

DROTRECOGIN ALFA ACTIVATED (RECOMBINANT HUMAN ACTIVATED PROTEIN C, XIGRIS)

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Our understanding of the immunopathophysiology of sepsis has made extraordinary progress during the past several decades, although therapeutic advances during the similar period have been extremely slow. During the past decade several clinical trials demonstrated promising results showing reduced morbidity and mortality in sepsis, although some had mixed outcomes. These trials have supported four major approaches: (1) maintenance of good tissue oxygenation by aggressive management of fluid and blood transfusion, (2) intensive insulin therapy to maintain the euglycemia, (3) low-dose corticosteroids, and (4) treatment with human recombinant activated protein C (drotrecogin alfa activated, Xigris, Eli Lilly and Company, Indianapolis, IN). These options will be briefly summarized below, but this chapter will concentrate on the epidemiology, pathophysiology, and management of sepsis with emphasis on the use of drotrecogin alfa activated (DAA) in the management of sepsis.

1 INTRODUCTION

In 1991, the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) held a “Consensus Conference” to define the terms *sepsis* and *organ failure* in a precise manner. At the conference, the term *systemic inflammatory response syndrome* (SIRS) was developed representing a clinical response arising from a wide variety of nonspecific

insults [1]. The syndrome complex includes, but is not limited to, more than one of the following: (a) a body temperature of $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$; (b) a heart rate of >90 beats/min; (c) tachypnea, as manifested by a respiratory rate of >20 breaths/min or hyperventilation, as indicated by a PaCO_2 of 32 Torr (<4.3 kPa); and (d) an alteration of the white blood cell (WBC) count of $>12,000$ cells/ mm^3 , or <4000 cells/ mm^3 , or the presence of $>10\%$ immature neutrophils (“bands”). *Sepsis* is defined as having SIRS with proven or highly suspected infection, while sepsis associated with organ dysfunction, hypoperfusion, or hypotension is defined as *severe sepsis*. Furthermore, *septic shock* is referred to sepsis with hypotension [a systolic blood pressure (BP) of <90 mmHg or reduction of >40 mmHg from baseline], despite adequate fluid resuscitation, along with the evidence of tissue hypoperfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status [1]. The introduction and use of these definitions were not without criticism for making the situation more confusing, and the term SIRS is nonspecific and too sensitive [2]. A decade later, in 2001, the 1992 original document [1] was revisited by the expert members of the SCCM, the ACCP, the European Society of Intensive Care Medicine (ESICM), the American Thoracic Society (ATS), and the Surgical Infection Society (SIS), and found no evidence to support a change to the definitions [3]. Therefore, in this chapter the 1992 consensus definitions will be used.