unopposed stimulation has dire consequences with pathologic vasodilation, hypoglycemia, hypoxia and capillary leakage. Recognition of the pathologic sequences and pharmacologic or immunologic blockade of the precursor steps at common pathways are the focus of current investigation. The approach offers

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the best opportunity for further improvements in the successful management of the sepsis syndrome with reduced fatality.

To understand cause and effect relations between bacteremia, shock and death in the sepsis syndrome requires keen appreciation for the unknown and scrupulous awareness of variability of factors involved. Whereas, in the scientific method, a cause and effect relation can be established when change in a single variable produces the effect, in biologic functions as complex as the sepsis syndrome, interrelated systems produce multiple variables. New drugs and therapy for shock have significantly increased rescue of compromised hosts from fatality resulting from sepsis with Gram negative bacilli, but patients with nonfatal underlying diseases, as a group, have not benefitted from new antimicrobial treatment, and may have been adversely affected by bacterial drug resistance. Further improvement in avoiding fatality from sepsis may require modalities adjunct to antimicrobial and convential shock therapy. Increasing knowledge of mediators of protective and pathologic host responses offers opportunities for new immunologic and pharmacologic treatment.

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