Review Article

A narrative review of coinfection by emerging respiratory viruses and invasive *Aspergillus* in the 21st century

Shan Hu[1,2,3#], Siyun Cheng[3#], Ying Yang[1^]

[1]Department of Biotechnology, Beijing Institute of Radiation Medicine, Beijing Key Laboratory of New Molecular Diagnosis Technologies for Infectious Diseases, Beijing, China; [2]Department of Laboratory Medicine, Xuzhou Tumor Hospital, Xuzhou, China; [3]Xuzhou Key Laboratory of Laboratory Diagnostics, Medical Technology School of Xuzhou Medical University, Xuzhou, China

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[#]These authors contributed equally to this work.

Correspondence to: Ying Yang. Department of Biotechnology, Beijing Institute of Radiation Medicine, Beijing Key Laboratory of New Molecular Diagnosis Technologies for Infectious Diseases, Beijing, China. Email: y_ying_77@163.com.

Objective: To investigate the status of coinfection by respiratory viruses and invasive *Aspergillus*. It is hoped that the review will help scientists better understand coinfection by respiratory viruses and invasive *Aspergillus*. The results of this analysis will raise scientist awareness to better facilitate protection and control research pertaining to this disease.

Background: According to the latest data from the World Health Organization, coronavirus disease 2019 (COVID-19) has affected more than 200 countries and regions around the world as of February 1, 2021, with a total of 27,864,529 confirmed cases and 2,234,239 deaths, posing a great challenge to human health. A retrospective analysis of 99 cases of COVID-19 was reported in *The Lancet* on January 29, 2020 and reported COVID-19 patients coinfected with *Aspergillus* for the first time.

Methods: PubMed and Web of Science databases were searched for all papers related to coinfection by emerging respiratory viruses and invasive *Aspergillus* in the 21st century on February 1, 2021. We sorted and organized these data into the following categories: patient age and sex, underlying diseases, *Aspergillus* strains, patient mortality information, and medication.

Conclusions: The development of new clinical laboratory diagnostic technology to reduce the cost of diagnosis is necessary for reducing the mortality rate of the patients coinfected with invasive *Aspergillus* and respiratory virus.

Keywords: Coronavirus disease 2019 (COVID-19); H7N9; Middle East Respiratory Syndrome (MERS); H1N1; severe acute respiratory syndrome (SARS)

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Introduction

Respiratory tract viruses refer to viruses that use the respiratory tract as an entry point, multiply on the mucosal epithelium, and cause local infection of the respiratory tract or other tissues and organs (1). In the past two decades, many pandemics have been caused by respiratory viruses. These include outbreaks of coronavirus disease 2019 (COVID-19) since the end of 2019, the H7N9 avian

^ ORCID: 0000-0002-8469-5908.

influenza in 2013, the Middle East Respiratory Syndrome (MERS) in 2012, the H1N1 influenza in 2009, and the severe acute respiratory syndrome (SARS) in 2002–2003 (2,3). Respiratory viruses can spread through the air and cause repeated infection, which is the main reason for their high prevalence (4).

Coinfection is a common complication of respiratory virus infections and infection with one pathogen leads to increased susceptibility to infection with another. This is the main cause of death in affected patients (4,5). In the past, bacterial coinfections with respiratory virus infections have been the main concern. However, in recent years, with the development of laboratory testing technology, the detection rate of fungal infections has become increasingly higher. In addition, the severe symptoms, complications, and treatment challenges observed in patients with fungal infections have gradually garnered more attention. An increasing number of reports of coinfection by respiratory viruses and invasive *Aspergillus* have been published (6). The number of spores produced by *Aspergillus* is often in the thousands, sometimes reaching tens of billions, hundreds of billions, or even more. *Aspergillus* spores can spread across long distances by airflow and grow and reproduce in large numbers under suitable environmental conditions, causing pollution and infection. *Aspergillus* spores are very small, with a diameter of 2–10 μm, and they produce aerosols between 0.01 and 10 μm in size that can enter the human respiratory system, where they may settle in the respiratory tract or the lungs (7). These spore characteristics help *Aspergillus* to spread and multiply in nature. Invasive *Aspergillus* spreads easily and extensively and is prone to causing recurrent infections. Therefore, invasive pulmonary aspergillosis (IPA) has been described as an important complication in patients with respiratory virus infections. The infection rate of IPA ranges from 1.4 per 100,000 to 78 per 100,000. This rate varies greatly between countries, with a lower rate in developed countries and a higher rate in developing countries, which may be closely related to the medical and healthcare conditions (8). The phenomenon of coinfection by respiratory viruses and invasive *Aspergillus* has attracted widespread global attention, particularly after the January 29, 2020 report in *The Lancet* first describing patients with COVID-19 who also had invasive *Aspergillus* coinfections (9).

The clinical manifestations of patients with invasive *Aspergillus* infection have no specific characteristics, so laboratory diagnosis is an important method used to diagnose invasive *Aspergillus* infection. However, *in vitro* culture of invasive *Aspergillus* is time consuming, and spores in the air may colonize the human body and contaminate the clinical specimens, which poses a challenge for the laboratory diagnosis of invasive aspergillosis. With the rapid development of clinical laboratory diagnostic techniques, some techniques based on molecular biology have been gradually adopted to aid in the early diagnosis of patients with fungal infections, gaining valuable time for treatment (10). It is particularly worrying that invasive *Aspergillus* has also shown drug resistance (11). However, some new antifungal drugs, such as echinocandin, have been gradually applied in clinical practice and provide more treatment options for invasive *Aspergillus* infection (12).

We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/jphe-21-6).

Methods and results

COVID-19 with invasive Aspergillus coinfection

A novel type of coronavirus, 2019-nCoV (lately named SARS-CoV-2), was recognized by the World Health Organization (WHO) on January 7, 2020. The WHO named the disease caused by SARS-CoV-2 COVID-19 on February 11, 2020. According to the latest report on February 1, 2021, there have been a total of 27,864,529 confirmed cases of COVID-19, resulting in 2,234,239 deaths, with a mortality rate of approximately 2%. The human population is generally susceptible to the virus and SARS-CoV-2 spreads extensively, continuously threatening human health around the world (13). In close contact between people, droplets generated when the infected person coughs, sneezes, or talks come into contact with the mouths or noses of surrounding people, causing the virus to spread. COVID-19 may also be spread by people who are asymptomatic (14).

Aspergillosis occurring in severe COVID-19 cases is named COVID-19-associated pulmonary aspergillosis (CAPA). As of August 10, 2020, a total of 210 CAPA cases in 19 countries (France, Austria, Germany, Italy, Belgium, Netherlands, Ireland, Brazil, Argentina, Switzerland, Pakistan, Spain, Denmark, Qatar, United States, Iran, China, UK, and Australia) were retrieved from the PubMed and Web of Science databases (15-18). More than 90% of these patients required treatment in the ICU. Of the people whose specific age was known, 83% of them were older than 60. Of patients with known sex, 75% were male.

Approximately 60% of reported CAPA patients were known to have died. It is worth noting that some countries with multiple cases, including Spain, the Netherlands, and the United States, have a mortality rate of 70–80%.

The elderly are the most susceptible group, and the high mortality rate of CAPA is of great concern. Medical institutions of all levels should pay high attention to the complications in the elderly and actively treat them. However, patients should not be treated negatively because of their age. CAPA has an unusually high incidence in men, even higher than that of what we commonly think of as some male predispositions such as lung cancer. It is unclear whether this male-to-female ratio is due to the susceptibility of the male population or due to the fact that, in some countries where COVID-19 treatment is costly, many families are financially constrained and women are not tested or treated. This is a question that requires further consideration.

Aspergillus fumigatus was the species with the most cases detected, followed by *Aspergillus flavus* and *Aspergillus niger*, and rare *Aspergillus* species such as *Aspergillus terreus*, *Aspergillus penicillioides*, *Aspergillus nidulans*, and *Aspergillus calidoustus* have also emerged. The traditional diagnostic methods for invasive *Aspergillus* infection include histopathology, microscopy, culture, and galactomannan (GM) (4). Culture is still the most common method used to detect *Aspergillus*, and GM and polymerase chain reaction (PCR) are widely used. High-throughput sequencing and matrix-assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF MS) are also involved. Voriconazole is the primary choice of drug for the treatment of invasive *Aspergillus* infection according to the clinical treatment guidelines. Of the patients receiving antifungal therapy, the better part of them were treated with voriconazole. Unfortunately, the available data show that the mortality rate of patients who use antifungal drugs is not much lower than that of patients who do not use antifungal drugs, most likely due to delayed treatment.

H7N9 avian influenza with invasive Aspergillus coinfection in 2013

An epidemic of a new H7N9 virus occurred in March 2013. According to the latest WHO data, this virus has caused infections in 1,567 patients and 615 deaths, with a mortality rate of 39.2% (19). There have been five major outbreaks of H7N9 avian influenza since March 2013. During the 5th outbreak from 2016 to 2017, the number of cases increased considerably when a new, highly pathogenic strain of H7N9 avian influenza virus emerged (20). The continuous evolution of this virus potentially poses a long-term threat to public health and the poultry industry. The source of infection is not yet clear. This virus can be transmitted through the respiratory tract or through close contact with infected poultry secretions or excrement. Infections can also be caused by direct contact with the virus. However, no definite evidence of human-to-human transmission of H7N9 virus has been shown (21). H7N9 avian influenza has a small epidemic area but a high mortality rate (22).

Although there are relatively few cases of H7N9 avian influenza, a study by Zou *et al.* found 18 cases of H7N9 avian influenza coinfected with invasive *Aspergillus* in a retrospective analysis of 355 patients with H7N9 avian influenza (23). Among the 18 patients with coinfection, 17 patients were coinfected with *A. fumigatus*, and only 1 patient was coinfected with *A. flavus*. Four out of the 18 patients with coinfection died, showing a mortality rate of 22%. Unlike CAPA, which leads to higher mortality rates than COVID-19 alone, due to the already high mortality of patients with H7N9 avian influenza alone there was no significant difference in the mortality of H7N9 patients with invasive *Aspergillus* coinfections and the patients with H7N9 avian influenza alone. It is impossible to determine whether the high mortality of the patients with invasive *Aspergillus* coinfection and H7N9 avian influenza was due to the H7N9 virus or the coinfection (23).

MERS with invasive Aspergillus coinfection in 2012

Patients with MERS caused by the coronavirus MERS-CoV were first diagnosed in April 2012, subsequently causing a global epidemic, with the Middle East most affected (24). The disease epidemic was relatively short and did not intensify in 2013, with only a few sporadic cases. According to the latest WHO data, a total of 2,519 cases and 866 deaths have been reported worldwide, with a mortality rate of 34.4% (25). The human-to-human transmission of MERS involves different modes, including droplets and contact transmission (26). One report showed that the infected persons had direct contact with camels, manifesting as MERS-CoV positive cases (27).

No cases of invasive *Aspergillus* coinfection with MERS have been retrieved from the PubMed or Web of Science databases, and there are no reports on MERS with bacterial or other fungal coinfections (28). It is noteworthy that MERS has an extremely high mortality rate, reaching

34.4%. A large number of patients with MERS had an unknown cause of death (29). Therefore, the possibility of invasive *Aspergillus* coinfection with MERS should not be completely ruled out. We speculate that the lack of detected *Aspergillus* coinfections may be related to the less advanced diagnostic technology in the Middle East in comparison to that in developed countries and the relatively low number of infected cases.

H1N1 influenza with invasive Aspergillus coinfection in 2009

The history of swine flu (influenza A) induced by the H1N1 virus can be traced back to 1918, when it infected nearly 500 million people worldwide (30,31) and caused approximately 50 million deaths (32). Since then, H1N1 influenza pandemics have occurred every few decades (33). A new recombinant influenza A virus subtype H1N1 infection was discovered in March 2009 and quickly spread around the world (34), causing 575,400 deaths (35). Subsequently, it has continued to spread repeatedly in many countries (36-39). Current forecasts estimate that during a pandemic, 12–30% of the human population will develop clinical influenza, 4% of which will require hospitalization, and 20% of hospitalized patients will require intensive care (40).

A total of 15 cases of coinfection by invasive *Aspergillus* and influenza A H1N1 virus have been retrieved from online databases (41-49). Among these 15 patients, there were 11 cases of *A. fumigatus*, 2 cases of *A. flavus*, 1 case of *A. terreus*, and 1 case of *A. fusispora* infection, indicating that the proportion of *A. fumigatus* infection was extremely high. Among these 15 patients, pathogenic fungi were detected by pure culture in 11 cases, by PCR in 1 case in India in 2020 (41), by a combination of PCR and serological method in 1 case (43), and by a combination of pure culture and serological method in 2 cases. During the epidemic of the recombinant influenza A H1N1 subtype virus infection, the detection of invasive *Aspergillus* mainly relied on pure culture methods. It should be noted that the pathogenic fungi in one patient were detected by autopsy (42). Patients with invasive *Aspergillus* infections are easily missed and misdiagnosed due to the lack of specificities in clinical symptoms, signs, and X-ray images. The patients who are not treated in a timely manner are prone to death due to unknown causes (50), and the cause of death can only be revealed through autopsy. All 15 patients with coinfection received antifungal treatment. The most commonly used antifungal drug was voriconazole (n=8 cases), followed by amphotericin B (n=2 cases), fluconazole (n=1 case), and itraconazole (n=1 case). Three patients received voriconazole combined with fluconazole, amphotericin B, or micafungin. A total of 11 patients were administered voriconazole, which had always been the drug of choice for the treatment of invasive *Aspergillus* infection. Sadly, even though these 15 patients were given antiviral and antifungal treatments, there were still 8 patients who died, resulting in an extremely high mortality rate of 53.3%.

SARS with invasive Aspergillus coinfection in 2002–2003

SARS is caused by SARS-CoV, which emerged and spread around the world in 2002 (51). During the SARS outbreak, a total of 8,098 cases were reported, with a death toll of 774 and a mortality rate of approximately 8.9%. In addition to the relatively high mortality rate, this epidemic also caused a worldwide economic loss of nearly 40 billion US dollars (2). SARS is spread through respiratory droplets over a short distance, contact with patient's respiratory secretions, and close contact with patients (52,53).

A literature search in the PubMed and Web of Science databases showed only three cases of invasive *Aspergillus* coinfection with SARS, including one case reported in China with a fatal outcome (54) and two cases reported in Canada (55). SARS was the first respiratory virus pandemic in the 21st century. At that time, there was little clinical experience with invasive *Aspergillus* coinfection. Despite being mentioned by experts, invasive *Aspergillus* coinfection in SARS cases did not draw a high level of attention. These reports did not provide a detailed description of the specific conditions of the patients. In addition, the molecular biology diagnostic technology was not mature at that time, and the diagnosis of invasive *Aspergillus* was based on pure culture. Due to the characteristics of invasive *Aspergillus* itself, many cases were missed or misdiagnosed (56,57). Moreover, during the outbreak of SARS, the treatment experience was limited, and the application of glucocorticoids in the treatment of SARS resulted in an increased risk of invasive *Aspergillus* coinfection (55).

Discussion

Since the 21st century, there have been global pandemics linked to five novel respiratory viruses, namely SARS-CoV-2, H7N9, MERS-CoV, H1N1, and SARS-CoV, all of which continue to pose a threat to human health (2,3).

The spores produced by *Aspergillus* are spread extensively through the air. *Aspergillus* spores are very small, small enough to form aerosols and spread extensively. In addition, these spores have strong growth and reproductive abilities under suitable environmental conditions that not only pollute the environment but also cause infections (7). Therefore, invasive *Aspergillus* spreads easily and extensively and recurrent infections are frequent, and IPA needs to be given more attention. Moreover, infection by one pathogen is more likely to lead to infection by another pathogen (58). The high mortality rate of patients coinfected with invasive *Aspergillus* makes it a problem that should not be ignored (59).

A. fumigatus and *A. flavus* are the two most common types of invasive *Aspergillus*. They are also the most common fungi found in invasive *Aspergillus* coinfections with the five aforementioned novel respiratory viruses. The traditional diagnostic methods for invasive *Aspergillus* infection include histopathology, microscopy, culture, and serology (60). The culture method as the gold standard for pathogen diagnosis is also the most important method for the diagnosis of respiratory virus infection with invasive fungal coinfection. However, *Aspergillus* is difficult to culture, with a long culture time (57). The serological detection method has good sensitivity to the presence of *Aspergillus* but also has major drawbacks due to its inability to test drug resistance or determine which invasive fungal strains are present (61). With the continuous development of new laboratory diagnostic technologies, molecular biotechnology has started to become widely used, especially in the COVID-19 outbreak since the end of 2019. PCR technology, as a representative of molecular biotechnology, has become an important measure for the early diagnosis of invasive *Aspergillus* infection. However, PCR procedures are easily contaminated and the number of pathogens diagnosed by PCR is limited, failing to diagnose all pathogens in patients. This is an important limitation in the clinical application of PCR (62). The continuous development of molecular biology techniques represented by second- and third-generation genome sequencing will have a positive impact on the early diagnosis of respiratory virus infections associated with invasive *Aspergillus* infection. However, given the high cost of metagenome-based second- and third-generation sequencing, only the specimens of severely and critically ill patients would have whole-genome sequencing performed in clinical practices. Thus, this new technology in the early diagnosis of invasive *Aspergillus* infection still has a long way to go before the clinical application (63).

Voriconazole is the primary choice of drug for the treatment of invasive *Aspergillus* infection according to the clinical treatment guidelines. Because of its low cost and good therapeutic effects, voriconazole has a wide range of clinical applications (64). In the cases involved in this review article, voriconazole was the antifungal drug of choice for invasive aspergillosis infections. However, invasive *Aspergillus* has become resistant to voriconazole in recent years (65). Clinicians may combine two or more antifungal drugs to gain treatment time for the patients before obtaining the results of drug susceptibility tests. Echinocandins, as a new class of antifungal drugs in clinical practice, have a low drug-resistance rate and low side effects and have gradually become a better choice for the clinical treatment of invasive *Aspergillus* infections (66). However, the cost of echinocandins is high. Thus, widespread use of echinocandins for clinical treatment remains difficult (67). In this review article, almost all cases of invasive *Aspergillus* coinfection with these novel respiratory viruses were treated simultaneously with antiviral and antifungal drugs. However, the mortality rate of these patients was still high.

Conclusions

Many medical institutions still rely on the culture method to diagnose invasive *Aspergillus*, which is difficult to culture, has a long culture period, and can easily colonize the human body. This makes diagnosis challenging and often leads to misdiagnosis, thereby causing delays in treatment. This is often the cause of unexplained deaths and high mortality in patients with coinfection of respiratory virus and invasive *Aspergillus* (68). The development of molecular biotechnology provides an important basis for the early diagnosis of invasive *Aspergillus* infections. Early detection and early treatment of patients with invasive *Aspergillus* infections greatly reduce the mortality rate (69). The development of new clinical laboratory diagnostic technology to reduce the cost of diagnosis and make diagnostic methods more widely used in medical institutions at all levels is essential for *Aspergillus* diagnosis and treatment and for reducing the mortality rate of patients coinfected with invasive *Aspergillus* and respiratory virus.

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Footnote

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