

The complex link between influenza and severe sepsis

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Severe sepsis is traditionally associated with bacterial diseases. While fungi and parasites can also cause sepsis, they are significantly less common than bacterial causes. However, viruses are becoming a growing cause of severe sepsis worldwide. Among these viruses, influenza is crossing all geographic boundaries and is causing larger epidemics and pandemics. As a consequence, more critically ill patients with severe sepsis caused directly by influenza viruses, or indirectly by influenza-induced secondary bacterial infections are being admitted to hospitals worldwide. This manuscript aims to provide a pathophysiological and clinical update on the link between influenza and severe sepsis.

Introduction

Regardless of the etiologic agent, the inflammatory response is highly interconnected with infection. In the initial response to an infection, severe sepsis is characterized by a pro-inflammatory state, while a progression to an anti-inflammatory state develops and favors secondary infections, such as bacterial infections and cytomegalovirus reactivation.¹ In the predominant pro-inflammatory state, Th1 cells activated by microorganisms increase transcription of pro-inflammatory cytokines such as tumor necrosis factor (TNF- α), interferon- γ (INF- γ), and interleukin-2 (IL-2).²⁻⁴ Different cytokines (TNF- α , interleukins, lymphokines, monokines, IFN- γ , CSF, and transforming growth factors) released from endothelial cells and subsequently from macrophages can induce lymphocyte activation and infiltration at the sites of infection and will exert direct antiviral effects. Subsequently, with the shift toward an anti-inflammatory state, activated Th2 cells secrete interleukin-4 (IL-4) and interleukin-10 (IL-10).^{2,4} In certain situations, T cells can become anergic, failing to proliferate and produce cytokines.² Type I IFN has a potent anti-influenza virus activity; it induces transcription of several interferon stimulated genes, which in turn restrict viral replication.⁵ However, influenza virus developed several mechanisms to evade IFN response: NS1 protein, and IFN-antagonist produced by the virus, PB1-F2 proteins that inhibits

IFN induction, viral polymerase that inhibit IFN function, and M2 protein prevents TLR induction.⁵

Viral infections such as the influenza virus can also trigger deregulation of the innate immune system with excessive cytokines release and potential harmful consequences.⁶ An abnormal immune response to influenza can lead to endothelial damage (through remodeling of the cellular cytoskeleton, loss of intercellular junctional integrity, cellular apoptosis), deregulation of coagulation, and the consequent alteration of microvascular permeability, tissue edema, and shock.⁷ This increased in permeability of the endothelium is mainly due to the intercellular pathways and to a lesser extent through transcellular leak.⁷ Such vascular hyperpermeability and multiorgan failure with severe edema, shock, acute lung injury, and even acute encephalopathy have been described in severe influenza infections.^{8,9}

Pathophysiology of Acute Influenza Infection

The pathology seen with different strains of influenza depends on the virulence of the strain and the strength of the host response. Although all influenza viruses can infect the respiratory epithelium from the upper airways to alveoli, seasonal H3N2, H1N1, and influenza A viruses cause primarily inflammation and epithelial necrosis of the large airways (trachea, bronchi, and bronchioles), while 1918 H1N1, pandemic 2009 H1N1, H5N1, and influenza A viruses all tend to infect not only the large airways, but also more frequently the alveoli.¹⁰⁻¹⁴ These differences are due to difference in the virulence factors (such as HA and viral polymerase) among seasonal and pandemic influenza. While in seasonal influenza hemagglutinin targets the epithelial cells of the upper respiratory tract by binding to α 2–6 sialylated glycans, in avian H5N1 influenza hemagglutinin binds to α 2–3 sialylated glycans of the type 2 pneumocytes in the lungs.^{15,16} Mutations in the hemagglutinins of the H5N1 would lead to cell tropism alteration (ability to bind to both α 2–3 and α 2–6 sialylated glycans) that might increase the severity of the disease.¹⁶⁻¹⁸ Similar mutations at the level of the viral RNA polymerase complex can lead to better viral replication or increase secretion of proinflammatory cytokines.¹⁶

Airway macrophages are the first line of defense following inhalation of the influenza virus. In addition to phagocytosis, early recognition of the virus by the innate immune system, macrophages synthesize, and release pro-inflammatory cytokines and interferons.¹⁹ It was recently shown that endothelial cells are the center of innate immune cell recruitment and early cytokine

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production.⁶ Lung macrophages use scavenger receptor A and macrophage receptor with collagenous structure (MARCO) to mediate uptake and clearance of different lung pathogens such as influenza viruses.²⁰ Ghosh et al. showed that in mice that MARCO suppressed protective early inflammatory response to influenza, which decreased viral clearance and delayed recovery.²⁰ Polymorphisms in human MARCO might partially explain differential innate immune response to influenza infections.²⁰ Tejaro et al., in a mice model of influenza infections demonstrated the key role of cytokines in the pathophysiology of severe influenza infections; they showed that agonism of sphingosine-1-phosphate₁ (S1P₁) receptor (expressed on endothelial cells and lymphocytes within the lung tissue) suppresses cytokine production and innate immune cell recruitment.⁶ Several animal studies demonstrated that early suppression of cytokine induction by targeting S1P receptors with the agonist R-2-amino-4 (4-heptyloxyphenyl)-methylbutanol (AAL-R), blunted early innate cellular response without altering viral clearance, and translated in increased animal survival rates.^{21,22} Cytokines (produced by macrophages, T cells, monocytes, endothelial cells, and platelets) also activate NFκB, a prerequisite pathway for influenza virus to infect human cells.²³ NFκB further regulates the genes encoding pro-inflammatory cytokines, adhesion molecules (VCAM-1 and ICAM-1), chemokines, growth factors, cyclooxygenase-2 (COX2), and inducible nitric oxide synthase, with subsequent endothelial dysfunction and edema.²⁴ Reactive oxygen species at low concentrations are important elements of host defense, potent vasodilators, and inflammatory cell chemotaxins, enhancing in this way the immune response and cellular migration through vascular epithelial barriers. At high concentrations, however, they may contribute to excessive cell apoptosis, exacerbating the pathology caused by the viral replication.^{13,25-28} Perrone et al. demonstrated that severity of influenza virus infections is determined by nitric oxide induction, with higher nitric oxide production in the lungs and lung-derived neutrophils of mice infected with highly pathogenic H5N1 and 1918 H1N1 strains than with low-pathogenic seasonal H1N1 strain.²⁸ Further, morbidity was reduced and time-to-death was prolonged if nitric oxide production was pharmacologically blocked.²⁸ Cytokines also induce endocytosis of VE-cadherin, disrupting transcellular links of VE-cadherins, leading to dissociation of intercellular adherence junctions and hyperpermeability.^{29,30} The counter-regulator of the cytokine-mediated endocytosis of VE-cadherins and stabilizer of the vascular barrier is the Robo-4-dependent Slit signaling mechanism.^{31,32} London et al. showed that administration of exogenous ligand Slit2N strengthens the endothelial barrier and limits vascular permeability in response to massive cytokine release.³³ Excessive accumulation of macrophages and neutrophils in the lung, in conjunction with the massive release of cytokines and reactive oxygen intermediates and then culminates in vascular injury, parenchymal damage, loss of functional alveolar surface area, and ineffective gas exchanges.²⁸

Macrophages are susceptible to infections by different influenza strains (H1N1, H7N7, H5N1), but non-permissive to virus propagation.³⁴ Excessive innate immune response was also

found in patients with severe H1N1 pandemic influenza A/2009, in which marked granulocyte and complement activation was observed in the viremic patients.³⁵ The specific inflammatory response and cytokine production depends on the influenza strain: Friesenhagen et al. showed that the inflammatory response of blood macrophages was much stronger to infections with H5N1 virus than that with H1N1 and H7N7 viruses.³⁴ In contrast, Cheung et al. and Sakabe et al. showed a more effective cytokine production with H1N1 virus.^{27,36} Hagau et al.³⁷ demonstrated that in critical ill patients with H1N1 influenza the cytokines IL-6, IL-8, and IL-15 had a positive correlation with hospital admission delay, but a negative correlation with PaO₂/FiO₂ ratio. From these data it seems that the immune response might be dependent on the viral strain, antigenic variant, and the inoculum size.³⁴ We have also to consider that the results from studies evaluating blood macrophages might not be applicable to lung macrophages and monocytes, as these cells are not part of a homogeneous population.³⁴

Another mechanism that can explain acute lung injury by influenza was described by Imal et al.²⁵ Stimulation of TLR4 in mice by inactivated H5N1 triggered the activation of the TLR4-TRIF-TRAF6 pathway (operative in lung macrophages), leading to upregulation of TLR4, production of reactive oxygen, ensuing IL-6 mediated acute lung injury.²⁵ TLR4^{-/-} mice and mice treated with the TLR4 antagonist eritoran were protected from lung injury due to influenza virus.^{38,39} TLR2, TLR3, and TLR7 have also an important contribution to innate defense against influenza infection.⁴⁰ The polymorphism of the TLR seems to play a role not only in the susceptibility to influenza infection, but also the severity of the disease.⁴⁰⁻⁴²

Several animal studies showed that host cellular trypsin-like proteases that activate viral fusion activity of hemagglutinin partially determine viral pathogenicity and infectivity.^{8,43,44} Influenza A virus has the ability to upregulate trypsin in the endothelial cells and in hippocampal neurons,⁴⁴ which can efficiently convert pro-MMP-9 to active MMP-9;⁴⁵ these both proteases can synergistically degrade the basement membrane proteins, including tight intercellular junctions and the blood-brain barrier.⁴⁶

Secondary Bacterial Infections, Pneumonia, and Sepsis

The association between influenza and bacterial pneumonia was first described by Laennec, but became well established following the 1918 pandemic; by mid-19th century, influenza A and B viruses were both known to predispose patients to bacterial infections (especially with *S. pneumoniae* and *S. aureus*).⁴⁷ Increased rates of pneumococcal pneumonia during influenza pandemics continued to be documented even recently, indirectly supporting an interaction between influenza virus and bacterial pneumonia.⁴⁸⁻⁵⁰ It has been estimated that, on average, 5–6% of invasive pneumococcal pneumonia⁵¹ and 6–10% of all invasive pneumococcal diseases can be attributed to influenza infections.⁵² What are the mechanisms that play a role in the pathogenesis of bacterial super-infection? The interactions between influenza

and bacteria are complex and not completely elucidated. Several studies demonstrated that viral replication denudes the respiratory epithelium, exposing basement membrane to which bacteria can adhere.⁵³⁻⁵⁶ At the same time, pro-inflammatory cytokines, might upregulate platelet-activating factor receptor (PAFr), providing a receptor for pneumococcal adherence and invasion.⁵⁵⁻⁵⁷ In addition, influenza impairs antibacterial defense mechanisms by increasing neutrophil apoptosis, neutrophil, and monocyte dysfunction, depressing chemotaxis, and suppressing phagocytosis.⁵⁸⁻⁶⁴ Hall et al., in a study in critically ill pediatric patients with influenza, reported an association between severe immune dysfunction and *S. aureus* bacterial co-infections, often fatal, which was not seen in patients co-infected with other bacteria.⁶⁴ The subjects with *S. aureus* infections displayed a greater degree of immune dysfunction (demonstrated by reduction in TNF- α production capacity) than those without secondary bacterial infection or infection with a different organism.⁶⁴ In another recent study, Passariello et al. demonstrated that viral hemagglutinin can promote internalization of the *S. aureus* into human pneumocytes during H1N1 influenza virus infection.⁶⁵ From these data, we can see that influenza virus infection favors secondary bacterial co-infections, especially pneumonia and sepsis, through several mechanisms. Of note, the progression to bacterial sepsis was increased by 6-fold in patients who presented with influenza pneumonia in a large American cohort.⁶⁶ Moreover, it seems that there might be some organism-specific interactions (with *S. aureus* and *S. pneumoniae*) that would potentially explain the higher incidence of the bacterial sepsis during epidemic and pandemic outbreaks of influenza. Interestingly, recent evidence indicates that antibiotics can alter the respiratory microbiome and increase the risk of infection and death by influenza viruses, at least in mouse models.⁶⁷ Prolonged use of broad-spectrum antibacterial agents can profoundly reduce the microbiome, resulting in a reduction in the constitutive secretion of Type 1 interferons. These animals now become at greater risk of lethality when animals are challenged with influenza viruses. It remains to be determined if a similar increase in susceptibility to influenza viruses exists in patients receiving prolonged courses of broad spectrum antibiotics.

Outcomes

Seasonal influenza epidemics cause an estimated average of 226000 hospitalizations and 36000 deaths per year, with most of the influenza-related deaths being the result of the exacerbation of an underlying condition or secondary to bacterial co-infections.^{68,69} During the first year of the pandemic 2009 H1N1, global mortality was estimated at 284500 cases, with a disproportionate number of deaths in southeast Asia and Africa.⁷⁰ If we look back at the previous influenza pandemics (H2N2 1890 Russian influenza, H2N2 1957 Asian influenza, and H3N2 1968 Hong Kong influenza), and yearly influenza epidemics, we can see U-shaped mortality curves with the highest death rates in the very young and the older patients.⁷¹⁻⁷⁵ Slightly different, the 1918 H1N1 Spanish and 2009 H1N1 pandemics showed that most mortality was seen in the very young and in the elderly, but it was also seen

in relatively healthy adolescents and adults, creating a W-shaped mortality curve.⁷⁵⁻⁷⁷ The time of adolescence and the onset of puberty generate substantial changes in the immune response of individuals and their intrinsic resistance to influenza-induced inflammation and death. While the majority (>80%) of deaths with typical seasonal influenza epidemics are estimated to occur in elderly (>65 y of age), those associated with the pandemic 2009 H1N1 strains were mainly in people younger than 65 y of age.⁷⁰ The mortality associated with influenza varies dramatically not only by season, but also by the predominant circulating influenza strains (H3N2, H1N1), as well as by how susceptible the population at risk is to these strains.⁶⁸ An influenza epidemiological model showed that influenza A (H3N2) viruses were associated with the highest attributable mortality rates, followed by influenza B and influenza A (H1N1) viruses.⁶⁸ Studies from Canada and Mexico described that patients with 2009 H1N1 influenza infection displayed symptoms for few days prior to hospitalization, then experienced rapid deterioration requiring ICU admission for respiratory failure within 1 to 3 d after admission; they also required more prolonged mechanical ventilation and vasopressors support.^{75,78} In contrast with seasonal influenza, previously healthy individuals, including healthy young adults, may develop severe disease with pandemic H1N1; up to 34% of the hospitalized patients required ICU admission due to respiratory failure.⁷⁹⁻⁸² A high proportion (64–96%) of pediatric and adult patients admitted to ICU with pandemic 2009 H1N1 required mechanical ventilation.^{75,78,83} Extrapulmonary complications such as renal failure, severe diarrhea, encephalopathy, myocarditis, hemophagocytosis, and multiorgan failure have been described in pandemic H1N1 influenza infections, and these complications have been attributed to high-level viral replication and cytokine dysregulation.^{78-81,84} The reported mortality rates in ventilated patients ranged from 8% to 50%.^{75,83,85,86} Pediatric patients with histories of complex medical conditions, higher PIM scores, and acute renal failure have poorer outcomes.⁸³ Adult patients who died were more likely to have higher APACHE II score at presentation, greater organ dysfunction (SOFA score, renal dysfunction, and thrombocytopenia), and to be female, particularly during pregnancy.^{75,78} APACHE II and/or SOFA scores might be helpful to identify the patients at risk for complicated course and death.⁷⁸ Obesity has also been found to be associated with poor outcomes in H1N1 infections,⁸⁷ and HIV-infected patients with pandemic influenza had higher morbidity and longer hospital stay.⁸⁸ The increased awareness during H1N1 pandemic may have led to earlier admissions to the hospital and ICU, lower threshold to start oseltamivir therapy, and more available immunization, all of which could explain the lower mortality reported in some centers.⁸⁹ In critically ill pediatric and adult patients, treatment with oseltamivir may have a positive impact on survival.^{83,90,91} Several studies showed that pro-inflammatory cytokine levels correlate with patients' outcome with severe influenza infections.^{64,92} Hall et al. showed that the serum pro-inflammatory cytokine levels in critically ill children with seasonal and pandemic 2009 H1N1 were significantly higher compared with those of outpatient control subjects.⁶⁴ Interestingly, the critically ill non-survivors were characterized by higher levels of serum pro-inflammatory mediators than critically

ill survivors.⁶⁴ However, critically ill non-survivors demonstrated marked impairment of the innate immune function characterized by leukopenia and impairment of ex vivo TNF- α production capacity; the degree of reduction in TNF- α production capacity (<250 pg/mL), and the severity of leukopenia (absolute monocyte count <288 cells/mm³) were highly predictive of mortality.⁶⁴ In an adult study in patients with severe pandemic 2009 H1N1 influenza pneumonia Lee et al. demonstrated sustained hyperactivation of the innate pro-inflammatory cytokines (IL-6, CXCL8/IL-8, CCL2/MCP-1, and sTNFR-1), and markedly suppressed adaptive Th1/Th17-immunity related cytokines (CXCL10/IP-10, CXCL9/MIG, and IL-17A).⁹² It is possible that in patients with severe influenza H1N1 cases, when cellular immunity is markedly impaired, further immunosuppression with steroids (used for treatment of sepsis, ARDS) could be potentially harmful.⁹²⁻⁹⁴ Several potential new therapy targets to decrease the influenza-related vascular leak are being currently evaluated in pre-clinical studies: Slit2N, doxycycline, vasculotide, activated protein C, atrial natriuretic peptide, and sphingosine-1-phosphate (S1P).⁹ Patients with influenza might benefit from a large number of immunomodulatory agents that target the host rather than the viral pathogen.⁹⁵

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Conclusions

Inflammatory response triggered by a severe influenza infection is a double-edged sword. It can effectively eliminate the infection, but a prolonged and excessive inflammatory response may result in poor outcomes. Influenza virus, like other viruses, displays significant interaction with the immune system, which can directly lead to severe sepsis or a secondary bacterial infection. This would raise important diagnostic and therapeutic questions: What biomarkers or biomarker-based algorithm would be useful to guide therapy? When (and if) adjunctive pro-inflammatory or anti-inflammatory agents would be beneficial for the treatment of severe influenza infections? Is there any role for INF- γ as an immune-stimulatory therapy in the early phases of severe influenza sepsis? Would GM-CSF therapy improve survival in critically ill and leukopenic patients with influenza? Sepsis directly and indirectly caused by influenza viruses requires substantial more basic and clinical research in order to improve today's diagnostic and therapeutic challenges.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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