Disponible en ligne sur
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com

Médecine et maladies infectieuses

Médecine et maladies infectieuses 44 (2014) 455–463

General review

Post-infectious immune suppression: A new paradigm of severe infections

L'immunodépression post-infectieuse : un nouveau paradigme des infections sévères

D. Grimaldi [a,*,b,c], J.F. Llitjos [b,c], F. Pène [b,c,d,e]

[a] *Réanimation médico-chirurgicale, centre hospitalier de Versailles, 177, rue de Versailles, 78150 Le Chesnay, France*
[b] *Institut Cochin, CNRS UMR8104, 75005 Paris, France*
[c] *Inserm U1016, 75005 Paris France*
[d] *Réanimation médicale, hôpital Cochin, AP–HP, 75005 Paris, France*
[e] *Université Paris Descartes, 75005 Paris, France*

Received 6 June 2014; received in revised form 24 June 2014; accepted 29 July 2014
Available online 29 August 2014

Abstract

Infectious diseases remain a major public health issue in both developing and developed countries. For instance, there is still a high rate of morbidity and mortality due to seasonal influenza outbreaks and severe bacterial sepsis, despite major advances in their prevention and treatment. It is now clear that severe influenza and bacterial infections promote susceptibility for superinfections worsening the prognosis. Various immune defects acquired during severe infection may result in complex immunosuppression and may affect both innate and adaptive components. Some animal models of these common clinical situations have demonstrated the increased susceptibility of infected hosts to secondary infectious insult and allowed assessing the regulatory mechanisms. Such pathophysiological advances may help create new immunomodulatory therapeutics for infected patients exposed to severe secondary sepsis.

Keywords: Influenza; Sepsis-induced immunosuppression; Immunotherapy; Superinfection; Severe sepsis

Résumé

Les maladies infectieuses demeurent un problème majeur de santé publique, y compris dans les pays développés. Par exemple, les épidémies grippales et les infections bactériennes demeurent grevées d'une morbi-mortalité importante malgré les avancées réalisées dans la prévention et le traitement de ces maladies. Il est maintenant clairement établi que les infections grippales et bactériennes graves induisent une susceptibilité accrue à des infections secondaires qui grèvent significativement le pronostic. En effet, au cours des états infectieux graves, diverses anomalies immunologiques acquises peuvent aboutir à une immunodépression complexe qui affecte à la fois les composants de l'immunité innée et de l'immunité adaptive. Des modèles animaux modélisant ces situations cliniques communes ont permis de mettre en évidence la susceptibilité accrue de l'animal infecté à une agression infectieuse secondaire et d'évaluer les mécanismes qui régulent ces phénomènes. Ces avancées physiopathologiques permettent maintenant d'envisager des perspectives thérapeutiques immunomodulatrices chez les patients septiques exposés à des complications infectieuses secondaires.

Mots clés : Grippe ; Immunodépression post-infectieuse ; Immunothérapie ; Infection secondaire ; Sepsis grave

1. Introduction

Infectious diseases remain a major public health issue in both developing and developed countries. For instance, there is still a high rate of morbidity and mortality due to seasonal influenza

* Corresponding author.
E-mail addresses: dgrimaldi@ch-versailles.fr (D. Grimaldi), frederic.pene@cch.aphp.fr (F. Pène).

http://dx.doi.org/10.1016/j.medmal.2014.07.017
0399-077X/

outbreaks and severe bacterial sepsis despite major advances in their prevention and treatment, and easy access to advanced medical care. However, it is clear from both examples that a high rate of the mortality is not due to the primary infection but is related to superinfections. The authors of epidemiological studies have often reported that influenza was especially susceptible to pulmonary bacterial superinfections [1]. Likewise, patients hospitalized in the intensive care unit (ICU) for severe sepsis and septic shock are prone to developing nosocomial infections associated with high morbidity and mortality rates. The prolonged use of invasive medical devices and the selection of resistant bacteria remain major determinants of ICU-acquired infections, but there is increasing evidence that some acquired immune dysfunctions might contribute to the increased susceptibility to superinfections despite recovery from the primary insult [2]. We reviewed the clinical and experimental data supporting the concept of post-infection immunosuppression in 2 common conditions: influenza and bacterial sepsis.

2. Post-infectious immune dysfunction: a case for translational research

The concept of post-infection immune suppression was demonstrated by both clinical and experimental studies and is a good example of translational research by combining human and animal studies (Table 1). The research on sepsis-induced immune dysfunction was initiated by Richard Hotchkiss with post-mortem studies of patients having died from sepsis [3]. Bedside investigations in patients are limited to circulating components of immunity, and a number of confounding factors may preclude assessing the involvement of sepsis-induced immune dysfunction in superinfections. In the past decade, the development of two-hit animal models aimed at mimicking influenza and bacterial sepsis complicated by superinfections allowed demonstrating the increased susceptibility of post-septic animals to a superinfection and addressing the mechanistic features of post-infection immunosuppression. Endotoxinic shock has been largely used as a surrogate of bacterial sepsis because of similarities in the inflammatory response. However, it is noteworthy that LPS challenge confers protection against a superinfection insult, suggesting that post-infection immunosuppression cannot be related to LPS tolerance which is more frequently associated with a vaccine-like effect [4]. Animals previously subjected to a primary bacterial infection such as polymicrobial peritonitis then display an enhanced susceptibility to superinfection challenge, related to a delayed and inappropriate host response, and are an interesting tool to model a complex clinical setting.

3. Influenza-induced impairment of lung immune defense

The authors of co-detection studies have clearly demonstrated the association between respiratory viral infections and bacterial pneumonias [5]. The authors of numerous epidemiological studies have long demonstrated the susceptibility of influenza patients to pulmonary bacterial superinfections. Post-mortem series from the Spanish flu pandemic in 1917–18 proved that bacterial pneumonia was a major cause of death before antibiotics became available. Bacterial infections accounted for up to 50% of deaths during the recent 2009 H1N1 influenza pandemic, [1]. Such superinfections occur quite early in the course of influenza with time intervals ranging from 1 to 11 days post-influenza. *Streptococcus pneumoniae, Staphylococcus aureus*, *Haemophilus influenza*, and *Streptococcus pyogenes* are the main bacteria identified in this setting. *S. pneumoniae* was considered as the most common cause of influenza-associated pneumonia, but *S. aureus* has recently become the first cause of bacterial coinfection in the USA [1], probably due to the broad pneumococcal vaccine coverage, and to the spread of the highly virulent *S. aureus* USA300 strain in the community [6].

Animal models of double infections, influenza and bacteria, have clearly demonstrated the susceptibility of influenza-infected animals to bacterial superinfections. Furthermore, such models have allowed deciphering the mechanisms involved in the defective antibacterial lung response in influenza-infected animals, and highlighted the respective contributions of virus-induced lung damage and impaired antibacterial immune response. Virus-induced lung damage may promote bacterial superinfection through several mechanisms. The influenza virus replicates preferentially within epithelial cells, thereby inducing apoptosis and disrupting epithelial barriers. This exposes numerous sites to bacterial adhesion, such as fibrin and fibrinogen, promoting bacterial invasion [6]. Moreover, the viral neuraminidase enzyme is able to cleave the sialic acid of several membrane molecules facilitating pneumococcal adherence.

However, the direct impact of viral infection on the respiratory epithelium does not fully account for the susceptibility to bacterial superinfections, suggesting the contribution of additional mechanisms. Most seasonal influenza strains do not cause severe lung injury in patients, but do increase bacterial susceptibility. Likewise, viral strains that cause minimal epithelial cell damage in mice remain associated with increased susceptibility to bacterial infections. Moreover, the deletion of neuraminidase in avian influenza viruses does not modify the course of secondary bacterial pneumonia [7]. Nonetheless, influenza viruses can subvert some antibacterial lung defense mechanisms. For instance, they specifically and transiently induce depletion and impairment of the phagocytic capacities of alveolar macrophages [6,7]. Neutrophil recruitment into infected lungs is also decreased as a result of down-regulated chemokine production [8,9]. Intracellular bacterial killing is also impaired within alveolar macrophages and neutrophils because of a decreased genesis of intracellular reactive oxygen species [10]. This functional defect of immune cells seems to be mediated by type-I interferons, released in response to viral infection [8,9]. Sun et al. suggested another interesting mechanism by showing that defective phagocytosis was related to an IFN-γ-dependent down-regulation of the scavenger receptor MARCO, which also acts as a recognition receptor of *S. aureus*. Accordingly, both IFN-γ deficient mice or wt mice treated with neutralizing anti-IFN-γ antibodies were protected from *S. aureus* pneumonia after influenza primary infection [7]. Pro-inflammatory cytokine production is also impaired in innate-like cells such as NK cells and γδ T-cells