Case Report
COVID-19-Associated Pulmonary Aspergillosis: A Year-Long Retrospective Case Series
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Abstract: COVID-19-associated pulmonary aspergillosis (CAPA) refers to co-infection with *Aspergillus* spp. in patients with COVID-19. It has a higher mortality rate when compared with patients only infected with COVID-19, but we still know little about the epidemiology, diagnosis, and best treatment options for patients with CAPA. We report our findings from a year-long retrospective case series of patients with CAPA in two tertiary hospitals in the United Kingdom. We included all patients admitted to critical care with CAPA between March 2020–2021. We used the European Confederation for Medical Mycology and the International Society for Human and Animal Mycology consensus criteria to categorise CAPA. Demographic data, patients’ co-morbidities, time to and method of diagnosis, COVID-19 and aspergillosis treatment, and outcomes were analysed. Thirteen patients were diagnosed with probable CAPA between October/2020–March/2021, and 54.8% also had hypertension. Diagnosis was established after a median of 18 days post-COVID-19 infection, and a median of 7 days post-intubation. All patients had received corticosteroids, as well as tocilizumab (7; 53.8%) and remdesivir (3; 23%). Eleven patients received antifungal treatment. Nine (69%) patients died by 30 days post-ICU admission, one patient died on day 32, and three (23%) patients survived. CAPA has a very high mortality rate. We also identified three areas that merit further investigation: lack of positive tests between March–October 2020; COVID-19 treatments and possible relationship with increased CAPA rates; and the rationale behind antifungal treatment in our hospitals compared to recommended treatment in the literature.

Keywords: COVID-19; SARS-CoV-2; CAPA; SARS Coronavirus 2; infection invasive pulmonary aspergillosis; pulmonary aspergillosis-invasive

1. Introduction
In December 2019, the first cases of pneumonia caused by severe respiratory syndrome coronavirus 2 (SARS-CoV-2) were reported from Wuhan, China [1]. The World Health Organisation (WHO) named the syndrome caused by this virus “COVID-19” and declared a pandemic in March 2020 [2]. To date (July 2022), COVID-19 has caused over 552,000,000 infections and over 6,300,000 deaths worldwide [2]. It is now known that patients with COVID-19 are at higher risk of co-infections with other organisms, including invasive pulmonary aspergillosis (IPA) [3,4]. IPA occurs at a rate of around 0.3–5.8% in the general ICU population [4]. The occurrence of IPA in the context of COVID-19 infection requiring intensive care is known as “COVID-19-associated pulmonary aspergillosis” (CAPA). The incidence varies from 2.5% to 35%, depending on the study [5–7]. Differentiation between IPA and COVID-19 pneumonia is not possible based on clinical signs and symptoms only, which makes classification and diagnosis challenging [5]. In addition, there are complications regarding testing, including reticence to perform aerosol-generating procedures such as bronchoalveolar lavages (BAL) for galactomannan testing and culture, and a lack of standardized guidelines in the clinical setting. Serum galactomannan testing for aspergillosis...
in patients with CAPA has poor diagnostic accuracy (20% at best, and patients with proven CAPA may test negative for serum galactomannan) [8,9].

The pathophysiology underlying the increased risk of this fungal superinfection is not fully understood, but it is likely a combination of viral-induced overexpression of anti-inflammatory cytokines (especially IL-10), impaired cell-mediated response, abnormal T-cell differentiation, damaged epithelial cells, and the administration of drugs that weaken the immune system, particularly steroids [3,10].

The aim of this study was to determine the number of cases, co-morbidities, and outcomes of adult patients with CAPA admitted to critical care in The Newcastle upon Tyne Hospitals NHS Foundation Trust between March 2020–March 2021 in order to further the knowledge of this emerging disease.

2. Methods
2.1. Hospital Setting

The study was conducted in two tertiary hospitals in Newcastle upon Tyne (UK), between March 2020 and March 2021. These hospitals are known together as the Newcastle upon Tyne Hospitals Foundation Trust (NUTH). Newcastle is one of the five designated centres for Airborne High Consequence Infectious Diseases in the UK. During the UK’s second COVID-19 wave (Winter 2020), we also received patients from other hospitals in the UK to help other critical care units across the country with hospital-bed pressures.

2.2. Study Design and Data Collection

We reviewed the electronic clinical records of all critically ill patients admitted to our intensive care units with confirmed COVID-19 infection. Patients were included who had isolated *Aspergillus* spp. From a respiratory sample, or who had a positive *Aspergillus* antigen test from a clinical sample, during the admission period.

The project was registered as a clinical service evaluation with The Newcastle upon Tyne Hospitals NHS Foundation Trust. We did not need to seek ethical approval. Electronic health records of identified patients were retrospectively reviewed by a team of medical doctors (A.R. and B.S.). We collected demographic data and clinical details, including co-morbidities, investigations, management, laboratory results, and outcome, at 30 days.

2.3. Definitions and Laboratory Analysis

COVID-19 is the disease caused by the SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) virus, in accordance with the WHO classification of diseases [11]. COVID-19-confirmed cases were identified via reverse-transcription polymerase chain reaction (RT-PCR) assay for SARS-CoV-2 from a respiratory sample.

There is no standardised clinical definition of CAPA, and our hospitals do not have any internal clinical guidelines specifically directed to this cohort of patients yet. We followed the European Federation for Medical Mycology and the International Society for Human and Animal Mycology (ECMM/ISHAM) consensus criteria proposed for research and clinical guidance, where CAPA is defined as “invasive pulmonary aspergillosis in temporal proximity to a preceding SARS-CoV-2 infection” in patients requiring critical care [12]. More precisely, the entry criteria stated that patients with a positive SARS-CoV-2 RT-PCR any time during two weeks between hospital admission and ICU admission, or positive RT-PCR within 72–96 h after admission to critical care were eligible. All our patients fulfilled these criteria.

In addition, the consensus group set a number of principles to classify CAPA as “possible”, “probable”, and “proven”. We adopted this model to classify CAPA in our cohort of patients, all of whom developed the co-infection within days of admission to critical care. “Proven” CAPA is defined as pulmonary or tracheobronchial infection demonstrated by histopathological or direct microscopic detection. No patients in our cohort underwent histological analysis, so all our patients were classified as non-proven but “probable” CAPA. This classification relied on *Aspergillus* culture from the respiratory
tract, and/or detection of antigen, as well as pulmonary infiltrate or nodules, or cavitating infiltrate on radiological evidence.

The presence of *Aspergillus* antigen (galactomannan, GM) in respiratory samples from bronchoalveolar lavage was tested using Platelia™ Aspergillus Antigen Kit by Bio-Rad Laboratories, with a cut-off value of >0.5 in serum and >1.0 in BAL. Culture of respiratory samples was performed in Sabouraud dextrose agar and brain heart infusion agar.

Isolates were molecularly identified using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF).

COVID-19-associated pulmonary-aspergillosis-related mortality was defined as death in the context of both COVID-19 and positive *Aspergillus* co-infection (positive respiratory culture and/or antigen) at 30 days following admission to critical care.

3. Results

Between March 2020 and March 2021, 496 patients were admitted to our ICUs due to COVID-19. Of those, we identified thirteen patients who had both COVID-19 and laboratory evidence of co-infection with *Aspergillus* spp., thus fulfilling the criteria for probable CAPA between October 2020–March 2021. This represents 2.6% of the total ICU cohort (March 2020–March 2021). Given that there were no surveillance protocols, the 13 CAPA cases were retrospectively collected and, therefore, the prevalence may be an underestimate.

Most patients were men (nine males vs. four females), and the average age was 67.2 years-old (53–81 years-old). The most common co-morbidity was hypertension, present in seven patients (53.8%). Other common conditions were chronic obstructive pulmonary disease (COPD) (4; 30.7%), cardiovascular disease (3; 23%), osteoarthritis (3; 23%), type-2 diabetes mellitus (3; 23%), and chronic kidney disease (3; 23%). Two patients were obese (BMI > 25), and two had hypercholesterolaemia. Of the 13 patients, only one was fit and well prior to admission to critical care. The vast majority (11; 85%) had at least three co-morbidities (average: 4 [range 3–7]).

All of them were intubated and ventilated after an average of 2.6 days (median: 1 day) following admission to the ICU, and patients that fulfilled the criteria for CAPA were admitted between October 2020 to February 2021. Only one patient was on steroids prior to admission to critical care due to a diagnosis of giant cell arteritis; the rest were not immunosuppressed before being admitted to the ICU. All received corticosteroids (dexamethasone) as part of the COVID-19 treatment protocol. In addition, seven (53.8%) received tocilizumab, and three (23%) received remdesivir.

Bronchoalveolar lavage (BAL) was performed in all patients. In 10/13 (77%) cases, *Aspergillus* spp. was isolated from a BAL, and in three cases, galactomannan antigen was detected in the patient’s BAL. The species identified in all patients was *Aspergillus fumigatus*. Diagnosis of aspergillosis was established after an average of 18.2 days (median: 18) (8–33 days) post-COVID-19 infection, 11 days (median: 9) (range 3–28 days) post-ICU admission, and 8.4 days (median: 7) (range 1–26) post-intubation. Previous or concomitant bacterial infections were found in 11 (85%) patients.

All patients had radiological evidence; there were pulmonary infiltrates in five cases (38.4%), consolidation in six cases (46.1%), and two patients (15.4%) had evidence of cavitation. The type of imaging performed was antero-posterior portable chest X-ray (nine patients) and CT scan (four patients).

Eleven (77%) patients received antifungal treatment: one received voriconazole followed by caspofungin due to an adverse reaction to voriconazole; one received anidulafungin followed by caspofungin followed by voriconazole; one patient only received caspofungin; three received monotherapy with voriconazole; one received empirical treatment with caspofungin, which was switched to voriconazole following positive *Aspergillus* culture; four received caspofungin monotherapy following positive *Aspergillus* culture, then switched to voriconazole.
Nine patients (69%) died within 30 days post-ICU admission; one patient died on day 32; and three (23%) patients survived.

4. Discussion

We described the findings from our retrospective cohort study of patients admitted to critical care with COVID-19, and subsequently confirmed superinfection with *Aspergillus* spp. on culture and/or antigen test from the respiratory sample fulfilling the diagnosis of “probable CAPA”. In light of our results, there are three areas that merit further discussion: the lack of positive tests between March–October 2020; the role of COVID-19 treatment and potential increased risk of CAPA due to it; and the rationale behind antifungal treatment.

4.1. Lack of Positive Tests between March–October 2020

There were no positive *Aspergillus* tests in patients between March–October 2020. This could be for several reasons: firstly, during the first COVID-19 wave in the UK (Spring 2020), there were few treatments available and experience of treating the condition was very limited. We have seen that in our cohort of patients, tests for aspergillosis were conducted, on average, 8.4 days post-intubation. Improvements in the management of critically unwell patients with COVID-19 over the months may explain why we only saw superinfection with *Aspergillus* spp. from October onwards, when treatment of this condition had advanced and longer lengths of stay in the ICU were more common.

Secondly, bronchoalveolar lavage is an aerosol-generating procedure, and clinicians may have been reluctant to perform such a test in COVID-19 positive patients. It is known that serum galactomannan has a low yield diagnostic accuracy [8], and in the absence of respiratory culture, the negative serum antigen result may explain (to some extent) the lack of CAPA between March–October 2020. However, secretions (if present) were sent for testing early in the COVID-19 pandemic, but additional testing for evidence of fungal infection may not have been common. In addition, later in the pandemic, isolation rules were relaxed such that after day 14, patients were nursed in open areas after fulfilling certain criteria, even if they were still ventilated, as they were considered non-infectious, and BAL was, therefore, easier to perform.

Thirdly, international consensus guidelines published in June 2021 recommend that patients with a positive PCR for SARS-CoV-2 test admitted to intensive care should be screened for galactomannan antigen from a respiratory sample regularly, ideally three times per week [12]. Repeated diagnostic tests increase the chances of detecting *Aspergillus*, and given that it is clinically impossible to differentiate between COVID-19 pneumonia from CAPA based on symptomatology, there may be value in introducing this practice routinely [5]. However, these consensus guidelines were not published until June 2021, and they remain a guideline only, with local practices continuing to vary.

4.2. Immunosuppression

All of the patients in our cohort were treated with immunosuppressive drugs, in accordance with national guidelines [13]. Dexamethasone was investigated in the RECOVERY trial in the treatment of hospitalized patients with severe COVID-19 infection. The trial showed that dexamethasone reduced 28-day mortality by 20% on patients receiving oxygen alone, and 35% on patients on mechanical ventilation [14]. The RECOVERY and REMAP CAP trials also investigated [15] the impact of tocilizumab, and found that 29% of the patients in the tocilizumab group died within 28 days compared with 33% of the patients in the usual care group: an absolute difference of 4% [16]. Among patients who were not on invasive ventilation when they entered the trial, tocilizumab reduced the chance of requiring mechanical ventilation or death from 38% to 33% [16].

Tocilizumab treatment induces a period with a low C-reactive protein, which may be used as part of the diagnosis of infection in intensive care. This diagnostic uncertainty introduced may have increased the propensity to perform BALs, along with general concerns of its immunosuppressive effects.
4.3. Antifungal Treatment Choice and Course Duration

In our cohort, only three patients received voriconazole as a first line agent, despite it being recommended in this role for the treatment of IPA and CAPA [12,17]. Voriconazole is a second-generation triazole broad-spectrum antifungal agent extensively metabolized via cytochrome P450 (CYP450) isoenzyme CYP2C19 and, to a lesser extent, CYP2C9 and CYP3A4 [18]. This makes it problematic in the critical care setting due to major drug–drug interactions [12]. Among others, this is the case with dexamethasone, leading to variation in voriconazole levels [19], and with proton-pump inhibitors, which are widely used in critical care [20]. Moreover, it has a narrow therapeutic window, which requires close monitoring [21].

Caspofungin is a broad spectrum echinocandin anti-fungal which is also licensed for the treatment of invasive aspergillosis; it has fewer drug interactions, and monitoring is not required. Although commonly used for the treatment of pulmonary aspergillosis, there is no phase III trial data on its non-inferiority to voriconazole. Evidence to support the ECMM/ISHAM recommendation that it should not be used as monotherapy for the treatment of CAPA is lacking. In addition, there were numerous supply issues with various antifungal agents throughout the study period, which affected choice.

Caspofungin monotherapy was, in most cases, the first-line antifungal used following positive Aspergillus detection in this cohort of patients. All antifungal treatment was guided by daily consultation with senior microbiologists experienced in the treatment of fungal diseases in critically ill patients.

4.4. Conclusions and Limitations

Our study has showed that when severe COVID-19 results in prolonged ventilation and is complicated with a superinfection with Aspergillus spp., the mortality rate is very high. This is in line with other research findings [6,8,22]. Though we do not have a compelling explanation as to why there were no positive respiratory cultures for Aspergillus between March–October, it is likely that the lack of CAPA in that time period reflects the difficulty in diagnosing this condition, and lower levels of immunosuppression. It is somewhat reassuring to note that since October 2020, there have been patients diagnosed with CAPA in our hospitals, which suggests that clinicians are now actively searching for this disease entity. Notwithstanding, it would be beneficial if consideration of this issue was included in UK COVID-19 guidelines, so that diagnosis of CAPA could occur in a timely fashion to allow early appropriate treatment.

We do not yet know if COVID-19 predisposes to superinfection with Aspergillus, or whether treatment or other factors are the contributors to a higher risk of CAPA. Research to investigate the true incidence, pathophysiology, management, and outcome are urgently needed.

Our report has several limitations: we used retrospective clinical data collected from individuals who had tested positive for COVID-19 and had also a positive Aspergillus result. Therefore, the outcome of interest had already occurred, but we could not control or assess exposure. This methodology is at risk of confounding bias, meaning that there may be a systematic distortion in the measure of association between exposure and outcome. As we did not screen patients prospectively for COVID-19 and Aspergillus, we may have missed patients that were positive for CAPA, but did not have the appropriate tests performed. At the time, BALs were not systematically tested for the presence of Aspergillus antigen, and it is not possible to perform this testing retrospectively. Finally, some data were not available due to inter-hospital transfers.

In summary, in this retrospective cohort study, acquisition of Aspergillus during prolonged ventilation for COVID-19 is associated with a high mortality. We believe that CAPA should be included in routine microbiological screening in this cohort, so that effective treatment can be initiated at an early stage.
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Institutional Review Board Statement: Ethical review and approval were not required because patients were not randomised, there were no changes to treatment or service for/to patients, and results were not generalisable as the evaluation was a snapshot of Newcastle Hospitals. Additionally, the data was all retrospective and freely available to the treating clinicians (authors). The study was looking for the prevalence and associated co-morbidities of those admitted with the condition and not analysing identifiable data. The study was registered as a service evaluation/clinical audit and therefore the governance falls within registration on the clinical effectiveness register of the Trust.

Informed Consent Statement: Informed consent was not required because patients were not randomised. The data was all retrospective and freely available to the treating clinicians (authors). The study was looking for the prevalence and associated co-morbidities of those admitted with the condition and not analysing identifiable data. The study was registered as a service evaluation/clinical audit.

Data Availability Statement: The data presented in this study is contained within the article and is not publicly available as it involved access to confidential patient information only available to the treating clinicians (authors).

Conflicts of Interest: The authors declare no conflict of interest.

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