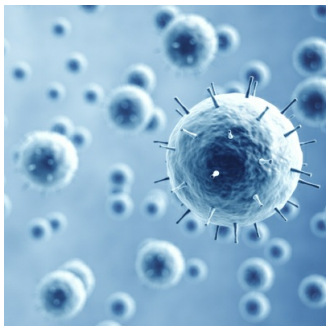
ICU
MANAGEMENT & PRACTICE

## Understanding the Influenza Virus



Diagnosis of the Influenza virus remains a challenge in the ICU. It is vital that knowledge of its pathophysiology and epidemiology is known so clinicians can make informed decisions regarding their patients' health.

The Influenza virus is found most commonly to replicate in the respiratory tract in humans. This is mainly due to the haemagglutinin (HA) which is cleaved in the respiratory epithelium, ultimately creating active virus particles. Influenza virus infection causes limited to no exchange of gas in the lungs. This can be as a result of several different symptoms caused by the virus including the airways being obstructed; alveolars in the lungs losing structure; the death of epithelial cells, ultimately leading to a loss in integrity; and extracellular matrix degradation. The latter of which being the most understudied and the pathway the least understood, even in healthy lungs.

As well as lung compromise and respiratory distress, lung inflammation is the most prominent pathophysiological feature of Influenza infection. This can either be caused by a direct viral infection or from the host immune response. If the lung inflammation is allowed to spread systemically, this can also lead to multi-organ failure. Cardiac sequelae is also a feature of Influenza infection and has linked the virus to increased risk of myocardial disease, although the mechanism behind this is still unknown.

## ARDS Caused by Influenza Virus

Acute respiratory distress syndrome (ARDS) is most commonly caused by Influenza A. It is the invasion of the epithelial cell lining that causes the severity of this infection. Once the epithelial cell lining has been breached the endothelial cells are exposed, releasing pro-inflammatory cytokines which are then able to trigger an immune response, both innate and adaptive. The physiological failure of the lungs is a result of the infectious response, either directly or passively through the subsequent damage.

Research for targeted therapies has therefore looked at inhibiting the downstream effects of the infection, with positive results found when targeting later in the response. For example, a mouse model of severe influenza infection showed that MT1-MMP collagenase inhibition led to decreased tissue damage and reports showed improved survival. These results were also mirrored in an influenza-pneumococcal co-infection.

As inflammation also contributes to the pathophysiology of Influenza infection, studies looking to target the innate immune pathways, decreasing amplification of immune signals, have also been popular. In a study, the activation of the inflammasome, an innate signalling complex, was suppressed by targeting NLRP3 (a vital protein for inflammasome signalling) and resulted in positive outcomes.

Also, studies have been conducted featuring the secondary cytokine and chemokine signalling pathways after inflammasome activation, as the neutrophils and monocytes recruited can be damaging to tissues. Blocking CXCR1/2 (needed for neutrophil recruitment) demonstrated the protection of murine infection models of influenza, Staphylococcus pneumoniae or a combined infection.

Further down the pathway, neutrophils can secrete extracellular traps (NETs) which amplify inflammation, this has also been studied for a target against Influenza infection. By depleting macrophages in a mouse model and allowing mainly neutrophils to infiltrate, the result of increased NETs led to increased acute lung injury. These circumstances are also seen in humans with severe Influenza disease.

The inhibition of mTOR, which reduces inflammasome activity, was found to suppress inflammation and led to positive outcomes against the pathophysiology of the infection. The effects of inhibiting the host response to infection on the severity of the disease shows how this plays a key role in severe influenza aetiology. As mTOR is involved with nutrient sensing, metabolic interventions must also be considered as a target for

treating Influenza virus infection. However, using metabolism to control viral infection has proven to be more complex, yielding different responses depending on the context. For example, the influence of the global metabolic state of a patient means that obese people are more likely to be susceptible to infection and lung injury. Although metabolic intervention comes with its challenges, the possibility remains that we may be able to inhibit viral metabolic pathways by targeting nutrients essential for the virus itself.

## From Influenza to Pneumonia and ARDS

The links between the Influenza virus and pneumonia are evident, with 30-40% of Influenza patients also being diagnosed with acute pneumonia. Some of the most common risk factors for this are patients who are either very young (<5 years) or the older patient (>65 years); patients of Caucasian descent; patients who reside in nursing homes; those with chronic lung and/or heart disease; and also, those with a history of smoking. Those most at risk may also be pregnant, extremely obese, or be of Native American descent or Alaska natives. However, pandemics of the Influenza virus have seen even previously healthy individuals outside of the parameters of these risk factors be admitted to the ICU due to pneumonia.

Previous studies have found that the statistics for Influenza-related ARDS for paediatrics or adults are not reliable. However, the main cause of ARDS is usually sepsis or it is brought about by a non-infectious aetiology (such as trauma, smoke inhalation or pancreatitis). The most common viruses to result in ARDS in paediatric patients are Influenza A and respiratory syncytial virus; while Influenza A is the most common cause in adults.

In adults, the main risk factors for obtaining ARDS from Influenza A are age (most common in the ages 36-55 years old), pregnancy and obesity. Whilst factors such as being female, having received the Influenza vaccine, and being infected with Influenza A (H3N2) or Influenza B proved to be protectors against contracting ARDS. Factors which increase the risk of fatality in these cases were with patients above the age of 55 and those with a higher infection severity score. In certain studies, it was found that the viral strain of infection could also be a risk factor, as the Influenza strain H7N9 was found to increase the patient's risk of ARDS. Also, during Influenza season, cardiac surgery could be a risk factor for influenza patients to contract ARDS if their surgery is conducted during this time.

There have been major difficulties in diagnosing pneumonia and ARDS, with 2/3 of Influenza patients not being clinically diagnosed. The link between pneumonia/ARDS and Influenza is normally only noted during an epidemic as it is difficult to distinguish between these infections solely based on their symptoms.

## Influenza and Sepsis

Due to their similar pathways, Influenza and bacterial sepsis present incredibly similarly. As the Toll-like receptors 2 and 4, found in gram-positive and gram-negative bacteria, have been linked to the pathogenicity of Influenza. However, the inflammatory response can vary. Influenza incidence has been found to increase the risk of secondary bacterial sepsis. Out of 1600 sepsis patients, 4% of cases were found to be caused by the Influenza virus.

## Viral-Bacterial Co-Infections

Viruses (such as Influenza, parainfluenza and coronavirus etc.) cause 1/3 of all community-acquired pneumonias (CAP). In 30-50% of adult and paediatric populations, these viruses are presented at the same time as bacterial CAP, and these co-infections were also found with 10-20% of patients with hospital-acquired pneumonia (HAP). As 2/3 of Influenza infections are not diagnosed, it is possible that up to 10-20% of sepsis patients could also be infected with a viral co-infection.

There is currently not enough evidence to stipulate whether co-infections lead to worse outcomes, however, the evidence is starting to suggest this is the case with results showing increased morbidity and mortality. For example, in a paediatric study, patients with a Staphylococcus aureus and an Influenza infection were found to have a nine-times increase in their risk of mortality.

As Influenza alters the lung environment (for example through alveolar macrophage depletion) this leaves patients more likely to be susceptible to bacterial co-infections. By triggering an inflammatory response, Influenza ultimately prompts the body's immune systems regulatory mechanism. As this suppressor activity is necessary to allow for tissue repair it also allows bacteria to bypass the immune system, increasing susceptibility to further infection.

## Rare Complications of Influenza Infection

Mostly occurring in children, acute myositis and rhabdomyolysis is a less common complication of infection with Influenza with patients with marked elevation of myoglobinuria and serum creatinine phosphokinase. Another clinical case observation has seen myocarditis and pericarditis in patients, but due to its rarity evidence has been shown in autopsy studies. The central nervous system has also been implicated due to Influenza infection in some cases, such as encephalitis, transverse myelitis, disseminated encephalomyelitis, aseptic meningitis and Guillain-Barre syndrome.

## Conclusion

In the ICU, it is important to suspect, and diagnose when possible, Influenza in ARDS, pneumonia and sepsis patients, especially during the winter. It is vital that precautions are met with patients presenting the typical symptoms and the atypical ones mentioned previously, and also with those with myocarditis, rhabdomyolysis and encephalitis.

Source: Critical Care

Image Credit: iStock

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