REVIEW

Seasonal respiratory viruses in adult ICU patients

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Abstract

Respiratory viruses are frequently detected in adult patients admitted to the intensive care unit (ICU) and are increasingly being recognised for their role as causal agents in severe respiratory tract infections. Diagnostic sensitivity and time to result have greatly improved with the advent of molecular diagnostics. However, the burden of viral respiratory tract infections in adults remains unclear, and challenges persist in the adequate interpretation of test results and clinical implications on the adult ICU, especially for non-influenza viruses. Many promising antivirals for influenza infection are in clinical development. This review describes the epidemiology, diagnostics, prevention, therapeutic interventions and clinical challenges of seasonal respiratory viruses in adult critically ill patients.

Introduction

Lower respiratory tract infections (RTIs) are the most deadly transmissible diseases worldwide.[1] After the influenza virus A (H1N1) pandemic in 2009-2010, which was associated with increased numbers of severe pneumonia with acute respiratory distress syndrome (ARDS) and multi-organ failure, recognition of respiratory viruses as causal agents in severe RTIs in adults

increased. In adult patients admitted to the intensive care unit (ICU), detecting respiratory viruses can have important implications for isolation measures, and rapid initiation of antiviral treatment in case of suspected or confirmed influenza infection.[2,3] With the advent of molecular diagnostics, detection of respiratory viruses has become rapid and highly sensitive. However, the burden of viral RTIs in adults remains unclear,[4] and challenges persist in the interpretation of test results and clinical implications on the ICU, especially for non-influenza viruses. This review describes the epidemiology, diagnostics, prevention, therapeutic interventions and clinical challenges of seasonal respiratory viruses in critically ill adult patients.

Epidemiology

In the general population viral RTIs are common, with over 260,000 cases of influenza-like-illness presenting to Dutch general practitioners each year.[5] On general hospital wards, seasonal respiratory viruses are detected in 15-29% of patients admitted with a community acquired pneumonia (CAP).[6-8] Respiratory viruses are highly contagious through contact and/or droplet transmission, and while most viruses can be detected year-round, they typically show seasonal epidemic peaks *(table 1)*. While viral infection in most adults typically leads to mild

Table 1. Characteristics of respiratory viruses

Virus	Typical peak**	Primary transmission	Incubation period	Infective period
Influenza virus	Winter	Large particle droplets	1-5 days	1 week
Respiratory syncytial virus	Winter	Large particle droplets, fomites	2-8 days	1 week*
Coronavirus	Winter (in cycles of 2-3 years)	Large droplets, fomites	2-10 days	First days after transmission
Human rhinovirus	Spring until Autumn	Aerosols, fomites	8 hours to 2 days	2-3 weeks*
Human metapneumovirus	Winter until Spring	Large droplets, fomites	5-6 days	Unknown
Adenovirus	Winter until Spring	Aerosols, fomites	1-12 days	Up to 2 weeks after start of symptoms
Parainfluenza virus	Depends on subtype	Large droplets, fomites	2-6 days	First days after transmission

* shedding up to several months has been observed in immunocompromised patients; ** infections can occur throughout the year

Table 2. Prevalence of respiratory virus detection in adult ICU patients

Author	Year	Diagnosis	n	Sample site	Total prevalence*	Influenza virus	Rhinovirus	Respiratory syncytial virus	Parainfluenza virus	Coronavirus	Human metapneumovirus	Adenovirus	Enterovirus	Bocavirus	Comments
Karhu[11]	2014	CAP	49	Nose and/or lung	49%	2%	31%	2%	2%	4%	0%	4%	4%	0%	
Hong[17]	2014	HAP	262	Nose and/or lung	23%	4%	6%	7%	7%	2%	1%	0%	0%	1%	Nose samples obtained in 66%, BAL in 41% of patients
Schnell[16]	2014	ARF	70	Nose and/or lung	49%	19%	9%	6%	3%	7%	6%	4%	-	-	
Wiemken[12]	2013	CAP	393	Nose	23%	23%	8%	?	10%	-	3%	?	-	-	
Østby[13]	2013	CAP or HAP	122	Throat	16%	8%	1%	2%	0%	2%	1%	1%	-	-	25% of samples obtained after ≥4 days of admission
Ong[18]	2013	ARF	158	Nose	18%	15%	-	4%	-	-	-	-	-	-	
Choi[14]	2012	CAP or HAP	198	Nose and/or lung	36%	6%	9%	5%	8%	2%	7%	1%	1%	0%	Nose samples obtained in 69%, BAL in 23% of patients
Cillóniz[15]	2011	CAP	362	Nose and/or lung	9%	?	?	?	?	?	-	?	?	-	Nose samples obtained in 50%, BAL in 49% of patients
Carrat[19]	2006	ARF	122	Nose	17%	7%	3%	5%	-	1%	2%	-	-	-	
Daubin[20]	2006	ARF	187	Lung	22%	4%	10%	1%	1%	1%	0%	1%	1%	-	Virus detection method differed between samples
Cameron[21]	2006	Exacerbation COPD	105	Nose	43%										
Legoff[36]	2005	CAP or HAP	41	Lung	32%	20%	0%	5%	5%	0%	0%	5%	0%	-	
Karhu[11]	2014	CAP	49	Nose and/or lung	49%	2%	31%	2%	2%	4%	0%	4%	4%	0%	0

* patients with more than 1 virus detected count as 1 virus-positive patient; - not tested; ? tested but not reported
ARF = acute respiratory failure; BAL = bronchoalveolar lavage; CAP = community acquired pneumonia; COPD = chronic obstructive pulmonary disease; HAP = hospital or healthcare associated pneumonia

and self-limiting disease, it may also cause critical illness and death. Seasonal respiratory viruses can cause primary viral pneumonia, are associated with coinfection and secondary bacterial pneumonia, and can cause exacerbations of chronic pulmonary and cardiac disease. Risk factors for complicated or severe influenza infection include age, chronic comorbidities such as chronic obstructive pulmonary disease (COPD), immunosuppression, pregnancy, and morbid obesity.[9] Although especially infants and the elderly are usually at risk, during the influenza A (H1N1) pandemic in 2009 another incidence peak of patients with severe illness was seen in young adults.[10] In contrast, risk factors for severe disease of non-influenza respiratory viruses are less well studied.

Prevalence in adult ICU patients
Several small observational studies in patients with severe CAP show detection rates of respiratory viruses between 9-49%

(table 2).[11-15] Although the extent of epidemic peaks may differ between viruses, seasons and regions, according to prospective studies influenza virus is generally found most often (in 2-23% of patients), followed by human rhinovirus (HRV), respiratory syncytial virus (RSV) and parainfluenza virus (PIV). However, there remains a paucity of data on the exact burden of respiratory viruses, as these studies are limited by small sample sizes,[11,13-16] and/or non-systematic screening (i.e. not all viruses were systematically tested).[13-15,17] Besides patients with CAP, also other patient groups in the ICU have been studied, showing a prevalence of 17-49% in unspecified acute (cardio)respiratory failure,[16,18-20] and 43-64% in patients admitted with an acute exacerbation of COPD.[16,21] Interestingly also in 23-43% of ICU patients admitted with a hospital or healthcare associated pneumonia (HAP) respiratory viruses are detected,[14,17] which is a group of patients commonly assumed not to be at risk for viral RTIs.

Influenza virus

Influenza viruses are single-stranded RNA viruses and belong to the family of Orthomyxoviridae. Influenza type A and B cause the typical influenza syndrome, with the distinction that type A can cause pandemics and type B does not. Influenza C infections are rare, and associated with mild and afebrile infections. An estimated 10-15% of the world population is infected with seasonal influenza type A and B each year,[22] with a peak of the annual epidemic between winter and early spring in the Netherlands.[23] Seasonal influenza causes an estimated 3-5 million severe infections worldwide (predominantly in risk groups) and a mortality of 250,000-500,000 patients each year.[24] Observational studies indicate a prevalence of 2-23% of influenza in patients admitted to the ICU with severe CAP.[11-14,18] The surface protein haemagglutinin is subject to a high rate of minor mutations which continuously leads to new variants (i.e. 'antigenic drift'). These new variants may escape prior acquired immunity and cause epidemics, and necessitate regular adjustment of the influenza vaccine. Influenza infection may cause diffuse interstitial shadowing and hypoxia,[22] and in the most severe cases patients may develop ARDS triggered by a virus-induced cytokine storm, even in previously healthy adults.[25] Often the abnormalities on chest X-ray appear less severe than one would expect based on the extent of hypoxia,[26] and clinical signs of typical influenza (fever, myalgia, headache and upper respiratory tract symptoms) may be absent in the elderly.[27,28] In addition to antigenic drift, also large numbers of amino acids can be substituted in the surface proteins, by combination of two influenza strains from, for example, humans and animals (i.e. 'antigenic shift'). This can give rise to variants against which there is no prior immunity in the population, or only in the elderly. The most recent influenza shift was the emergence of influenza A (H1N1) in 2009, which could cause ARDS and multi-organ failure especially in 30-60 year-olds and pregnant women.

Respiratory syncytial virus

Respiratory syncytial virus (RSV) is a single-stranded RNA virus in the *Paramyxoviridae* family, with subtypes A and B causing the majority of disease in humans. RSV infection is the most frequent cause of hospitalisation in children,[29] with a peak incidence similar to influenza in the winter season. The virus is detected in 2-7% of adults admitted to the ICU with severe pneumonia.[11,13,14,17,18] The infective period is typically 5-8 days after infection, however prolonged virus shedding for up to months has been observed in immunocompromised patients.[29] In previously healthy adults RSV infection infrequently results in hospital admissions. However, in the elderly and high-risk adults, a disease burden similar to that of seasonal influenza was observed with an estimated 16% of infections leading to hospital admission, and mortality of 8% in these patients.[30,31]

Human rhinovirus

Human rhinovirus (HRV) is a single-stranded RNA virus in the *Picornaviridae* family. HRV is the most frequent cause of the common cold, and detected in 25-50% of patients presenting with an upper RTI, across all age groups.[32] The virus causes infections throughout the year, with a peak incidence between spring and autumn, and the infective period can last up to 3 weeks. In patients admitted with severe CAP or HAP, HRV is found in 1-31%;[11-14,17] however, studies on the disease burden of HRV in adult patients admitted to the ICU are limited. In smaller studies mortality rates between 32-83% have been observed in patients after stem cell transplantation,[33,34] which suggests that the disease burden can be high in specific patients groups.

Human coronavirus

Human coronaviruses (HCoV) are enveloped RNA viruses belonging to the *Coronaviridae* family. Of all upper RTIs in adults, an estimated 15% is caused by HCoV.[35] The incidence of infection peaks in the winter season, and typically follows a cyclic pattern with epidemics every 2 to 3 years. In adults admitted to hospital with CAP the virus can be detected in 2-17% of cases, more often in the lower than in the upper respiratory tract.[6,8,35] The estimated prevalence in adults admitted to the ICU with severe pneumonia is 0-4%.[11,13,36] Seasonal coronavirus may cause pneumonia, mainly in high-risk groups, but the exact burden in adult ICU patients has not been investigated.[35] It is clear that there is a difference in virulence between different HCoV strains. The strain causing severe acute respiratory syndrome (SARS) between 2002 and 2004 had a mortality of 11%; however, it has not been detected since 2004.[37] In 2012 the 'Middle East respiratory syndrome coronavirus' (MERS-CoV) emerged, with currently 2037 confirmed cases and 710 related deaths. MERS-CoV appears to cause more severe disease in the elderly and those with chronic illness, and transfer between persons seems to be difficult unless there is close contact.[38]

Human metapneumovirus

Human metapneumovirus (hMPV) is an RNA virus belonging to the *Paramyxoviridae* family, and was discovered in 2001.[39] The virus causes respiratory infections in all age categories, with yearly epidemics between winter and spring, although the virus can be detected throughout the year, in both the upper and lower respiratory tract.[40] Clinical signs and symptoms may resemble those of RSV infection, although fever is not always present.[40] The burden of hMPV in adult ICU patients is unclear. Small observational studies show a prevalence of 0-7% in patients with CAP.[11,12,14,36] In stem cell transplantation patients mortality rates of up to 80% have been reported in the first weeks after transplantation.[41]

Adenovirus

Adenoviruses are double-stranded non-enveloped DNA viruses. They are often detected in patients with an upper RTI, and infections occur throughout the year with a peak between winter and spring.[42] The infective period is approximately 2 weeks after the start of symptoms; however, some patients may asymptomatically shed the virus for months. Adenovirus can cause different clinical syndromes, depending on the serotype: upper and lower RTIs, conjunctivitis, gastroenteritis, cystitis, meningitis and encephalitis.[43] In particular young children and immunocompromised patients have an increased risk of severe disease due to adenovirus infections, but septic shock and death may also occur in previously healthy subjects.[44,45] Observational studies in adult patients admitted to the ICU with CAP or HAP show a prevalence of 1-5%.[11,13,14,36] There is a paucity of data regarding the burden of adenovirus infections in adults, however studies in small cohorts show a mortality rate of up to 50% in immunocompromised patients.[46,47]

Parainfluenza virus

Parainfluenza virus (PIV) is a single-stranded RNA virus belonging to the family of *Paramyxoviridae* and has four subtypes. PIV-1 and PIV-3 are detected most frequently in humans, in autumn and in spring/summer respectively. PIV can cause both upper and lower RTIs, and severe disease is predominantly seen in children, the elderly and the immunocompromised.[48] There is a paucity of data regarding the burden of PIV in adults. In hospitalised adults with pneumonia the virus can be detected in up to 10% of cases;[49] observational studies in adult ICU patients show a prevalence between 0-10%.[11-14,17,36] Mortality rates are 6-8% in patients after lung or bone marrow transplantation.[50]

Challenges in assessment of burden of respiratory viruses in adult ICU patients

While there is no question about the pathogenicity of the influenza virus, it remains challenging to interpret the clinical significance of other respiratory viruses in adult ICU patients. Respiratory viruses can be detected in up to 15% of asymptomatic subjects,[51] it therefore remains unclear if a virus detected in an individual patient is associated with critical illness or merely an innocent bystander. Observational studies indicate that patients admitted with pneumonia in whom viruses are isolated have similar mortality rates to those with bacterial infections and mixed viral/bacterial infections.[13,14] However, these comparisons of crude mortality rates in small cohorts are not adjusted for confounding factors. Furthermore, these observational studies suffered from small sample sizes,[11,13,16] and/or incomplete diagnostic efforts.[13-15,17] Also, several studies rely on only upper airway sampling,[12-14,18,19,21] and it is unclear if virus detection in the upper airways reflects true viral illness in critically ill patients. Therefore, the attributable morbidity and mortality of non-influenza viral RTIs on the adult ICU remains to be determined.

Diagnostic testing

Techniques

The number of diagnostic methods to detect respiratory viruses has greatly increased over the last decade. Traditionally, viruses are isolated by cell culture and virus antigens detected by immunofluorescence. Cell culture is still considered the golden standard as it can isolate intact virus particles. While this method is highly specific, it can take several days up to two weeks to obtain results. Furthermore, several viruses, such as hMPV, are difficult to culture. Antigen tests are cheap and generally fast, but they lack sensitivity. The development of RT-PCR assays has greatly increased sensitivity, specificity and processing speed of virus detection, and many hospitals have since adopted this technique in monoplex or multiplex as their primary diagnostic method for screening. Nevertheless, interpretation of PCR results remains challenging, as it solely detects the presence of viral DNA or RNA, and not viable virus particles. The advent of real time semi-quantifiable PCR methods has provided an additional layer of information about the quantity. However, for many viruses there is still uncertainly about the association between viral load and disease severity.[52]

Challenges in practice of virus diagnostics

There is no consensus on which patients to test on the adult ICU for the presence of respiratory viruses, and which samples to use. Diagnostic guidelines, including the Surviving Sepsis Guidelines, advise to 'consider testing' in patients with CAP during local epidemics.[3,53,54] They, however, remain unclear as to whether all patients with CAP in the season should be tested, if patients with HAP or exacerbation of chronic lung and heart disease should be tested, and if testing a lower respiratory tract sample should be preferred to an upper respiratory tract sample if possible. It remains challenging to select a more specific patient group, because an accurate history of symptoms is difficult in critically ill patients, and typical influenza symptoms are often absent in a hospitalised population.[55] There is currently no clinical algorithm that can distinguish viral from bacterial pneumonia without microbiological testing.[56] As a consequence, viral infections may be missed due to lack of testing. Indeed, a large retrospective study from the USA estimates that 90% of cases of influenza infection on the adult ICU are either not diagnosed or not reported.[57] A prospective study in two Dutch centres shows that only 46% of ICU patients with severe CAP were tested by the attending staff for the presence of a respiratory virus during the winter season, and only 13% of patients admitted with HAP,[58] while the prevalence of influenza virus detection in this cohort was 14% and 10% respectively. As detection of influenza virus has consequences for treatment and quarantine measures, it is important to increase virus diagnostics in patients with suspected CAP or HAP during the winter season.

Preventive measures

Vaccination

Annual influenza vaccination is a cornerstone of preventive medicine, and is offered to risk groups for severe disease and healthcare workers. In the Netherlands the vaccine consists of inactivated influenza virus containing the three strains predicted to circulate most dominantly in the next season. While vaccine efficacy varies from year to year,[59-63] on average vaccination reduces the chances of acquiring infection from 10% to approximately 2-3% per season,[64] and has been shown to reduce acquisition of secondary bacterial infections.[65] Furthermore, vaccination of healthcare personnel is also an effective preventive measure to enhance patient safety: a systematic review of several cluster randomised trials and observational studies shows that personnel vaccination is associated with a reduction of influenza-like-illness and all-cause mortality in patients.[66] For children in high-risk groups for RSV infection, passive immunisation with palivizumab is available, and currently several clinical studies are being conducted with RSV vaccines[29] in children, pregnant women and the elderly.[67]

Isolation measures

Infection prevention measures are crucial to prevent transmission of viruses and bacteria between patients. Several ICUs in the Netherlands have adopted continuous barrier isolation with gowns and glove use for all patient contact during their stay. For viral RTIs in adults, the current Dutch isolation guidelines indicate droplet isolation for suspected and confirmed influenza infections and both droplet and contact isolation for adenovirus infections.[68] Some ICUs also have local guidelines recommending infection prevention measures for hMPV, RSV and PIV. Factors influencing duration of isolation include resolution of symptoms and duration of viral shedding. Severity of primary influenza infection is associated with prolonged shedding of influenza virus,[69] with observed shedding over three weeks. There is, however, a paucity of data regarding shedding dynamics in adult ICU patients, especially for non-influenza viruses.

Treatment

Registered treatment options for viral RTIs in adults are currently very limited. For confirmed or strongly suspected influenza infection it is recommended to start a neuraminidase inhibitor as soon as possible.[70] Neuraminidase is an enzyme that plays a key role in releasing newly formed influenza virus from the cell surface, which is an important step for the virus in order to invade other cells. For this reason it has been suggested that administration of the neuraminidase inhibitor should be as soon as possible, before too many cells are infected by the virus. Oral oseltamivir is often the first choice, and in case of oseltamivir resistance or allergy, zanamivir inhalation can be started in non-intubated patients. In intubated patients with severe gut dysfunction and/or infection with oseltamivir-resistant influenza virus, intravenous zanamivir can be considered. Another group of antivirals are the adamantanes (e.g. amantadine, rimantadine), which are ion channel blockers, but these are no longer recommended because of high resistance profiles in circulating strains. Oseltamivir and zanamivir have been shown to be effective in reducing the duration of illness, virus shedding and disease severity and complications, and suggest most benefit if started within 48 hours after onset of symptoms.[71,72] There is, however, ongoing discussion about their effectiveness in severe influenza infections and start of treatment more than 48 hours after onset, as the use in this population has not been properly investigated and neuraminidase inhibitor use on the adult ICU is in fact off-label. Nevertheless, in critically ill patients with proven influenza, antiviral treatment is usually commenced even if symptoms have started more than 48 hours previously. Although strong evidence is lacking, five days of antiviral treatment is the usual recommended duration. Nevertheless, longer treatment durations can in some cases be deemed necessary in severely ill or immune compromised patients. In these cases consultation with a clinical virologist or clinical microbiologist is recommended. The most frequently used dose is 75 mg twice daily. There is some discussion regarding the possible benefit of using 150 mg twice daily in ICU patients, which originated from animal studies.[73] However, evidence supporting this higher dose is as yet lacking as clinical studies were unable to show a clinical outcome benefit when higher doses were used.[74,75]

In the USA, Japan and South Korea intravenous peramivir is registered, and in Japan laninamivir. There is hesitance for registry in other countries, as studies for these newer neuraminidase inhibitors have shown effects on viral shedding, but not on clinical outcomes.[76,77]

In addition to neuraminidase inhibitors, many promising antivirals for influenza infection are in clinical development. These include sialidases, such as Fludase/DAS181,[78] nitazoxanide,[79,80] polymerase inhibitors such as pimodivir,[81] favipiravir[82] and S-033188,[83] as well as broadly neutralising antibodies with the potential to target multiple current and hopefully future strains of influenza.[84-86] Furthermore, multiple mechanisms of action targets provide opportunities for combination therapies.[87] Many of these drugs are in phase II or phase III RCTs, with results expected in the coming year.[88]

In severe influenza infection it is not recommended to use systemic corticosteroids, unless indicated for other reasons.[70] Recently, a Cochrane meta-analysis of observational studies showed no association between the use of corticosteroids and clinical outcomes, while an association with a higher prevalence of secondary bacterial infection was observed.[89] However, as the analyses only included observational studies, the quality of data remains low.

For other viruses, there are no registered treatment options for adults. For children with severe RSV infection ribavirin is

recommended, and some small studies suggest positive effects in adults as well.[90] Currently, several clinical studies in RSV are planned or ongoing with entry inhibitors such as Anti-F mAB,[91] fusion and non-fusion inhibitors,[92] and replication inhibitors.[93,94]

Conclusions

Respiratory viruses are frequently found in patients admitted to the ICU with CAP, but also in those with other reasons of admission, including HAP and exacerbation of chronic respiratory or cardiac disease. Interestingly, screening for the presence of respiratory viruses in this latter group of patients is still uncommon practice. The advent of molecular diagnostics has enabled sensitive and rapid detection of respiratory viruses, however challenges remain in the interpretation of positive findings in critically ill patients. In at least a proportion of patients, viral pathogens are associated with critical illness, and future studies may help in identifying causal relationships. The development of diagnostic algorithms based on RT-PCR may aid in improving antibiotic stewardship and infection control measures. Many promising new antivirals, especially for influenza, are currently in phase II or phase III studies, and may reduce the burden of viral RTIs in the future.

Disclosures

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