Invasive pulmonary aspergillosis complicating severe influenza: epidemiology, diagnosis and treatment

Lore Vanderbeke[a,b], *Isabel Spriet*[c,d], *Christine Breynaert*[e]
Bart J.A. Rijnders[f], *Paul E. Verweij*[g,h], *and Joost Wauters*[b,i]

Purpose of review
Bacterial super-infection of critically ill influenza patients is well known, but in recent years, more and more reports describe invasive aspergillosis as a frequent complication as well. This review summarizes the available literature on the association of invasive pulmonary aspergillosis (IPA) with severe influenza [influenza-associated aspergillosis (IAA)], including epidemiology, diagnostic approaches and treatment options.

Recent findings
Though IPA typically develops in immunodeficient patients, non-classically immunocompromised patients such as critically ill influenza patients are at high-risk for IPA as well. The morbidity and mortality of IPA in these patients is high, and in the majority of them, the onset occurs early after ICU admission. At present, standard of care (SOC) consists of close follow-up of these critically ill influenza patients with high diagnostic awareness for IPA. As soon as there is clinical, mycological or radiological suspicion for IAA, antifungal azole-based therapy (e.g. voriconazole) is initiated, in combination with therapeutic drug monitoring (TDM). Antifungal treatment regimens should reflect local epidemiology of azole-resistant *Aspergillus* species and should be adjusted to clinical evolution. TDM is necessary as azoles like voriconazole are characterized by nonlinear pharmacokinetics, especially in critically ill patients.

Summary
In light of the frequency, morbidity and mortality associated with influenza-associated aspergillosis in the ICU, a high awareness of the diagnosis and prompt initiation of antifungal therapy is required. Further studies are needed to evaluate the incidence of IAA in a prospective multicentric manner, to elucidate contributing host-derived factors to the pathogenesis of this super-infection, to further delineate the population at risk, and to identify the preferred diagnostic and management strategy, and also the role of prophylaxis.

Keywords
antifungals, aspergillosis, *Aspergillus fumigatus*, ICU, influenza

INTRODUCTION

Worldwide, 3–5 million people develop severe influenza infection every year, leading to 50 000–100 000 deaths annually in the European Union and USA. Of the hospitalized patients, 5–10% needs ICU admission. These patients initially present with typical influenza symptoms, but develop rapidly evolving respiratory deterioration, potentially leading to acute respiratory distress syndrome (ARDS) associated with high mortality [1,2]. Bacterial super-infection, mainly with *Streptococcus pneumoniae* and *Staphylococcus aureus,* is a well known complication of severe influenza, and its pathophysiology has been widely studied [3]. In recent years, however, an increasing number of publications on influenza-associated aspergillosis are reported, and the largest

[a]KU Leuven Department of Microbiology and Immunology, Laboratory of Clinical Bacteriology and Mycology, [b]University Hospitals Leuven, Department of General Internal Medicine, Medical Intensive Care Unit, [c]KU Leuven Department of Pharmaceutical and Pharmacological Sciences, Laboratory of Clinical Pharmacology and Pharmacotherapy, [d]University Hospitals Leuven, Department of Pharmacy, [e]KU Leuven Department of Microbiology and Immunology, Laboratory of Clinical Immunology, Leuven, Belgium, [f]Department of Internal Medicine, section of Infectious Diseases, Erasmus University Medical Center, Rotterdam, [g]Department of Medical Microbiology, Radboud University Medical Centre, Nijmegen, [h]Centre of Expertise in Mycology, Radboudumc/CWZ, Nijmegen, The Netherlands and [i]KU Leuven Department of Microbiology and Immunology, Laboratory for Clinical Infectious and Inflammatory Disorders, Leuven, Belgium

Correspondence to Lore Vanderbeke, MD, Department of General Internal Medicine, University Hospitals Leuven, Herestraat 49, Leuven, Belgium. Tel: +3216 345 145;
e-mail: lore.vanderbeke@uzleuven.be; lore.vanderbeke@gmail.com

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KEY POINTS

- IAA is a frequent and severe super-infection in the ICU.
- IAA may occur in any patient and shows a rapid disease progression with a high mortality.
- A broader awareness of this complication and prompt antifungal treatment initiation are crucial.
- Detailed knowledge about the underlying pathophysiological mechanisms and better risk assessment scores are urgently needed.

retrospective case study on the subject was recently published [4▪▪]. This review will focus on epidemiological data from published cases of influenza-associated aspergillosis (IAA) up to June 2018, and also on new insights related to the diagnosis and treatment of this infection in the ICU-admitted patient. A brief note on the pathogenesis and suggested topics for further research are presented as well. References were identified using PubMed and Embase searches (January 1950–June 2018) of both English and foreign language literature using the search terms 'influenza' and 'aspergillus', 'aspergillosis' or 'invasive aspergillosis'. References of identified case reports and case series (http://links.lww.com/COID/A27) were reviewed to identify additional articles for inclusion.

EPIDEMIOLOGY

There is a remarkable increase in published cases over time: the first report of probable IAA dates back to 1952, with up to six case reports per decade thereafter. A sharp increase in reported cases occurred after the 2009 H1N1 influenza pandemic (Fig. 1). Whether this is associated with an increasing trend of *Aspergillus* super-infection or with improved diagnostics remains unclear, though the latter is much more likely. Up to June 2018, 128 IAA cases have been published, which are summarized in Table 1 [5–50,51▪,52▪,53–54]. Most cases had at least one underlying medical condition, yet 28% were reported as previously healthy. The most frequently observed underlying conditions were the use of one or more immunosuppressive drugs for a variety of underlying diseases ($n = 32$, 25%), haematological malignancy ($n = 19$, 15%) and diabetes ($n = 19$, 15%). Only 9% ($n = 11$) of patients were reported to take corticosteroid therapy before influenza diagnosis, whereas 48% ($n = 61$) were treated with corticosteroids during hospitalization. Antiviral and antifungal therapy was administered in the majority of cases (69 and 89%, respectively). Most IAA cases were found in patients with influenza A infection ($n = 111$, 87%), predominantly associated with H1N1 virus. IAA diagnosis was frequently made early after ICU admission [median of 5 days after admission; interquartile range (IQR) 2–11.5]. Diagnosis of IAA was largely based on culture ($n = 89$, 70%). Galactomannan antigen was reported positive in serum in half of the patients ($n = 60$, 47%) and in bronchoalveolar lavage (BAL) fluid in one-third of the patients ($n = 39$, 31%). Bronchoscopy revealed fungal tracheobronchitis in 19 patients (15%). These results need to be interpreted with caution, because not all diagnostic techniques were available in every medical centre, and case definitions differed. Therefore, these numbers in no way

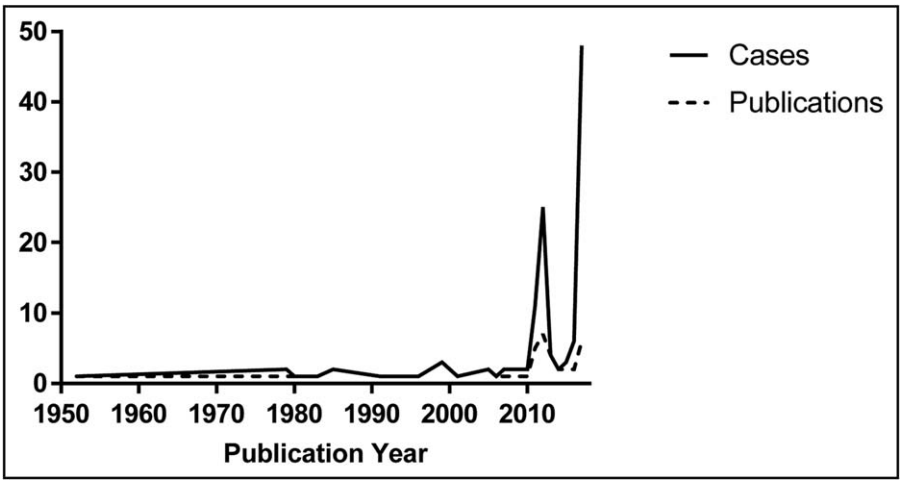

FIGURE 1. Overview of IAA cases and publications in literature over time (1952–2017 period) [5–50,51▪,52▪,53,54]. IAA, influenza-associated aspergillosis.

Table 1. Summary of 128 cases of influenza-associated aspergillosis (literature review of cases and case series [5–50,51▪,52▪,53,54])

Characteristic	Number (%) or median (IQR range)
Demographics	
Age	59 (IQR 51–63)
Male	79 (62%)
Risk factors	
Cirrhosis	6 (5%)
COPD	10 (8%)
Corticosteroids before hospitalisation	11 (9%)
Diabetes mellitus	19 (15%)
Haematological malignancy	19 (15%)
Haematological transplant	5 (4%)
Immunosuppression	32 (25%)
Neutropenia	12 (9%)
Previously healthy	36 (28%)
Solid organ malignancy	11 (9%)
Solid organ transplant	10 (8%)
Aspergillosis classification	
Proven	40 (31%)
EORTC probable	31 (24%)
AspICU putative	31 (24%)
Unclassifiable	47 (37%)
Influenza type	
Influenza A	111 (87%)
A, H1N1	65 (59%)[a]
A, H3	5 (4%)[a]
A, not specified	41 (37%)[a]
Influenza B	12 (9%)
Not specified	5 (4%)
Aspergillosis diagnostics[b]	
BAL culture positive	46 (36%)
1–3-β-D-glucan positive	5 (4%)
Computed tomography	37 (29%)
EORTC defined lesions	13 (35%)[c]
Atypical lesions	24 (65%)[c]
Galactomannan BAL positive	39 (31%)
Galactomannan serum positive	60 (47%)
Lung biopsy	20 (17%)
Necropsy	23 (18%)
PCR positive	4 (3%)
Sputum culture positive	43 (34%)
Tracheobronchitis	19 (15%)
Time from influenza diagnosis to *Aspergillus* diagnosis (days)[d]	5 (IQR: 2–11.5)
Therapy	
Antiviral treatment	88 (69%)
Not specified	1 (1%)[e]
Oseltamivir only	82 (93%)[e]
Oseltamivir and peramivir	3 (3%)[e]

Table 1 (*Continued*)

Characteristic	Number (%) or median (IQR range)
Oseltamivir and zanamivir	2 (2%)[e]
Antifungal treatment	114 (89%)
Corticosteroids during hospitalisation	61 (48%)
Outcome	
Mechanical ventilation	100 (78%)
ECMO	14 (11%)
Mortality	73 (57%)
Time to death (days)[f]	21 (IQR 13–26.5)

BAL, bronchoalveolar lavage; COPD, chronic obstructive pulmonary disease; CT, computed tomography; ECMO, extracorporeal membrane oxygenation; EORTC, European organisation for research and treatment of cancer; IQR, interquartile range.
[a]Percentages relative to total number of influenza A cases reported.
[b]Since multiple diagnostic techniques were employed in a majority of reported cases, the total percentage in the diagnosis category adds up to more than a 100%. All subcategories are listed relative to the total number of 128 cases, even though not every technique was employed in every case.
[c]Percentages relative to total number of CT scans reported.
[d]Time from influenza diagnosis to aspergillosis diagnosis only reported in 70 reports.
[e]Percentages relative to total number of antiviral use.
[f]Time from admission to death only reported in 44 reports.

reflect the sensitivity or specificity of these tests. IAA was proven through pathological examination in 40 patients (31%), of which 19 (48%) were proven only at autopsy. Most patients required mechanical ventilation ($n = 100$, 78%), and overall mortality was 57% ($n = 73$). Though there may be regional differences in prevalence, reports have occurred in all world continents, except South America and Antarctica (Table 2).

Additionally, four recent large retrospective studies in ICU patients need to be mentioned. In the first of these four studies, Martin-Loeches *et al.* studied the occurrence of super-infection in 2901 critically ill influenza patients from a large number of ICUs in Spain between 2009 and 2015. In this dataset, 16.6% ($n = 482$) had a super-infection, and of those, *Aspergillus* was found in 7.2% ($n = 35$) in the 2 days after ICU admission [55]. The second study is a retrospective cohort of 134 patients on extracorporeal membrane oxygenation (ECMO) in a tertiary care centre in the United Kingdom during 2012–2016. Ten of them had evidence of an invasive *Aspergillus* infection, and influenza A was an independent risk factor for IPA [hazard ratio 11.4, 95% confidence interval (CI) 1.97–65.86] [56]. In the third study, Cavayas *et al.* studied the risk factors for fungal infection in an international database of 2129 ECMO patients. Here again, influenza was an independent risk factor for IPA in ECMO patients [odds ratio (OR) 2.48] [57▪▪]. Finally, in a study on 432 patients with influenza admitted to seven ICUs in the Netherlands and Belgium over a period of 7 years, 19% ($n = 83$) were diagnosed with invasive aspergillosis. Of the 315 influenza patients without a typical host factor that would put them at risk for invasive aspergillosis, the incidence remained high at 14%. A comparison of influenza patients with severe non-influenza pneumonia patients allowed the identification of influenza as an independent risk factor for IPA [adjusted OR (aOR) 5.2, 95% CI 2.6–10.3]. Moreover, IAA was diagnosed very early after ICU admission (median of 3 days after admission), which highlights the need for a structured and prompt diagnostic approach [4▪▪].

DIAGNOSIS

Microbiological detection of influenza can be performed on nasopharyngeal or lower respiratory tract samples. Nucleic acid testing is both rapid and highly sensitive, making it the preferential detection method in most hospitals. Viral culture has similar sensitivity, yet is time and labour-intensive. Direct antibody testing, though clearly less sensitive, is rapid and does not require specialized skills [58]. Sampling of the lower respiratory tract (LRT) has a higher diagnostic yield, and positivity in LRT is associated with worse outcome in critically ill influenza patients [59].

Diagnosing IPA is less straightforward. Histological identification of acute-angle branching septated hyphae invading lung tissue is needed to prove a diagnosis of IPA. Lung biopsy is, however, rarely performed in critically ill patients because of the risk of respiratory complications and bleeding.

Table 2. Overview of published IAA cases from case reports and case series in the period 1952–June 2018, listed per country [5–50,51▪,52▪,53,54]

Continent	Country	Publications ($n=50$)	Year of publication	IAA cases per country
Africa				$n=1$
	South Africa	1	1985	1
Asia				$n=36$
	Japan	6	1992, 1999, 2001, 2005–2007	7
	Korea	5	2012–2014	5
	Taiwan	4	2013, 2017	24
Australia				$n=1$
	Australia	1	1999	1
Europe				$n=68$
	Belgium	2	2012, 2017	10
	France	3	1999, 2011, 2012	7
	Germany	2	2012, 2013	6
	Ireland	1	2018	2
	Italy	1	2011	1
	Poland	1	2011	1
	Spain	3	1996, 2011, 2012	8
	Switzerland	2	1985, 2016	2
	The Netherlands	3	2012, 2015, 2017	26
	United Kingdom	5	1952, 1980, 1982, 1983, 1991	5
North America				$n=22$
	United States of America	10	1979, 2005, 2010–2012, 2015–2018	22

A recent national survey in the Netherlands showed a hospital mortality of 61% in 23 ICU patients with IAA. Patients who survived had received antifungal therapy at a median of 2 days after influenza diagnosis, compared with 9 days in patients who had died, indicating that early diagnosis and treatment are critical [51▪]. Awareness of invasive aspergillosis as a potential cause of secondary infection is important as IAA occurs in non-typical host groups, and characteristic computed tomography (CT) images such as 'halo-sign' might be absent. Therefore, any respiratory specimen harbouring *Aspergillus* species in culture or a positive Galactomannan antigen should not be disregarded in ICU patients with severe influenza. A bronchoscopy with BAL appears the preferred diagnostic approach as the performance of Galactomannan antigen detection and culture showed good sensitivity in IAA, that is, 94 and 78%, respectively [51▪]. As up to 15% of patients may develop *Aspergillus* tracheobronchitis, the presence of plaques in the trachea or bronchi should be noted during bronchoscopy, which is recommended by the Infectious Diseases Society of America (IDSA) [60]. As radiological manifestations of tracheobronchitis are subtle or may be absent, visualization of plaques is regarded the best way to diagnose this condition [61].

In addition to Galactomannan antigen detection in BAL, serum Galactomannan antigen was also positive in 64–71% of IAA patients, which is a high sensitivity, considering that most patients were non-neutropenic [4▪▪,51▪]. A positive serum Galactomannan antigen increases the probability of IAA and helps to distinguish invasive infection from respiratory colonization. Any positive serum Galactomannan antigen in a patient with severe influenza therefore should prompt immediate antifungal treatment, even if pre-existing risk factors are absent. The logistics of Galactomannan antigen detection, however, might cause diagnostic delay as in many centres Galactomannan antigen testing is performed only once or twice a week. Recently, lateral flow device (LFD) tests became available for detection of *Aspergillus* antigens in serum and BAL. The main advantage of the LFD assay is that results are available within 30 min, although the concentration of the antigen is not quantified [62].

In geographical regions in which azole resistance has been described, the detection of resistance should be pursued in clinically relevant isolates [63]. As mixed infections (e.g. azole-susceptible and azole-resistant co-infection) have been reported in patients with IAA, multiple colonies should be investigated in culture-positive patients. Screening through agar-based systems such as the VIPcheck test enables detection of resistance within 24–48 h. If the screening test indicates resistance, minimum inhibitory concentration (MIC) testing can be performed [64]. Culture and phenotypic resistance screening and MIC testing can take up to a week or longer, and therefore may be too late to guide antifungal therapy. Indeed, a recent study in culture-positive patients with invasive aspergillosis indicated that initial voriconazole therapy corresponded with a 27% higher mortality in patients with voriconazole-resistant *A. fumigatus* compared with patients with voriconazole-susceptible infection. Despite resistance screening and MIC testing, the median time to change to appropriate antifungal therapy was 10 days, indicating that resistance information should be available earlier to prevent mortality [65]. In culture-negative patients, resistance PCR can be performed directly on clinical specimens. Two commercial PCR tests are available (MycoGenie and AsperGenius), which detect one or two common resistance markers. Generally, the assays show acceptable sensitivity when done on BAL fluid, and results are available within a working day [66,67]. In culture-positive patients, these PCR tests can also be performed directly on a suspension of multiple colonies with excellent sensitivity and with additional advantage that, compared with phenotypic resistance testing, the PCR result will be available the same day. The limitation is that resistance mechanisms other than the mutations included in the PCR will go unnoticed.

Given the rapid disease progression in IAA, a diagnostic pathway could include early BAL, followed by LFD, and, if positive, *Aspergillus* and resistance PCR. Although such a strategy still needs to be validated, IAA diagnosis could be made within 48 h including information regarding the presence of resistance markers.

TREATMENT

In this section, an overview of current knowledge on the pharmacological treatment, comprising antivirals, antifungals and corticosteroid therapy, is given. Respiratory organ support techniques, such as prone positioning and ECMO contribute to improved survival, but fall outside the scope of this review [68].

Antiviral therapy

Neuraminidase inhibitors (NAIs) (oseltamivir, zanamivir and very recently peramivir) form the only drug class that are licensed and recommended for the treatment of influenza infection in Europe [69,70]. Current evidence supports the use of oseltamivir in severe influenza, if administered early. Timely administration has indeed shown reduced ICU length of stay, reduced mechanical ventilation days and improved survival in several cohorts of ICU patients [71–73]. During the pandemic 2009 H1N1 infection, the WHO listed oseltamivir as a 'core drug', and advised to treat with oseltamivir at a higher dose (150 mg twice daily instead of 75 mg twice daily) and for longer duration (standard treatment duration being 5 days) in severely ill patients [1]. These recommendations are based on animal models, with only limited evidence for benefit in human cohorts [74]. No prospective studies on optimal duration of treatment in critically ill influenza patients exist; yet extended treatment duration with oseltamivir was associated with a trend towards improved mortality in a retrospective analysis of 19 892 adult ICU patients [75]. Regarding the optimal dosing of oseltamivir in severe influenza patients, the evidence is inconclusive as well. The only three prospective studies comparing standard and high-dose oseltamivir in hospitalized patients show conflicting evidence on improved virological clearance without obvious clinical benefit of high-dose therapy [76–78]. Additional retrospective studies corroborate the absence of effect on clinical outcome such as ICU length of stay or mortality [79▪▪,80]. In light of this conflicting data, the WHO downgraded oseltamivir on its drug list [81]. Furthermore, pharmacokinetic analysis in critically ill pandemic H1N1 influenza virus patients showed that enteric absorption of oseltamivir at standard dose was adequate, resulting in trough levels and area under the curve of the active carboxylate metabolite well above the 50% maximal inhibitory concentration of the influenza virus [82].

Dosing of oseltamivir in critically ill patients should be adapted to the provided organ support. Despite the fact that ECMO can alter pharmacokinetics, by increasing the volume of distribution and sequestration of drugs in the circuit among others, no dose adjustment for oseltamivir seems warranted based on current reports [83–85]. Dose reduction to 75 mg once daily is, however, recommended in patients on renal replacement therapy (RRT), depending on type of RRT and patient characteristics [83,84,86–88]. Recommendations are based on limited available evidence in small patient

populations; thus better evidence is clearly required. Present research is focusing on new NAIs (such as peramivir), new antiviral drug classes (e.g. endonuclease inhibitors) and the role of combination therapy [89,90].

Antifungal therapy

Voriconazole, the current gold standard therapy for IPA according to ECIL/ESCMID-ECMM-ERS/IDSA guidelines, led to a higher overall survival compared to conventional amphotericin B [60,63,91]. The intravenous formulation is used in ICU setting, to avoid erratic absorption and to warrant therapeutic plasma levels. Although voriconazole has earned its merit, its use is hindered by nonlinear pharmacokinetics, risk for neuro- and hepatotoxicity, and frequent involvement in drug–drug interactions. These factors underscore the need for therapeutic drug monitoring (TDM), aiming at trough levels of 2–5.5 mg/l [60,63]. Especially during ECMO, TDM is warranted because voriconazole sequestration and subsequent saturation of binding sites of the ECMO circuit can significantly alter drug levels [92,93]. Moreover, multiple drugs are known to interact with voriconazole based at the level of cytochrome P450 metabolizing enzymes [94,95]. Next to these classic CYP450-mediated interactions, also other interactions have been described in literature. A new and clinically relevant interaction was described between flucloxacillin and voriconazole showing sub-therapeutic levels of voriconazole in 11 of 20 patients treated simultaneously with both drugs [96▪].

Isavuconazole is a new extended-spectrum triazole that can be administered as a pro-drug via oral or intravenous formulation. Its longer half-life compared to voriconazole allows once daily dosing after an initial 2-day period of three times daily loading. Compared to voriconazole, isavuconazole has a more favourable profile, regarding safety and spectrum (including some of the Mucorales) while being non-inferior for primary treatment of suspected invasive mould disease [97–99]. This is reflected in current treatment guidelines; isavuconazole has the same level of evidence as voriconazole [60,63]. More clinical data are needed to provide insight in the efficacy and safety of isavuconazole at the ICU, the need for therapeutic drug monitoring and optimal dosing in patients on ECMO [100,101].

For many years, the polyene conventional amphotericin B was the mainstay therapy for invasive mould infection, and its liposomal formulations have been associated with a better safety profile. However, its use is, at present, limited to patients in whom voriconazole is contra-indicated, for example, in case of hepatic insufficiency or in cases of suspected or proven azole resistance. Importantly, with the widespread use of azoles in the environment, resistance has been observed worldwide, with resistance rates of up to 26% in certain Dutch ICUs [102▪,103]. Recent guidelines recommend to start voriconazole-echinocandin combination or liposomal amphotericin B as initial therapy in regions with environmental resistance rates of above 10% [63]. If susceptibility testing demonstrates azole-susceptible *Aspergillus* (voriconazole MIC $\leq$ 1 mg/l), voriconazole monotherapy is recommended, whereas in azole-resistant *Aspergillus* (voriconazole MIC >2 mg/l), ongoing therapy should consist of an antifungal drug to which the recovered species is susceptible [104,105]. Furthermore, combination therapy is recommended in IDSA guidelines for salvage therapy [60]. Regardless of the initial treatment regimen, timely administration of appropriate antifungal therapy is the single most crucial intervention to improve outcome; therefore initiation of treatment at suspicion of aspergillosis is advocated [60,106]. Primary prophylaxis with posaconazole is, at present, only recommended in high-risk patient groups (i.e. acute myelogenous leukaemia or myelodysplastic syndrome receiving induction chemotherapy) [63]. The effect of prophylactic antifungal administration in critically ill influenza patients requires further investigation.

Corticosteroids

Corticosteroid treatment is frequently used in the ICU, both as adjunctive treatment in septic shock and in the late phase of ARDS, although its value in septic shock remains a matter of debate [107–109]. Moreover, guidelines on treatment of severe pneumonia are being reviewed, considering corticosteroid treatment early in the disease course to improve morbidity and mortality [110▪,111]. Influenza pneumonia is, however, deemed an exception, based on low-quality evidence showing an association between corticosteroids and prolonged viral shedding with increased risk of mortality [1,112–114]. The available evidence on the value of corticosteroids in patients with influenza argues against its use as long as data from a prospective randomized clinical trial are lacking. Additionally, corticosteroids were an independent risk factor for the development of IPA in ICU patients in general, but very recently also in patients admitted with influenza [4▪▪,35,115,116,117▪▪].

PATHOGENESIS

The underlying mechanisms that render influenza patients prone to develop IAA remain to be

elucidated and are mainly derived from studies regarding influenza–bacterial super-infection. Influenza induces damage to the respiratory tract epithelial lining, interferes with normal mucociliary clearing and, in this way, can provide a gateway for *Aspergillus* infection. Moreover, immunological host responses are altered in the setting of severe influenza, with dysregulation of Th-cell differentiation and impaired cell-mediated immunity [3,118]. Additionally, treatment strategies in the ICU may enhance susceptibility to secondary aspergillosis. Corticosteroids are well known to down-regulate innate and more importantly adaptive immunity, contributing to IPA development. *In vitro*, NAIs are able to diminish viral–bacterial synergism that may contribute to severe influenza lethality [119]. The opposite might be true for the influenza–aspergillosis association as initial *in-vivo* experiments in immunodeficient mice show more severe IPA development in cortisone-treated animals exposed to oseltamivir compared to controls, a difference that was not observed in neutropenic mice [120▪▪]. Further research is needed to clarify the multiple contributing factors in the pathophysiology of this disease.

CONCLUSION AND PERSPECTIVES

Influenza-associated aspergillosis is a frequent and severe complication of influenza in ICU, occurring early after admission. High diagnostic awareness, incorporating a multiple biomarker-diagnostic strategy and prompt initiation of antifungal treatment are crucial to improve outcome. We recommend considering *Aspergillus* infection in all ICU patients with severe influenza, irrespective of previous medical history. Although the optimal diagnostic work-up remains to be validated, early bronchoscopy and BAL with the use of biomarkers seem to be important to diagnose IAA as early as possible. If initial assessments are negative for aspergillosis, this strategy should be repeated in case of respiratory deterioration. Further studies are needed to provide better epidemiological insights; at present, a multicentre observation trial is ongoing (NCT03391492); to investigate the potential of antifungal prophylaxis (NCT03378479) and to elucidate the pathophysiology of this super-infection.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

1. World Health Organization. WHO guidelines for pharmacological management of pandemic (H1N1) 2009 influenza and other influenza viruses. Geneva, Switzerland; 2010.
2. W.I.V. Influenza [Internet]. Wetenschappelijk Instituut Volksgezondheid; 2017. https://www.wiv-isp.be/nl/gezondheidsonderwerpen/influenza-0 [Accessed 15-12-2017].
3. McCullers JA. The co-pathogenesis of influenza viruses with bacteria in the lung. Nat Rev Microbiol 2014; 12:252–262.
4. ▪▪ Schauwvlieghe AFAD, Rijnders BJ, Philips N, *et al.* Invasive aspergillosis in patients admitted to the intensive care unit with severe influenza: a retrospective cohort study. Lancet Resp Med 2018; doi:10.1016/S2213-2600(18)30274-1 [Epub ahead of print].

Largest retrospective study showing that influenza is an independent risk factor for invasive aspergillosis.

5. Abbott JD, Fernando HV, Gurling K, Meade BW. Pulmonary aspergillosis following postinfluenzal bronchopneumonia treated with antibiotics. Br Med J 1952; 1:523–525.
6. Fischer JJ, Walker DH. Invasive pulmonary aspergillosis associated with influenza. J Am Med Assoc 1979; 241:1493–1494.
7. Jariwalla AG, Smith AP, Melville-Jones G. Necrotising aspergillosis complicating fulminating viral pneumonia. Thorax 1980; 35:215–216.
8. McLeod DT, Milne LJ, Seaton A. Successful treatment of invasive pulmonary aspergillosis complicating influenza A. Br Med J 1982; 285:1166–1167.
9. Horn CR, Wood NC, Hughes JA. Invasive aspergillosis following postinfluenzal pneumonia. Br J Dis Chest 1983; 77:407–410.
10. Urban P, Chevrolet JC, Schifferli J, *et al.* Invasive pulmonary aspergillosis associated with an acute influenza virus infection. Rev Mal Respir 1985; 2:255–257.
11. Lewis M, Kallenbach J, Ruff P, *et al.* Invasive pulmonary aspergillosis complicating influenza A pneumonia in a previously healthy patient. Chest 1985; 87:691–693.
12. Hovenden JL, Nicklason F, Barnes RA. Invasive pulmonary aspergillosis in nonimmunocompromised patients. Br Med J 1991; 302:583–584.
13. Kobayashi O, Sekiya M, Saitoh H. A case of invasive broncho-pulmonary aspergillosis associated with influenza A (H3N2) infection. Nihon Kyobu Shikkan Gakkai Zasshi 1992; 30:1338–1344.
14. Alba D, Gomez-Cerezo J, Cobo J, *et al.* [Invasive pulmonary aspergillosis associated with influenza virus]. An Med Interna 1996; 13:34–36.
15. Boots RJ, Paterson DL, Allworth AM, Faoagali JL. Successful treatment of postinfluenza pseudomembranous necrotising bronchial aspergillosis with liposomal amphotericin, inhaled amphotericin B, gamma interferon and GM-CSF. Thorax 1999; 54:1047–1049.

16. Funabiki Y, Ishii K, Kusaka S, *et al.* Aspergillosis following influenza A infection. Nihon Ronen Igakkai Zasshi 1999; 36:274–278.
17. Vandenbos F, Mondain-Miton V, Roger PM, *et al.* Invasive pulmonary aspergillosis during influenza: a fortuitous association? Presse Med 1999; 28:1755.
18. Matsushima H, Takayanagi N, Ubukata M, *et al.* Invasive pulmonary aspergillosis following influenza A infection. Nihon Kokyuki Gakkai Zasshi 2001; 39:672–677.
19. Hasejima N, Yamato K, Takezawa S, *et al.* Invasive pulmonary aspergillosis associated with influenza B. Respirol 2005; 10:116–119.
20. Lee FE, Daigle CC, Urban MA, *et al.* Fever and progressive respiratory failure in three elderly family members. Chest 2005; 128:1863–1867.
21. Sugino K, Homma S, Takaya H, *et al.* Fatal invasive pulmonary aspergillosis triggered by influenza B virus infection in an individual with idiopathic pulmonary fibrosis. Nihon Kokyuki Gakkai Zasshi 2006; 44:207–214.
22. Ohnishi T, Andou K, Kusumoto S, *et al.* Two cases of successfully treated invasive pulmonary aspergillosis following influenza virus infection. Nihon Kokyuki Gakkai Zasshi 2007; 45:349–355.
23. Lat A, Bhadelia N, Miko B, *et al.* Invasive aspergillosis after pandemic (H1N1) 2009. Emerg Infect Dis 2010; 16:971–973.
24. Helbig G, Wozniczka K, Wieczorkiewicz A, *et al.* Irreversible marrow aplasia after single course of 2-chlorodeoxyadenosine for hairy cell leukaemia preceding by A pandemic 2009-H1N1-associated pneumonia. Med Oncol 2011; 28:1601–1603.
25. Adalja AA, Sappington PL, Harris SP, *et al.* Isolation of *Aspergillus* in three 2009 H1N1 influenza patients. Influenza Other Respir Viruses 2011; 5:225–229.
26. Carfagna P, Brandimarte F, Caccese R, *et al.* Occurrence of influenza A (H1N1)v infection and concomitant invasive pulmonary aspergillosis in a patient with chronic obstructive pulmonary disease. Mycoses 2011; 54:549–551.
27. Garcia-Vidal C, Barba P, Arnan M, *et al.* Invasive aspergillosis complicating pandemic influenza A (H1N1) infection in severely immunocompromised patients. Clin Infect Dis 2011; 53:e16–e19.
28. Passouant O, Mateu P, Commandini M, *et al.* Pulmonary aspergillosis in nonimmunocompromised patient with acute respiratory distress syndrome during A (H1N1) infection. Ann Fr Anesth Réanim 2011; 30:e75–e76.
29. Kim SH, Kim MN, Lee SO, *et al.* Fatal pandemic influenza A/H1N1 infection complicated by probable invasive pulmonary aspergillosis. Mycoses 2012; 55:189–192.
30. Bagdasarian N, Smith J, Chenoweth C. Invasive pulmonary aspergillosis in patients with 2009 H1N1 influenza infection. Infect Dis Clin Pract 2012; 20:422–424.
31. Guervilly C, Roch A, Ranque S, *et al.* A strategy based on galactomannan antigen detection and PCR for invasive pulmonary aspergillosis following influenza A (H1N1) pneumonia. J Infect 2012; 65:470–473.
32. Hoyo-Ulloa I, Cobos-Trigueros N, Puig-de la Bellacasa J, Martinez-Martinez JA. Influenza A (H1N1) complicated by invasive aspergillosis in nonseverely immunocompromised patients. Enferm Infecc Microbiol Clin 2012; 30:583–584.
33. Vehreschild JJ, Brockelmann PJ, Bangard C, *et al.* Pandemic 2009 influenza A (H1N1) virus infection coinciding with invasive pulmonary aspergillosis in neutropenic patients. Epidemiol Infect 2012; 140:1848–1852.
34. Otterspoor LC, Smit FH, van Laar TJ, *et al.* Prolonged use of extracorporeal membrane oxygenation combined with prone positioning in patients with acute respiratory distress syndrome and invasive aspergillosis. Perfusion 2012; 27:335–337.
35. Wauters J, Baar I, Meersseman P, *et al.* Invasive pulmonary aspergillosis is a frequent complication of critically ill H1N1 patients: a retrospective study. Intensive Care Med 2012; 38:1761–1768.
36. Kim MJ, Kim MK, Kang CK, *et al.* A case of acute cerebral aspergillosis complicating influenza A/H1N1pdm 2009. Infect Chemother 2013; 45:225–229.
37. Kwon OK, Lee MG, Kim HS, *et al.* Invasive pulmonary aspergillosis after influenza a infection in an immunocompetent patient. Tuberc Respir Dis (Seoul) 2013; 75:260–263.
38. Toh H-S, Jiang M-Y, Tay H-T. Invasive pulmonary aspergillosis in severe complicated influenza A. J Formos Med Assoc 2013; 112:810–811.
39. Yildirim Y, Pecha S, Sill B, *et al.* Severe bacterial superinfection based on influenza A (H1N1) pneumonia in a heart-lung transplant recipient. Thorac Cardiovasc Surg 2013; 61:255–257.
40. Lee JY, Joo EJ, Yeom JS, *et al. Aspergillus* tracheobronchitis and influenza A co-infection in a patient with AIDS and neutropenia. Infect Chemother 2014; 46:209–215.
41. Park DW, Yhi JY, Koo G, *et al.* Fatal clinical course of probable invasive pulmonary aspergillosis with influenza B infection in an immunocompetent patient. Tuberc Respir Dis (Seoul) 2014; 77:141–144.
42. Alshabani K, Haq A, Miyakawa R, *et al.* Invasive pulmonary aspergillosis in patients with influenza infection: report of two cases and systematic review of the literature. Expert Rev Respir Med 2015; 9:89–96.
43. Kolwijck E, Scheper H, Beuving J, *et al.* Invasive pulmonary aspergillosis in influenza. Ned Tijdschr Geneeskd 2015; 159:A7431.
44. Pietsch U, Muller-Hocker C, Enzler-Tschudy A, Filipovic M. Severe ARDS in a critically ill influenza patient with invasive pulmonary aspergillosis. Intens Care Med 2016; 42:1632–1633.
45. Crum-Cianflone NF. Invasive aspergillosis associated with severe influenza infections. Open Forum Infect Dis 2016; 3:ofw171.
46. Nulens EF, Bourgeois MJ, Reynders MB. Postinfluenza aspergillosis, do not underestimate influenza B. Infect Drug Resist 2017; 10:61–67.
47. Su P-A, Yu W-L. Failure of extracorporeal membrane oxygenation to rescue acute respiratory distress syndrome caused by dual infection of influenza A (H1N1) and invasive pulmonary aspergillosis. J Formos Med Assoc 2017; 116:563–564.
48. Hou K, Sutherland A. Bacterial Pneumonia with Influenza Coinfection Complicated by Aspergillosis, ARDS, and Septic Shock in a Cirrhotic. C62 CASE REPORTS: PULMONARY INFECTIONS - MISCELLANEOUS. American Thoracic Society International Conference Abstracts: American Thoracic Society; 2017. p. A6026-A.
49. Ku YH, Chuang YC, Yu WL. Postinfluenza A (H3N2) refractory invasive pulmonary aspergillosis. J Formos Med Assoc 2017; 116:404–405.
50. Ku YH, Chan KS, Yang CC, *et al.* Higher mortality of severe influenza patients with probable aspergillosis than those with and without other coinfections. J Formos Med Assoc 2017; 116:660–670.
51. ■ van de Veerdonk FL, Kolwijck E, Lestrade PP, *et al.* Influenza-associated aspergillosis in critically ill patients. Am J Respir Crit Care Med 2017; doi: 10.1164/rccm.201612-2540LE [Epub ahead of print]

Large case series showing high incidence and mortality of critically ill influenza patients with secondary aspergillosis.

52. ■ Shah MM, Hsiao EI, Kirsch CM, *et al.* Invasive pulmonary aspergillosis and influenza co-infection in immunocompetent hosts: case reports and review of the literature. Diagn Microbiol Infect Dis 2018; 91:147–152.

Review of epidemiology and risk factors for influenza-associated aspergillosis.

53. Talento AF, Dunne K, Murphy N, *et al.* Postinfluenzal triazole-resistant aspergillosis following allogeneic stem cell transplantation. Mycoses 2018; doi: 10.1111/myc.12770 [Epub ahead of print]
54. Ajmal S, Mahmood M, Abu Saleh O, *et al.* Invasive fungal infections associated with prior respiratory viral infections in immunocompromised hosts. Infection 2018; doi: 10.1007/s15010-018-1138-0 [Epub ahead of print]
55. Martin-Loeches I, J. Schultz M. Vincent JL, *et al.* Increased incidence of co-infection in critically ill patients with influenza. Intensive Care Med 2017; 43:48–58.
56. Rodriguez-Goncer I, Thomas S, Foden P, *et al.* Invasive pulmonary aspergillosis is associated with adverse clinical outcomes in critically ill patients receiving veno-venous extracorporeal membrane oxygenation. Eur J Clin Microbiol Infect Dis 2018; 37:1251–1257.
57. ■■ Cavayas YA, Yusuff H, Porter R. Fungal infections in adult patients on extracorporeal life support. Crit Care 2018; 22:98.

Large retrospective analysis of an international ECMO database identifying influenza as a risk factor for positive *Aspergillus* cultures in ECMO patients.

58. Paules C, Subbarao K. Influenza. Lancet 2017; 390:697–708.
59. Reddy KP, Bajwa EK, Parker RA, *et al.* Relationship between upper respiratory tract influenza test result and clinical outcomes among critically ill influenza patients. Open Forum Infect Dis 2016; 3:ofw023.
60. Patterson TF, Thompson GR 3rd, Denning DW, *et al.* Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis 2016; 63:e1–e60.
61. Krenke R, Grabczak EM. Tracheobronchial manifestations of *Aspergillus* infections. ScientificWorldJournal 2011; 11:2310–2329.
62. Eigl S, Prattes J, Lackner M, *et al.* Multicenter evaluation of a lateral-flow device test for diagnosing invasive pulmonary aspergillosis in ICU patients. Crit Care 2015; 19:178.
63. Ullmann AJ, Aguado JM, Arikan-Akdagli S, *et al.* Diagnosis and management of *Aspergillus* diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline. Eur J Clin Microbiol Infect Dis 2018; 24(Suppl 1):e1–e38.
64. Buil JB, van der Lee HAL, Rijs A, *et al.* Single-center evaluation of an agar-based screening for azole resistance in *Aspergillus fumigatus* by using VIPcheck. Antimicrob Agents Chemother 2017; 61. doi:10.1128/AAC.01250-17.
65. Lestrade P, Bentvelsen RG, Schauwvlieghe AFAD, *et al.* Voriconazole resistance and mortality in invasive aspergillosis: a multicenter retrospective cohort study. Clin Infect Dis 2018 (in press).
66. Buil JB, Zoll J, Verweij PE, *et al.* Molecular detection of azole-resistant *Aspergillus fumigatus* in clinical samples. Front Microbiol 2018; 9:515.
67. Chong GM, van der Beek MT, von dem Borne PA, *et al.* PCR-based detection of *Aspergillus fumigatus* Cyp51A mutations on bronchoalveolar lavage: a multicentre validation of the AsperGenius assay® in 201 patients with haematological disease suspected for invasive aspergillosis. J Antimicrob Chemother 2016; 71:3528–3535.
68. Buchner J, Mazzeffi M, Kon Z, *et al.* Single-center experience with venovenous ECMO for influenza-related ARDS. J Cardiothorac Vasc Anesth 2018; 32:1154–1159.
69. Pasi P, Mike C. ECDC expert opinion on efficacy and effectiveness of neuraminidase inhibitors published for public consultation. Influenza Other Respir Viruses 2016; 10:152–153.

70. European Medical Agency. Alpivab: EPAR: Public Assessment Report. London: European Medicines Agency; 2018; 108.

71. Rodriguez A, Diaz E, Martin-Loeches I, *et al.* Impact of early oseltamivir treatment on outcome in critically ill patients with 2009 pandemic influenza A. J Antimicrob Chemother 2011; 66:1140–1149.

72. Richard F, Mahieu R, Gullou-Guillemette HL, *et al.* Prognosis factors of severe influenza in ICU and introduction delay of oseltamivir. Ann Intensive Care 2017; 7:21–22.

73. Hernu R, Chroboczek T, Madelaine T, *et al.* Early oseltamivir therapy improves the outcome in critically ill patients with influenza: a propensity analysis. Intensive Care Med 2018; 44:257–260.

74. Flannery AH, Thompson Bastin ML. Oseltamivir dosing in critically ill patients with severe influenza. Ann Pharmacother 2014; 48:1011–1018.

75. Kiser T, Burnham E, Ho M, *et al.* 660: Extended-duration versus standard-duration oseltamivir in critically ill patients with influenza. Crit Care Med 2018; 46:316.

76. Network SEAIDCR. Effect of double dose oseltamivir on clinical and virological outcomes in children and adults admitted to hospital with severe influenza: double blind randomised controlled trial. Br Med J 2013; 346:f3039.

77. Lee N, Hui DS, Zuo Z, *et al.* A prospective intervention study on higher-dose oseltamivir treatment in adults hospitalized with influenza a and B infections. Clin Infect Dis 2013; 57:1511–1519.

78. Kumar A; ROSII Study Investigators. Viral clearance with stan-dard or triple dose oseltamivir therapy in critically ill patients withpandemic (H1N1) 2009 influenza. Programs and abstracts of the 53rd Interscience Conference on Antimicrobial Agents and Chemotherapy (Denver). Washington, DC: American Society for Microbiology; 2013: 1470.

79. ■■ Kiser T, Burnham E, Ho M, *et al.* 656: Evaluation of high-dose versus standard-dose oseltamivir in critically ill patients with influenza. Crit Care Med 2018; 46:314.

Retrospective analysis of 19 892 critically ill influenza patients receiving either high-dose or standard-dose oseltamivir, showing no clinical benefit of high-dose therapy.

80. Welch SC, Lam SW, Neuner EA, *et al.* High-dose versus standard dose oseltamivir for treatment of severe influenza in adult intensive care unit patients. Intensive Care Med 2015; 41:1365–1366.

81. Kmietowicz Z. WHO downgrades oseltamivir on drugs list after reviewing evidence. Br Med J 2017; 357:j2841.

82. Ariano RE, Sitar DS, Zelenitsky SA, *et al.* Enteric absorption and pharmacokinetics of oseltamivir in critically ill patients with pandemic (H1N1) influenza. CMAJ 2010; 182:357–363.

83. Eyler RF, Heung M, Pleva M, *et al.* Pharmacokinetics of oseltamivir and oseltamivir carboxylate in critically ill patients receiving continuous venovenous hemodialysis and/or extracorporeal membrane oxygenation. Pharmacotherapy 2012; 32:1061–1069.

84. Mulla H, Peek GJ, Harvey C, *et al.* Oseltamivir pharmacokinetics in critically ill adults receiving extracorporeal membrane oxygenation support. Anaesth Intensive Care 2013; 41:66–73.

85. Lemaitre F, Luyt CE, Roullet-Renoleau F, *et al.* Impact of extracorporeal membrane oxygenation and continuous venovenous hemodiafiltration on the pharmacokinetics of oseltamivir carboxylate in critically ill patients with pandemic (H1N1) influenza. Ther Drug Monit 2012; 34:171–175.

86. 39th ESCP European symposium on clinical pharmacy & 13th SFPC congress: clinical pharmacy at the front line of innovations. 21–23 October 2010, Lyon, France. Int J Clin Pharm 2011; 33:285–467.

87. Kromdijk W, Sikma MA, van den Broek MPH, *et al.* Pharmacokinetics of oseltamivir carboxylate in critically ill patients: each patient is unique. Intensive Care Med 2013; 39:977–978.

88. Eschenauer GA, Lam SW. Supratherapeutic oseltamivir levels during continuous dialysis: an expected risk. Intensive Care Med 2011; 37:371.

89. Ison MG. Antiviral treatments. Clin Chest Med 2017; 38:139–153.

90. Naesens L, Stevaert A, Vanderlinden E. Antiviral therapies on the horizon for influenza. Curr Opin Pharmacol 2016; 30:106–115.

91. Herbrecht R, Denning DW, Patterson TF, *et al.* Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med 2002; 347:408–415.

92. Spriet I, Annaert P, Meersseman P, *et al.* Pharmacokinetics of caspofungin and voriconazole in critically ill patients during extracorporeal membrane oxygenation. J Antimicrob Chemother 2009; 63:767–770.

93. Ruiz S, Papy E, Da Silva D, *et al.* Potential voriconazole and caspofungin sequestration during extracorporeal membrane oxygenation. Intensive Care Med 2009; 35:183–184.

94. Li TY, Liu W, Chen K, *et al.* The influence of combination use of CYP450 inducers on the pharmacokinetics of voriconazole: a systematic review. J Clin Pharm Ther 2017; 42:135–146.

95. Andes D, Azie N, Yang H, *et al.* Drug-drug interaction associated with mold-active triazoles among hospitalized patients. Antimicrob Agents Chemother 2016; 60:3398–3406.

96. ■ Muilwijk EW, Dekkers BGJ, Henriet SSV, *et al.* Flucloxacillin results in suboptimal plasma voriconazole concentrations. Antimicrob Agents Chemother 2017; 61. doi:10.1128/AAC.00915-17.

Small case series highlighting the need for therapeutic drug monitoring when coadministering flucloxacillin and voriconazole.

97. Maertens JA, Raad II, Marr KA, *et al.* Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by *Aspergillus* and other filamentous fungi (SECURE): a phase 3, randomised-controlled, noninferiority trial. Lancet 2016; 387:760–769.

98. Ledoux MP, Toussaint E, Denis J, Herbrecht R. New pharmacological opportunities for the treatment of invasive mould diseases. J Antimicrob Chemother 2017; 72(Suppl_1):i48–i58.

99. Marty FM, Ostrosky-Zeichner L, Cornely OA, *et al.* Isavuconazole treatment for mucormycosis: a single-arm open-label trial and case-control analysis. Lancet Infect Dis 2016; 16:828–837.

100. Stott KE, Hope WW. Therapeutic drug monitoring for invasive mould infections and disease: pharmacokinetic and pharmacodynamic considerations. J Antimicrob Chemother 2017; 72(Suppl_1):i12–i18.

101. Bassetti M, Carnelutti A, Righi E. Issues in the management of invasive pulmonary aspergillosis in nonneutropenic patients in the intensive care unit: a role for isavuconazole. IDCases 2018; 12:7–9.

102. ■ Resendiz Sharpe A, Lagrou K, Meis JF, *et al.* Triazole resistance surveillance in *Aspergillus fumigatus*. Med Mycol 2018; 56(Suppl_1):83–92.

Review of current knowledge on triazole resistance, including worldwide epidemiology and expert opinion.

103. van Paassen J, Russcher A, In 't Veld-van Wingerden AW, *et al.* Emerging aspergillosis by azole-resistant *Aspergillus fumigatus* at an intensive care unit in the Netherlands, 2010 to 2013. Euro Surveill 2016; 21. doi:10.2807/1560-7917.ES.2016.21.30.30300.

104. Verweij PE, Ananda-Rajah M, Andes D, *et al.* International expert opinion on the management of infection caused by azole-resistant *Aspergillus fumigatus*. Drug Resist Updat 2015; 21-22:30–40.

105. Bassetti M, Garnacho-Montero J, Calandra T, *et al.* Intensive care medicine research agenda on invasive fungal infection in critically ill patients. Intensive Care Med 2017; 43:1225–1238.

106. Nivoix Y, Velten M, Letscher-Bru V, *et al.* Factors associated with overall and attributable mortality in invasive aspergillosis. Clin Infect Dis 2008; 47:1176–1184.

107. Thompson BT, Chambers RC, Liu KD. Acute respiratory distress syndrome. N Engl J Med 2017; 377:1904–1905.

108. Cooper MS, Stewart PM. Corticosteroid insufficiency in acutely ill patients. N Engl J Med 2003; 348:727–734.

109. Venkatesh B, Finfer S, Avni T, *et al.* Adjunctive glucocorticoid therapy in patients with septic shock. N Engl J Med 2018; 378:797–808.

110. ■ Stern A, Skalsky K, Avni T, *et al.* Corticosteroids for pneumonia. Cochrane database Syst Rev 2017; 12:Cd007720.

Systematic review on the use of systemic corticosteroids in pneumonia patients, showing improved morbidity and mortality with hyperglycaemia as major side-effect.

111. Prina E, Ceccato A, Torres A. New aspects in the management of pneumonia. Crit Care 2016; 20:267.

112. Giannella M, Alonso M, Garcia de Viedma D, *et al.* Prolonged viral shedding in pandemic influenza A (H1N1): clinical significance and viral load analysis in hospitalized patients. Eur J Clin Microbiol Infect Dis 2011; 17:1160–1165.

113. Nedel WL, Nora DG, Salluh JIF, *et al.* Corticosteroids for severe influenza pneumonia: a critical appraisal. World J Crit Care Med 2016; 5:89–95.

114. Delaney JW, Pinto R, Long J, *et al.* The influence of corticosteroid treatment on the outcome of influenza A (H1N1pdm09)-related critical illness. Crit Care 2016; 20:75.

115. Meersseman W, Lagrou K, Maertens J, Van Wijngaerden E. Invasive aspergillosis in the intensive care unit. Clin Infect Dis 2007; 45:205–216.

116. Lionakis MS, Kontoyiannis DP. Glucocorticoids and invasive fungal infections. Lancet 2003; 362:1828–1838.

117. ■■ Bassetti M, Bouza E. Invasive mould infections in the ICU setting: complexities and solutions. J Antimicrob Chemother 2017; 72(Suppl_1): i39–i47.

Review addressing the problems of diagnosing and treating IPA in the ICU.

118. Bermejo-Martin JF, Martin-Loeches I, Rello J, *et al.* Host adaptive immunity deficiency in severe pandemic influenza. Crit Care 2010; 14:R167.

119. Walther E, Xu Z, Richter M, *et al.* Dual acting neuraminidase inhibitors open new opportunities to disrupt the lethal synergism between *Streptococcus pneumoniae* and influenza virus. Front Microbiol 2016; 7:357.

120. ■■ Dewi IMW, Cunha C, Vanderbeke L, *et al.* Oseltamivir affects host defense against invasive pulmonary aspergillosis. Abstract presented at ECCMID 2018; Madrid.

Conference abstract showing effect of oseltamivir on host susceptibility to *Aspergillus in vivo* and *in vitro*.