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Practice Points

Implementation of a diagnostic algorithm for COVID-19-associated pulmonary aspergillosis

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Introduction

Early in the COVID-19 pandemic, COVID-19-associated pulmonary aspergillosis (CAPA) was identified as an important complication among ventilated patients. Although the exact pathophysiology remains unclear, predisposing factors include: prolonged mechanical ventilation, severe COVID-19 pneumonitis, and immunosuppression (including with corticosteroids and interleukin-6 inhibitors) [1].

Diagnosis of CAPA is made challenging by the lack of definitive case criteria, difficulty in obtaining diagnostic samples, and in differentiating angio-invasive infection from aspergillus colonization. The true incidence of CAPA is unclear, with rates ranging from 1% to 2% in the largest post-mortem analysis to date, to 14% in observational studies with clinical criteria applied [2–4].

The most widely accepted diagnostic algorithm for CAPA (the European Confederation of Medical Mycology (ECMM)/International Society for Human and Animal Mycology (ISHAM) consensus criteria) stresses the importance of deep respiratory sampling, together with serum fungal biomarkers (galactomannan and (1–3)-β-D-glucan) [5]. Strict application of these criteria in clinical settings is problematic, particularly in healthcare systems over-stretched by the pandemic. Furthermore, during the first wave of the pandemic, little was known about the diagnostic performance of fungal biomarkers in COVID-19 patients. However, treatment for CAPA is not without consequences as it carries financial cost, important side-effects, and is a significant challenge for anti-fungal stewardship programmes, particularly at times of international drug shortages [6]. Therefore, clinicians managing these complex patients face difficult decisions that must balance possible inappropriate medication use with failure to treat a potentially fatal condition, all against a backdrop of significant diagnostic uncertainty.

We present our experience of implementing a new diagnostic algorithm for CAPA in the UK's largest intensive therapy unit (ITU) facility (across three hospital sites) during the first wave of the COVID-19 pandemic.

Methods

In January 2021 a multi-disciplinary group was formed, consisting of infectious disease clinicians, microbiologists, and intensivists at University Hospitals Birmingham NHS Foundation Trust (UHB), to develop a diagnostic algorithm for CAPA. The group performed a thorough review of the available peer-reviewed literature and assessed possible approaches in the

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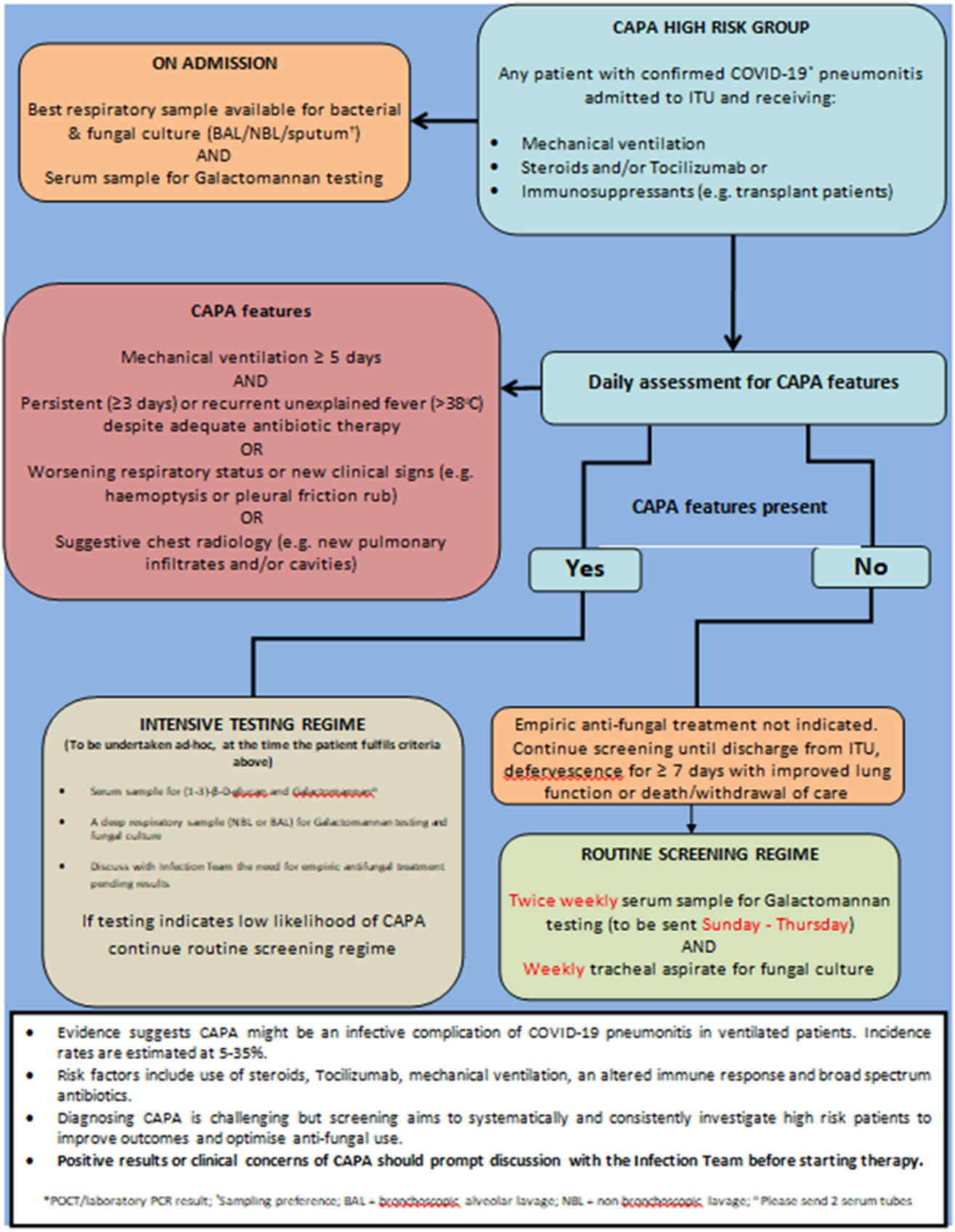

Figure 1. University Hospitals Birmingham NHS Foundation Trust COVID-19-associated pulmonary aspergillosis (CAPA) screening algorithm in ventilated COVID-19 patients, February 2021. BAL, bronchoalveolar lavage; NBL, non-directed BAL; COVID-19-associated pulmonary aspergillosis; ITU, intensive therapy unit; POCT, point-of-care testing; PCR, polymerase chain reaction.

context of local patient characteristics and access to diagnostic tests. The resulting algorithm (Figure 1) was considered a pragmatic approach, adapted from the literature available at the time, including the ECMM/ISHAM consensus criteria [5]. Patients were risk stratified by clinical and radiological features into regimens of intensive screening (requiring serum galactomannan and (1–3)-β-D-glucan and bronchoalveolar lavage (BAL) or non-directed BAL (NBL) testing) or routine screening (requiring twice-weekly serum galactomannan and weekly tracheal aspirate for fungal culture). Positive fungal culture results were interpreted with caution, considering the possibilities of environmental contamination and airway colonization versus angio-invasive disease. Locally defined diagnostic criteria were applied (Box 1) to classify cases as possible, probable, or proven CAPA.

Alternative approaches including universal anti-fungal prophylaxis were also considered. Engagement in the project was gained from clinical teams, pharmacy, laboratories, IT, and liaison with the national reference laboratory. The algorithm was approved by the UHB Medical Scientific Advisory Group.

The algorithm was disseminated and implemented with the help of daily infection specialist ITU rounds, and education sessions delivered to the ITU clinical teams. A month-long pilot screening programme was performed from February 1st, 2021, followed by retrospective collection of clinical, radiological, laboratory, and prescribing data.

Box 1
COVID-19-associated pulmonary aspergillosis diagnostic criteria

Possible CAPA.

- Radiological findings of evolving pulmonary infiltrate or cavitating infiltrate (not attributed to another cause)

and at least one of the following:

- Positive non-BAL respiratory culture
- Single positive NBL GM

Probable CAPA.

- Radiological findings of evolving pulmonary infiltrate or cavitating infiltrate (not attributed to another cause)

and at least one of the following:

- Positive BAL culture
- Positive serum GM
- Raised serum (1–3)-β-D-glucan
- Positive BAL GM

Proven CAPA.

- Histopathological or direct microscopic detection of fungal hyphae, showing invasive growth with associated tissue damage

or

- *Aspergillus* spp. Recovered by culture/microscopy/histology/PCR obtained by a sterile aspiration or biopsy from a pulmonary site, showing an infectious disease process

CAPA, COVID-19-associated pulmonary aspergillosis; BAL, bronchoalveolar lavage; NBL, non-directed BAL; GM, galactomannan; PCR, polymerase chain reaction.

Results

During February 2021, 205 patients underwent CAPA screening (65% male). The number of ventilated COVID-19 patients ranged from 55 to 69 per day. Regarding prescribing, 56% of patients received tocilizumab, 95% dexamethasone, and 40% voriconazole. The 30-day, all-cause mortality was 16.6%.

During this period, 829 fungal biomarker tests were performed: 709 serum galactomannan, 101 serum (1–3)-β-D-glucan and 19 deep respiratory galactomannan tests.

Nineteen (9.3%) patients were identified with possible and 14 (6.8%) with probable CAPA. Serum galactomannan testing alone had a sensitivity of 44% and specificity of 96% for probable CAPA. There was no correlation between serum galactomannan index value and likelihood of a diagnosis of CAPA.

Of the 82 patients who received voriconazole, 30% of prescriptions were considered appropriate (in patients fulfilling criteria of possible or probable CAPA). All patients with probable CAPA were treated with voriconazole. The compliance with CAPA screening among patients prescribed voriconazole was 74%.

Discussion

Although we were able to implement a CAPA diagnostic algorithm during the first wave of the pandemic, and compliance to screening among those prescribed voriconazole was good, we did not observe risk-stratified voriconazole prescribing.

Future steps include a reassessment of the diagnostic accuracy of fungal biomarkers in this cohort in the subsequently published literature, feedback from ITU clinicians and redesign of the algorithm with education to users. The changing epidemiology of COVID-19 and differing workload pressures within the ITU and the laboratory may provide the opportunity to perform more BALs and NBLs and to use this specimen type more frequently. This would be beneficial as serum galactomannan has demonstrated low sensitivity and needs to be considered with other diagnostic elements, including clinical and radiological indicators as well as fungal culture and fungal biomarkers from different specimen types.

Conflict of interest statement
None declared.

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