

Introduction

Severe community acquired pneumonia update: mortality, mechanisms and medical intervention

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Severe community-acquired pneumonia (CAP) in the intensive care unit (ICU) is associated with a high mortality rate of about 30% [1], and this rate has remained largely unaltered since the discovery of antibiotics in the 1950s [2]. Until now, no therapies have been designed specifically as adjunct agents for the treatment of severe CAP. In the majority of cases, broad-spectrum antibiotics or pathogen-directed therapies are effective in eradicating the causative organism(s), but they do not address causative effects from pathways of inflammation and coagulation, which are characteristic of the host response to infection.

Initially activated as a protective host response, these inflammatory and coagulation pathways may become unregulated and paradoxically may cause tissue damage in the setting of severe CAP. A major component of both of these pathways is tissue factor (TF), a microvascular endothelial glycoprotein that becomes exposed to the systemic circulation after tissue damage. TF is an attractive therapeutic target for adjunctive treatment in severe CAP because it is the initiating factor in the TF coagulation pathway (which ultimately results in thrombin generation and fibrin deposition) [3] and has been shown to stimulate directly the production and release of proinflammatory cytokines (through the protease-activated receptor system) [4].

The largest phase III randomized, placebo-controlled study ever undertaken in patients with severe CAP is currently underway to investigate whether targeting the TF pathway with a specific TF pathway inhibitor can significantly reduce 28-day all-cause mortality in the primary target population.

The objective of this symposium is to review the epidemiology of severe CAP, examine current clinical practice and treatment guidelines, and investigate the evidence supporting the potentially central role of TF in the pathophysiology of severe CAP.

Jordi Rello MD, PhD is Chief of the Critical Care Department at the Joan XXIII University Hospital in Tarragona, Spain.

Professor Rello has been actively involved in clinical research for the past 20 years, focusing on the prevention and control of hospital-acquired infections, severe CAP and treatment of infections in critically ill patients. His presentation focused on the epidemiology, diagnosis and severity scoring of severe CAP, and the impact that treatment guidelines have had [5].

Tom van der Poll MD, PhD is Head of the Centre for Experimental and Molecular Medicine in the Academic Medical Centre in Amsterdam. His research is based in the Centre for Infection and Immunity Amsterdam (CINIMA) and focuses on innate immune responses to bacterial and mycobacterial infection. He also serves on the Steering Committee of the International Sepsis Forum. His presentation focused on the pathogenesis of severe CAP, in particular covering the roles played by TF as a critical component of the infectious, inflammatory and coagulation pathways [6].

Pierre-François Laterre MD is Head of the Intensive Care Unit at St. Luc University Hospital, Université Catholique de Louvain in Brussels, Belgium. Professor Laterre's professional and scientific activities have focused on the diagnosis, investigation and treatment of sepsis, particularly its interaction with the coagulation cascade. As Co-Chair for the symposium, his presentation focused on the rationale for TF as a therapeutic target in severe CAP and reviewed the design of the ongoing phase III CAPTIVATE study of tifacogin [7].

Jean-Paul Mira MD is Professor of Critical Care Medicine and Chair of the Medical Intensive Care Unit at the Cochin University Hospital; he is also Head of the Variability of Innate Immunity Research Laboratory at the Cochin Institute, both in Paris, France. His research interests are cellular responses to micro-organisms, Toll-like receptor signalling, functional genomics, genetic predisposition to sepsis and sepsis-induced immunosuppression. His presentation focused on the potential for biomarkers to assist physicians in the diagnosis of severe CAP and their possible future role in directing appropriate treatment [8].

The second Co-Chair, Steve Opal MD, who is Professor of Medicine from the Brown Medical School, Pawtucket, Rhode Island, USA, hosted the questions from the audience and directed responses from faculty.

Competing interests

PFL was engaged in the conduct of the CAPTIVATE study, is a member of the clinical evaluation committee of the CAPTIVATE study, and served as a consultant for Novartis and received speaker fees.

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