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NARRATIVE REVIEW

Critical care management of adults with community-acquired severe respiratory viral infection

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Abstract

With the expanding use of molecular assays, viral pathogens are increasingly recognized among critically ill adult patients with community-acquired severe respiratory illness; studies have detected respiratory viral infections (RVIs) in 17–53% of such patients. In addition, novel pathogens including zoonotic coronaviruses like the agents causing Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS) and the 2019 novel coronavirus (2019 nCoV) are still being identified. Patients with severe RVIs requiring ICU care present typically with hypoxemic respiratory failure. Oseltamivir is the most widely used neuraminidase inhibitor for treatment of influenza; data suggest that early use is associated with reduced mortality in critically ill patients with influenza. At present, there are no antiviral therapies of proven efficacy for other severe RVIs. Several adjunctive pharmacologic interventions have been studied for their immunomodulatory effects, including macrolides, corticosteroids, cyclooxygenase-2 inhibitors, sirolimus, statins, anti-influenza immune plasma, and vitamin C, but none is recommended at present in severe RVIs. Evidence-based supportive care is the mainstay for management of severe respiratory viral infection. Non-invasive ventilation in patients with severe RVI causing acute hypoxemic respiratory failure and pneumonia is associated with a high likelihood of transition to invasive ventilation. Limited existing knowledge highlights the need for data regarding supportive care and adjunctive pharmacologic therapy that is specific for critically ill patients with severe RVI. There is a need for more pragmatic and efficient designs to test different therapeutics both individually and in combination.

Keywords: Acute respiratory distress syndrome, Influenza, Neuraminidase inhibitor, Antiviral therapy, Coronavirus, Antiviral therapy

Introduction

With the expanding use of molecular assays, viral pathogens are increasingly detected among critically ill adult patients with respiratory illness; studies have reported a prevalence between 17% and 53% of patients (Table 1), depending on study design, sample type, duration of illness, and assay methods. Common viruses that can cause severe respiratory viral infections (RVIs) include influenza A and B viruses, picornaviruses (rhinovirus, enterovirus [e.g., enterovirus D68]), human coronaviruses (229E, NL63, OC43, HKU1), respiratory syncytial virus (RSV), human metapneumovirus, parainfluenza virus, and adenovirus (Tables 1 and 2). Novel pathogens including zoonotic coronaviruses like the agents causing Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS) and the 2019 novel coronavirus (2019 nCoV) are still being identified (Table 2).

Establishing causation between viruses detected in respiratory specimens and the clinical illness is sometimes difficult, because (1) detection of some agents

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(e.g., picornaviruses) in the upper respiratory tract may indicate asymptomatic or mild infection, (2) upper respiratory tract samples may be negative despite positive lower respiratory tract ones, and (3) secondary bacterial and less often fungal infections are commonly co-identified [1]. However, it is generally believed that most respiratory viruses by themselves can cause severe illness, especially so in the elderly, persons with co-morbidities (particularly immunosuppression), and occasionally in previously healthy persons, in addition to predisposing to secondary infections [2].

The objective of this narrative review is to outline current knowledge on the management of adults requiring ICU admission for community-acquired severe acute respiratory infection (SARI) due to RVIs. This review focuses on viral pathogens transmitted via the respiratory route. Respiratory infections with other viral pathogens, such as cytomegalovirus and herpes simplex viruses, are not discussed in this review.

Antiviral therapy

Generally available antiviral agents for different RVIs are summarized in Table 3 [3]. Very few randomized-controlled trials have been completed in patients hospitalized for severe RVIs; recently completed trials of nitazoxanide in SARI patients and of the RSV inhibitor presatovir in adult RSV patients yielded negative results [4, 5]. Antiviral therapeutics for influenza have been studied most extensively and are discussed briefly below. A number of other antiviral agents for influenza, RSV, and other RVIs are advancing in clinical study [6]. Controlled studies of lopinavir/ritonavir combined with interferon-beta in hospitlized MERS patients (NCT02845843) and of lopinavir/ritonavir and interferon-alpha 2b in hospitalized 2019-nCoV patients (ChiCTR2000029308) are currently in progess.

Neuraminidase inhibitors

Among the neuraminidase inhibitors (NAIs), oral oseltamivir is the most widely available agent. In an individual participant data meta-analysis of hospitalized patients with influenza A(H1N1)pdm09 virus infection ($n = 29\,234$ patients from 78 studies), NAI treatment (almost exclusively oseltamivir) was associated with a reduction in mortality compared with no treatment, including in the subgroup of ICU patients. Early treatment (within 2 days of symptom onset) was associated with a reduction in mortality compared with later treatment [7]. Observational data also indicate reduction in influenza A(H5N1)-associated mortality with timely oseltamivir treatment before the onset of respiratory failure [8]. The importance of timing of oseltamivir treatment has been demonstrated in an observational study of 1950 patients admitted to ICUs with influenza A(H1N1) pdm09, which showed a trend toward improved survival for those treated earliest [9]. Nevertheless, the Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA) recommends oseltamivir for all hospitalized patients with influenza, regardless of illness duration prior to hospitalization [10].

Take-home message

Evidence-based supportive care is the mainstay for management of severe respiratory viral infection.
Early treatment with neuraminidase inhibitors is associated with reduced mortality in severe influenza.
There is a need for pragmatic and efficient trial designs, to test a variety of investigational therapeutics, individually and in combination.

In observational studies of critically ill patients with influenza, higher compared to standard doses of oseltamivir did not demonstrate benefit [11–13]. An RCT of standard versus double-dose oseltamivir in hospitalized children and adults found no advantage with respect to virologic and clinical endpoints [14]. Additionally, a study demonstrated accumulation of oseltamivir in patients on both extracorporeal membrane oxygenation and continuous venovenous hemodiafiltration leading to 4-to 5-fold increase in plasma levels [15]. The IDSA recommends against the routine use of higher doses of US Food and Drug Administration-approved NAI drugs for the treatment of seasonal influenza [10].

Duration of treatment is traditionally 5 days, but treatment duration is often extended to 10 days for severely ill patients with ARDS or pneumonia or those who are immunocompromised [10]. This approach is supported by data showing slow influenza viral clearance from the lower respiratory tract in critically ill patients with influenza A(H1N1)pdm09 [16]. Of concern is the recent observation of emergence of oseltamivir resistance in 23% of 22 critically ill A(H1N1)pdm09 patients, and its association with persistent virus detection and much higher mortality [17].

Nebulized zanamivir solution has been administered to mechanically ventilated patients on compassionate use basis, but the commercial formulation contains lactose and should not be used for nebulization, because its use has been associated with blockage of the ventilator circuit.

Peramivir is the only intravenous influenza antiviral agent currently approved by the US Food and Drug Administration (FDA). Intravenous zanamivir has been recently approved by the European Medicines Agency (EMA) (Table 3). These agents appear to have comparable activity to oseltamivir in hospitalized

Table 1 Prevalence of community-acquired respiratory viral infections (RVIs) in critically ill patients

Study	Population	Patients (*N*)	Samples	Country	Assays	Overall prevalence or RVI	Influenza	Picornaviruses (rhinovirus, enterovirus)	Human coronaviruses (229E, NL63, OC43, HKU1)	Respiratory syncytial virus	Human metapneumovirus	Parainfluenza virus	Adenovirus
Daubin 2006	IMV for > 48 h	187	TA	France	Viral culture, IFA, NAAT	32 (17%)	Influenza A 7 (4%)	Rhinovirus 19 (10%) Enterovirus 2 (1%)	1 (0.5%)	2 (1%)	0 (0%)	1 (0.5%)	1 (0.5%)
Cameron 2006	COPD exacerbation requiring NIV or IMV	105	PS	Australia	IFA, viral culture, NAAT, serology	46 (43%)	Influenza A 14 (13%) Influenza B 6 (6%)	Rhinovirus 7 (7%) Enterovirus 2 (2%)	3 (3%)	7 (7%)	3 (3%)	11 (10%)	0 (0%)
Schnell 2014	Acute respiratory failure	70, 47 (67%) mechanically ventilated	PS, BAL	France	IFA, NAAT	34 (49%)	Influenza A 11 (16%) Influenza B 2 (3%)	Rhinovirus 6 (9%)	5 (7%)	4 (6%)	4 (6%)	1 (1%)	3 (4%)
Legoff 2005	Acute pneumonia admitted to ICU	41	BAL	France	Viral culture, IFA, NAAT	13 (32%)	Influenza A 7 (17%) Influenza B 1 (2%)	0 (0%)	0 (0%)	2 (5%)	0 (0%)	2 (5%)	2 (5%)
Wiemken 2013	Severe CAP admitted to ICU	468, 84% adults	PS	USA	NAAT	106 (23%)	Influenza 38 (8%)	Rhinovirus 40 (9%)	0 (0%0	8 (2%)	15 (3%)	4 (1%)	1 (0.2%)
Karhu 2014	Severe CAP	49	PS, BAL, TA	Finland	NAAT	24 (49%)	1 (2%)	Rhinovirus 15 (30%) Enterovirus 2 (4%)	2 (4%)	1 (2%)	0 (0%)	1 (2%)	4 (8%)
Tramuto 2016	ILI admitted to ICU	233	PS, BAL	Italy	NAAT	102 (44%)	57 (24%)	Rhinovirus 7 (3%) Enterovirus 14 (6%)	11 (5%)	8 (3%)	16 (7%)	16 (7%)	0 (0%)
Choi 2019[a]	Severe CAP admitted to ICU	1559	PS, BAL	Republic of Korea	NAAT	Not reported	109 (7.0%)	Rhinovirus 120 (8%)	56 (4%)	52 (3%)	50 (3%)	71 (5%)	Not reported
Shorr 2018	Severe CAP and HCAP requiring IMV	364	sputum, TA, BAL	USA	NAAT	65 (18%)	Influenza A 12 (3%) Influenza B 1 (0.3%)	Rhinovirus/ Enterovirus 20 (5%)	Not reported	11 (3%)	8 (2%)	7 (2%)	6 (2%)
Legoff 2018	Hematology patients admitted to ICU	747	PS	France	NAAT	163 (22%)	20 (3%)	92 (12%)	22 (3%)	18 (2%)	4 (0.5%),	12 (2%)	5 (0.6%)

Table 1 (continued)

Study	Population	Patients (*N*)	Samples	Country	Assays	Overall prevalence or RVI	Influenza	Picornaviruses (rhinovirus, enterovirus)	Human coronaviruses (229E, NL63, OC43, HKU1)	Respiratory syncytial virus	Human metapneumovirus	Parainfluenza virus	Adenovirus
Voiriot 2016	Severe CAP admitted to ICU	174	PS, TA, BAL	France	NAAT	93 (53%)	Influenza A 32 (18%) Influenza B 6 (3%)	Rhinovirus/ Enterovirus 22 (13%)	14 (8%)	9 (5%)	12 (7%)	3 (2%)	3 (2%)
Arabi 2018	Severe acute respiratory infection admitted to ICU	222	PS, TA, BAL	Saudi Arabia	NAAT	43 (19%)	Influenza A 29 (13%) Influenza B 3 (1%)	Rhinovirus 9 (4%) Enterovirus 0 (0%)	5 (2%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)

Overall prevalence is reported here for influenza, picornaviruses (rhinovirus, enterovirus), human coronaviruses (229E, NL63, OC43, HKU1), respiratory syncytial virus, human metapneumovirus, parainfluenza virus, and adenovirus. Please refer to the online supplement for references. Studies varied in the approach for sampling and in the used assays; in some studies, specimen collection and assays were standardized across all patients, while in other studies, sampling and assays were performed selectively. All percentages represent % of patients; some patients had more than one viral pathogen isolated

IMV invasive mechanical ventilation, *TA* tracheal aspirate, *IFA* immunofluorescence assay, *NAAT* (nucleic acid amplification test) includes commercial and in-house PCR, RT-PCR, and PCR multiplex, *COPD* chronic obstructive pulmonary disease, *NIV* non-invasive ventilation, *PS* nasopharyngeal specimen including nasopharyngeal or oropharyngeal aspirates or swabs, *BAL* bronchoalveolar lavage, *CAP* community-acquired pneumonia, *ILI* influenza-like illness, *HCAP* healthcare-associated pneumonia

[a] Multiple publications exist from the same cohort. We included the most recent one (Supplementary references)

influenza patients, although one RCT comparing two dose levels of intravenous zanamivir to oral oseltamivir found trends toward shorter illness duration in the subset of ICU patients given higher dose intravenous zanamivir [18]. One the other hand, one RCT failed to demonstrate a clinical benefit with intravenous peramivir in hospitalized patients with influenza [19]. Because its spectrum of activity includes most oseltamivir-resistant viruses, intravenous zanamivir is indicated for treatment of severe influenza A or B when the patient's influenza virus is known or suspected to be resistant to anti-influenza antivirals other than zanamivir, and/or other antivirals, including inhaled zanamivir, are not suitable (Table 3).

Baloxavir

Two phase III trials in non-hospitalized patients with influenza found that single-dose baloxavir was superior to placebo in alleviating influenza symptoms, and was superior to both oseltamivir and placebo in reducing viral replication [20, 21]. Baloxavir is inhibitory for strains resistant to current agents. However, high frequencies of emergence of variants with reduced susceptibility have been observed during monotherapy. A double-blind RCT comparing oseltamivir to the combination of oseltamivir and baloxavir is currently in progress in hospitalized patients (NCT03684044). Data on baloxavir's pharmacokinetics and optimal dose regimen in critical influenza illness leading to ICU admission are needed [20]. At present, baloxavir is approved in the US, Japan, and over ten other countries.

Adjunctive pharmacologic interventions

A wide variety of agents have been proposed for managing immunopathologic host responses that contribute to the pathogenesis of severe RVIs [6]. As summarized below, those that have progressed to clinical study include macrolides, corticosteroids, cyclo-oxygenase2 inhibitors, mTOR inhibitors like sirolimus, statins, and high-dose vitamin C. However, until further evidence becomes available, these agents should not be used for managing severe RVIs unless there is another indication or as part of a clinical trial.

Macrolides

Macrolide antibiotics, due to putative anti-inflammatory and possible antiviral effects, have been studied in patients with RVIs but with inconsistent results. In an open-label RCT of hospitalized patients with influenza ($n=107$), early combination therapy with clarithromycin, naproxen, and oseltamivir was associated with reduced mortality and hospital length of stay compared to oseltamivir monotherapy [22]. On the other hand, in a multicenter observational study ($n=733$), macrolides

Table 2 Common and uncommon community-acquired respiratory viruses that may cause severe respiratory viral infection

Virus	Epidemiologic and clinical features	Additional infection control precautions[a]
Common respiratory viruses		
Influenza A and influenza B	Only influenza type A viruses are known to have caused pandemics Currently circulating seasonal influenza A viruses in humans: subtype A(H1N1)pdm09 and A(H3N2) strains Currently circulating influenza B viruses: A/Victoria-like, A/Yamagata-like strains May be associated with acute myocardial infarction, myocarditis, rhabdomyolysis, acute renal failure, encephalopathy/encephalitis, and other non-pulmonary complications	Droplet
Picornaviruses (rhinovirus, enterovirus)	Frequently detected in critically ill patients with severe acute respiratory infection. May cause severe illness in the elderly, persons with co-morbidities including immunosuppression.	Droplet
Human coronaviruses (229E, NL63, OC43, HKU1)		Contact
Respiratory syncytial virus		Contact
Human metapneumovirus		Contact
Parainfluenza (1-4)		Contact
Adenoviruses		Droplet + contact
Uncommon and emerging viruses		
Avian influenza A/H5N1, A/H5N6, A/H7N9 and other subtypes	Residence in or travel to Southeast and East Asia Exposure to poultry or visit to poultry market	Airborne + contact
MERS-CoV	Residence in or travel to the Arabian Peninsula Exposure to dromedary camel (in endemic areas) Nosocomial transmission risk to other patients and to healthcare workers	Airborne + contact
SARS-CoV	No cases have been reported since 2004 Nosocomial transmission risk to other patients and to healthcare workers	Airborne + contact
2019 Novel coronavirus (2019 nCoV)	As of February 4, 2020, 20630 cases were reported from China and 23 other countries	Droplet + contact and wherever possible airborne[b]
Measles[c]	Incomplete vaccination Characteristic rash. Progressive giant cell pneumonia without rash may occur in immunocompromised (Hecht's pneumonia)	Airborne
Hantaviruses (e.g., Sin Nombre, Andes)[c]	Residence in or travel to affected areas of North, Central, or South America Exposure to rodent excretions particularly when cleaning buildings	Standard
Varicella-zoster virus[c]	Incomplete vaccination, pregnancy Often with characteristic rash	Airborne + contact

Please refer to the online supplement for references

Infection control precautions are based on the Centers for Disease Control and Prevention at: https://www.cdc.gov/infectioncontrol/guidelines/isolation/appendix/type-duration-precautions.html#M, https://www.cdc.gov/coronavirus/mers/infection-prevention-control.html, https://www.cdc.gov/infectioncontrol/guidelines/isolation/appendix/standard-precautions.html, https://www.cdc.gov/flu/professionals/infectioncontrol/healthcaresettings.htm (all accessed on Dec 10-2019)

[a] All suspected or confirmed RVIs require minimum of standard precautions. Eye protection is a reasonable addition to droplet isolation as the ocular route of infection has been documented for several common respiratory viruses

[b] Data on the novel coronavirus are based on the WHO interim report as of February 4, 2020

[c] Other viral pathogens with respiratory routes of acquisition

were not associated with improved survival in critically ill patients with influenza A(H1N1)pdm09 [23]. In patients with MERS ($n=349$), macrolide therapy is not associated with a reduction in 90-day mortality or improvement in MERS-CoV RNA clearance [24]. A study of clarithromycin combined with the cyclooxygenase inhibitor flufenamic acid in hospitalized patients with influenza is underway (NCT03238612). In addition, macrolides are also examined in one of the domains of the REMAP-CAP trial (Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia, NCT02735707).

Corticosteroids

Data on the use of corticosteroids in severe RVIs are largely observational. Several studies demonstrated the association of corticosteroid use with mortality, bacterial and fungal infection and the emergence of antiviral resistance in influenza-associated pneumonia or ARDS [25]. A study ($n=607$) that accounted for time-dependent

Table 3 Antiviral agents for community-acquired respiratory viral infections (RVIs) and relevance to critically ill patients

	Mechanism of action	Target Virus	Resistance	Formulation	Applicability to critically ill patients
Amantadine	M2 ion channel blockers	Influenza A	High levels of resistance	Oral	Not recommended
Rimantadine	M2 ion channel blockers	Influenza A	High levels of resistance	Oral	Not recommended
Oseltamivir	Neuraminidase inhibitor(NAI)	Influenza A and B	Uncommon (1-3% of circulating isolates) but higher for treatment-emergent in critically ill and immunocompromised	Oral	Needs dose adjustment in patients with renal impairment No dose adjustment is necessary in patients with mild to moderate hepatic impairment Extemporaneous formulation possible or gastric delivery in intubated patients
Zanamivir	NAI	Influenza A and B	Rare	Intravenous; nebulized solution (investigational); inhaled dry powder (commercial formulation)	Inhibitory for most strains resistant to oseltamivir Nebulized formulation (investigational) with limited use in severely ill patients Limited systemic absorption and distribution to extrapulmonary sites of inhaled commercial product Lactose-containing powder commercial preparation with lactose carrier should not be given nebulized as it may cause ventilator circuit obstruction Intravenous formulation similar in efficacy to oseltamivir in hospitalized patients. Intravenous zanamivir is approved by the European Medicines Agency (EMA)
Peramivir	NAI	Influenza A and B	Uncommon (see oseltamivir above)	Intravenous	Intravenous formulation (multiple doses) similar in efficacy to oseltamivir in hospitalized patients Peramivir is approved by the FDA and EMA for uncomplicated influenza
Laninamivir	NAI	Influenza A and B	Rare	Inhaled, single dose, long acting	Not suitable for mechanically ventilated patients. Approved in Japan only
Favipiravir	Polymerase inhibitor (PB1 transcriptase), viral mutagen	Influenza A, B and other RNA viruses	Not seen in clinical strains	Oral	Under study in hospitalized patients in combination with NAIs Teratogenicity risk PK altered in critically ill with reduced drug exposure– appropriate dose regimen uncertain Approved only for stockpiling in Japan
Baloxavir	Polymerase inhibitor (PA cap-dependent endonuclease)	Influenza A, B	Treatment-emergence resistance common with monotherapy	Oral	Under study (multiple-dose) in combination with NAIs in hospitalized patients Not studied and PK uncertain in critically ill patients Inhibitory for strains resistant to M2Is and/or NAIs At present, baloxavir is approved in the US, Japan, and over eight other countries
Nitazoxanide	Host-directed and influenza HA	Influenza and other RVIs	Not seen in clinical strains	Oral	Not effective in hospitalized SARI patients. Not recommended.
Ribavirin	Host-directed effects, transcriptase inhibitor, viral mutagen	RSV, influenza, measles other RVIs	Not seen in clinical strains	Aerosolized, oral, intravenous (investigational)	Aerosol formulation approved in RSV-infected children but of uncertain value. All 3 formulations have been used in treating RSV-infected HSCT and SOT patients Anecdotal use of systemic ribavirin in severe measles and other paramyxovirus infections Not recommended in combination with interferons for MERS Teratogenicity risk Aerosol delivery presents risk of healthcare worker exposure

Table 3 (continued)

	Mechanism of action	Target Virus	Resistance	Formulation	Applicability to critically ill patients
Cidofovir	DNA polymerase inhibitor	Adenovirus		Intravenous	Anecdotal use in severe adenovirus infections and in immunocompromised patients
Acyclovir	DNA polymerase inhibitor	VZV, HSV	Uncommon except in immunocompromised	Intravenous, oral	Intravenous recommended in VZV pneumonia; addition of systemic corticosteroids recommended by some experts

Please refer to the online supplement for references

SARI severe acute respiratory infection, *RSV* respiratory syncytial virus, *HSCT* hematopoietic stem-cell transplantation, *SOT* solid-organ transplantation, *MERS* Middle East Respiratory Syndrome, *VZV* varicella-zoster virus, *HSV* herpes simplex virus, *NAI* neuraminidase inhibitors, *EMA* European Medicines Agency, *FDA* Food and Drug Agency

patient-level confounders found no independent influence of corticosteroids on mortality of influenza [26]. The IDSA recommends against corticosteroid adjunctive therapy in patients with influenza unless clinically indicated for other reasons [10]. In a study of patients hospitalized with RSV ($n=50$), corticosteroid therapy was not associated with significant differences in peak viral load, duration of RSV shedding, nasal cytokines, or lymphocyte subsets, although antibody responses to RSV were slightly blunted [27]. In one randomized-controlled trial that included 16 non-ICU SARS patients, "early" (< 7 days of illness) hydrocortisone therapy was associated with a higher subsequent plasma viral load [28]. In a study on MERS patients ($n=309$), corticosteroid therapy was not associated with significant change in 90-day mortality after adjustment for time-varying confounders, but was associated with delayed MERS-CoV RNA clearance [29].

Cyclooxygenase-2 inhibitors

Cyclooxygenase-2 may modulate excessive pro-inflammatory responses in severe influenza [30]. In addition to the above study of naproxen–clarithromycin added to oseltamivir [23], preliminary results from a RCT ($n=120$) showed that the combination of celecoxib-oseltamivir compared to oseltamivir alone reduced mortality and cytokine levels, although not viral titers, in hospitalized influenza A(H3N2) patients without increased adverse effects [31].

Sirolimus

Inhibitors of the mTOR pathway like sirolimus combined with oseltamivir have shown inconsistent effects in murine models of severe influenza [32, 33]. Sirolimus also can modulate inflammatory responses through its immunosuppressive properties [34]. In a small RCT ($n=28$), treatment with sirolimus compared to no sirolimus in patients with influenza A(H1N1) pneumonia receiving invasive mechanical ventilation (in addition to oseltamivir and corticosteroids) resulted in improvement in hypoxia, multiple organ dysfunction and virus clearance, and in shorter duration of mechanical ventilation [34]. Further study of sirolimus without systemic corticosteroids is planned among patients hospitalized with influenza (NCT03901001).

Statins

Because of the putative anti-inflammatory effects, statins have been proposed as adjunctive therapy in influenza (NCT02056340), although large clinical trials in patients in ARDS have not demonstrated clinical benefit [35]. A secondary analysis of data from RCTs using latent class analysis suggested that patients with ARDS may be classified into hyper-inflammatory and hypo-inflammatory

subphenotypes, and treatment with simvastatin compared to placebo was associated with improved survival in the hyper-inflammatory but not in the hypo-inflammatory subphenotype [36]. Further studies are needed to examine whether adjunctive pharmacologic interventions would be beneficial in targeted subphenotypes of severe RVI.

Immune therapy

Studies in which various antibody immunotherapies have been added to neuraminidase inhibitor treatment in hospitalized influenza patients have yielded inconsistent results. A small randomized-controlled trial ($n=35$) demonstrated that treatment of severe influenza A(H1N1)pdm09 patients with hyperimmune globulin (H-IVIG) containing high titers of virus-specific neutralizing antibodies within 5 days of symptom onset was associated with a lower viral load and reduced mortality compared to low-titer IVIG [37]. Two recent phase III trials have been completed in seasonal influenza patients. The FLU-IVIG RCT found no overall effect of anti-influenza hyperimmune IVIG compared to placebo on the primary outcome measured by a six-point ordinal scale of clinical status on day 7, although antiviral and clinical benefits were noted in the subgroup of patients with influenza B virus infection [38]. The second trial of high-titer versus low-titer anti-influenza immune plasma was terminated for futility because of the lack of effect on the same primary outcome [39]. A placebo-controlled, randomized trial of the anti-hemagglutinin stem monoclonal antibody MHAA4549A did not demonstrate benefit over oseltamivir alone [6]. The results from these recent trials suggest that polyclonal antibody therapies may not significantly improve outcomes in severe seasonal influenza A, although their possible value in treating severe RVI by novel influenza strains remains to be determined.

Vitamin C

The recent CITRIS-ALI trial demonstrated that 96-h infusion of vitamin C compared with placebo in a relatively small number ($n=167$) of patients with sepsis and ARDS did not improve the primary outcome of organ dysfunction scores or alter markers of inflammation and vascular injury. However, mortality, which was one of the forty-six pre-specified secondary endpoints, was significantly lower with vitamin C [40]. Results of other ongoing larger trials are awaited, and data on severe RVI are needed.

Antibacterial therapy

Co-infections with bacterial pathogens occur often with RVI. Co-infection with *Staphylococcus aureus* is common with influenza pneumonia and can be especially virulent [10]. The recent 2019 ATS/IDSA clinical practice guidelines recommend standard antibacterial therapy to be initially prescribed for adults with community-acquired pneumonia who test positive for influenza [10]. The guidelines provide details on when to consider empiric therapy for methicillin resistant *Staphylococcus aureus* and *Pseudomonas aeruginosa* and provide guidance for de-escalation of antibacterial therapy in patients with confirmed influenza [10]. Clinicians should be aware of the reports of invasive pulmonary aspergillosis in severely ill influenza patients especially those with underlying conditions or receiving corticosteroids, although up to 30% of patients with influenza-associated aspergillosis had been previously healthy [41].

Supportive care

Patients with severe RVI present typically with pneumonia, acute respiratory distress syndrome (ARDS), decompensated heart failure, or exacerbation of chronic lung disease; leading frequently to acute hypoxemic, and less commonly hypercapnic, respiratory failure. Except for several influenza and novel coronavirus studies noted below, most of the data regarding supportive care strategies come from studies that have not documented specific RVIs. In many ARDS trials, patients with pneumonia constituted a majority of enrolled patients; but detailed description of etiologic pathogens is often lacking. Given the high prevalence of viral pathogens as outlined earlier, it is likely that severe RVIs constitute a considerable proportion. There are general pathophysiologic and clinical similarities between ARDS and pneumonia caused by severe RVIs and those due to other pathogens or etiologies, and therefore, the extrapolation of findings from unselected populations to patients with severe RVIs can be justified in the absence of specific data. At the same time, there are important differences that may lead to heterogeneity in response to treatment.

Non-invasive ventilation

Data on non-invasive ventilation (NIV) in severe RVI are limited. In patients with severe RVI resulting in chronic obstructive pulmonary disease (COPD) exacerbations or cardiogenic pulmonary edema, NIV may be effective in reducing the need of endotracheal intubation and decreasing ventilator-associated complications and mortality [42].

However, NIV in patients with severe RVI causing acute hypoxemic respiratory failure and pneumonia is of uncertain benefit. Observational studies reported variable results for NIV in patients with severe influenza A(H1N1)pdm09 with some reporting NIV failure in up

to 85% [43]. In one multicenter observational study of 1898 critically ill patients with acute hypoxemic respiratory failure due to influenza, 806 underwent initial NIV, and 56.8% of them required conversion to invasive ventilation. Patients with SOFA ≥ 5 had a higher risk of NIV failure. Similar to other studies, NIV failure was associated with increased ICU mortality compared with invasive mechanical ventilation [44].

Data from uncontrolled studies suggested that NIV might have been effective and safe in the management of some patients with SARS [45], while others highlighted concerns of increased SARS transmission risk to healthcare workers [46]. In a multicenter cohort of 302 MERS critically ill patients, NIV was used initially in 35% of patients, but the vast majority of them (92.4%) required conversion to invasive mechanical ventilation; however, NIV was not independently associated with 90-day mortality [47].

A recent single-center RCT in patients with unselected patients with ARDS ($n = 83$, 45% pneumonia) showed that treatment with helmet NIV resulted in significant reduction of intubation rates and in 90-day mortality [48]. Further studies in patients with severe RVI are needed, as helmet NIV may be more effective than traditional masks and may be associated with less risk of transmission due to aerosol generation.

Based on available evidence, NIV in severe RVI may be used in selected patients in early stages and milder forms of acute hypoxemic respiratory failure, excluding those in shock or multiorgan failure, with the recognition that for patients who do not show signs of early recovery, NIV may well delay but not avoid invasive ventilation [42].

High-flow nasal cannula

High-flow nasal cannula has emerged as an alternative to NIV to prevent intubation in patients with acute hypoxemic respiratory failure. In one trial ($n = 310$, 72% community-acquired pneumonia), treatment with high-flow oxygen, standard oxygen, or NIV did not result in significantly different intubation rates; however, there was a significant difference in favor of high-flow nasal cannula in 90-day mortality [49]. A small cohort of patients with severe RVI with influenza A(H1N1)pdm09 ($n = 25$) showed that high-flow nasal cannula was associated with avoidance of intubation in 45% of patients, although almost all patients with higher severity of illness and shock were eventually intubated [50].

Invasive ventilation

Based on current evidence, patients with ARDS due to severe RVI should be managed with lung-protective strategy with low tidal volumes (6 ml/kg predicted body weight) and plateau pressures < 30 to 35 cmH_2O. In adults with acute lung injury or ARDS due to various causes, an individual patient data meta-analysis of 2299 patients from three trials (50% with pneumonia) found that higher positive end-expiratory pressure (PEEP) levels were associated with improved survival among the subgroup of patients with ARDS (defined by $PaO_2/FiO_2 \leq 200$ mmHg) [51]. A recent RCT of over 1000 patients with moderate-to-severe ARDS (55% with pneumonia) demonstrated that prolonged and high-pressure recruitment maneuvers was associated with increased 28-day mortality [52]. Titration of PEEP to achieve optimal oxygenation, perhaps without aggressive recruitment maneuvers, remains a reasonable strategy for most patients.

High-frequency oscillatory ventilation (HFOV)

HFOV ventilates the lung with tidal volumes lower than anatomical dead space while achieving relatively high mean airway pressures [53]. In patients with influenza A(H1N1)pdm09 influenza, HFOV has been used as a rescue therapy for those not responding to conventional ventilation [53]. Two randomized clinical trials showed that HFOV in moderate-to-severe ARDS was not associated with improved outcomes compared to conventional ventilation [54, 55]. However, a meta-analysis of 1552 patients (55% with pneumonia) found that the HFOV treatment effect depended on baseline severity of hypoxemia, with harm among patients with mild-moderate ARDS but possibly decreased mortality in patients with very severe ARDS [56]. Therefore, while HFOV is not recommended for routine use in ARDS, there may still be a role as rescue therapy [53].

Prone positioning

A multicenter RCT ($n = 474$, 60% with pneumonia) demonstrated that early application of prone positioning (at least 16 h per session) in patients with severe ARDS ($PaO_2/FiO_2 < 150$ mmHg, with an $FiO_2 \geq 0.6$, PEEP of ≥ 5 cmH_2O, and a tidal volume close to 6 ml/kg predicted body weight) resulted in decreased mortality [57]. Prone positioning in patients with avian A(H7N9) influenza-related severe ARDS has been associated with improved oxygenation, sustained after returning to a supine position, and with decreased carbon dioxide retention [58].

Neuromuscular blockers

In patients with severe ARDS, in one trial ($n = 339$, 38% community-acquired pneumonia), early administration of a neuromuscular blocking agent improved the adjusted 90-day survival and increased the time off the ventilator without increasing muscle weakness [59]. However, in a recent larger trial that enrolled patients with

moderate-to-severe ARDS ($n=1006$, 59% pneumonia), treated with a strategy involving high PEEP, there was no significant difference in mortality at 90 days between patients who received an early, continuous cisatracurium infusion and those who were treated with a usual-care approach with lighter sedation targets [60]. Specific data on neuromuscular blockade in severe RVI are lacking.

Extracorporeal membrane oxygenation (ECMO)

The latest RCT for ECMO (EOLIA) included 249 patients with severe ARDS, 18% with viral etiologies, and found that ECMO did not reduce mortality at day 60 [61]. Yet, a post hoc Bayesian analysis found that the interpretation of benefit versus no benefit in this trial is critically dependent upon the range of prior assumptions reflecting varying degrees of skepticism and enthusiasm of previous evidence for the benefit of ECMO—clinicians with more enthusiasm for the benefit of ECMO may be justified in considering it for certain patients [62].

Indeed, observational studies reported lower hospital mortality among patients with ARDS related to influenza A(H1N1)pdm09 with transfer to an ECMO center compared with matched non-ECMO-referred patients [63]. A case–control study also suggested survival benefit for ECMO in patients with severe MERS [64]. ECMO is likely to be associated with better outcomes when used among patients with limited organ failures and good premorbid functional status, and should be considered for patients who fail other evidence-based oxygenation strategies according to individual patient characteristics and a potential risk–benefit determination.

Cardiovascular management

Timely adequate fluid resuscitation is an essential element of the management of patients with severe RVI and shock. However, in those with ARDS ($n=1000$, 47% pneumonia), a conservative strategy of fluid management improved lung function and shortened the duration of mechanical ventilation without increasing non-pulmonary-organ failures [65]. In addition, aggressive fluid administration may worsen ventricular function. This may be particularly relevant for patients with severe RVI. Myocardial involvement is not uncommon with severe influenza A or B virus infection, and multiple studies have shown an association between influenza and acute myocardial infection and myocarditis [66–68]. Echocardiographic findings often include right- and left-ventricular dysfunction [66]. Therefore, clinical assessment of fluid responsiveness is important along with quantification of right- and left-ventricular size and function using echocardiography and/or dynamic minimally invasive cardiovascular monitoring, if available. Myocarditis has associated with longer duration of vasoactive agents and mortality and may sometimes require ECMO or other types of supportive care [69, 70].

Infection prevention and control

Table 2 summarizes infection control precautions for different RVIs as recommended by the Centers for Disease Control and Prevention (please refer to Table 2 footnote for CDC references). In patients presenting with severe RVIs, contact plus droplet precautions are recommended; droplet precautions may be discontinued when adenovirus and influenza have been ruled out. For patients with a history of recent travel (10–21 days) to countries with active outbreaks of SARS, MERS, or avian influenza, airborne plus contact precautions and eye protection are recommended.

Aerosol-generating procedures, such as bronchoscopy, endotracheal intubation, and open suctioning of the respiratory tract, tracheotomy, manual ventilation before intubation, nebulizer treatment, high-flow nasal cannula, non-invasive ventilation, and chest compressions, have been implicated with transmission of infectious agents to healthcare personnel. However, these findings were identified from limited studies, mainly during the SARS outbreak [71]. Nevertheless, it is recommended during aerosol-generating procedures on patients with suspected or proven infections transmitted by aerosols (for example influenza, MERS, SARS) to wear a fit-tested N95 mask in addition to gloves, gown, and face/eye protection. Closed-circuit suctioning may reduce the exposure to aerosols. Performing these procedures in an airborne isolation room when feasible is recommended.

RCTs comparing N95 respirators to medical masks in health care personnel working in outpatient and ward settings have not shown significant differences in protection from laboratory-confirmed influenza or other RVIs [72, 73]. The relevance of these observations to the ICU setting is uncertain, given the frequent use of aerosol-generating procedures in critically ill patients. Cloth masks are clearly inferior to medical masks in protecting HCWs from RVIs [74]. Other aspects of prevention strategies to prevent transmission when caring for patients with severe RVIs include annual influenza vaccination of healthcare workers, adherence to standard precautions, including hand hygiene, during the care of any patient and appropriate management of ill healthcare workers (please refer to Table 2 footnote for CDC references). Recently, antiseptic hand rubbing using ethanol-based disinfectants (EBDs) was found to be less effective than hand washing with running water in inactivating influenza virus in undried mucus under experimental conditions; [75] also nonenveloped viruses like adenovirus which are not easily inactivated by EBDs. The implications of these observations for clinical practice remain

to be determined but hand washing with soap and water or hand rubbing with EBD for longer than 30 s may be warranted.

Future directions for research

The Global Influenza Programme has published the updated WHO Public Health Research Agenda for Influenza, in which research priorities were identified for several domains including patient management [76]. Existing knowledge highlights the need for data regarding supportive care and adjunctive pharmacologic therapy that is specific for critically ill patients with severe RVI. Data on supportive management in resource-restricted settings are severely lacking. There is a need for more pragmatic and efficient designs to test antiviral therapeutics, individually and in combination in patients with severe RVI who are at increased risk for complications from both the disease and treatments. Adaptive randomized-controlled trial that tests several treatments, such as the REMAP-CAP trial (NCT02735707), may represent an efficient approach.

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Conflicts of interest
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