National Institute for Health and Care Excellence

NICE COVID-19 rapid guideline: managing COVID-19

[J] Evidence review COVID-19 Associated Pulmonary Aspergillosis (CAPA) – Diagnostics

NICE guideline NG191

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Guideline version (Final)

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Background

COVID-19 disease is known to have a range of potential complications and co-infections. Secondary fungal infections (aspergillus) have been reported in patients following hospitalisation (Chong et al., 2021a). Although the incidence is low, the mortality rate is high. Recommendations on identifying, diagnosing, and treating secondary fungal infections are required to ensure consistent practice and help improve outcomes for people with these infections (Chong et al., 2021b).

Objective

This review aims to describe the tests that can be carried out to confirm a diagnosis of CAPA and does not evaluate the performance or accuracy of each test type.

Review questions

A description of the relevant population, intervention, comparison and outcomes (PICO) for this review was developed by NICE for the topic (see appendix A for more information). The review question for this evidence review is:

1. What tests should be carried out to confirm a diagnosis of CAPA?

Methodology

The evidence review was developed using NICE interim process and methods for guidelines developed in response to health and social care emergencies.

A recent taskforce report was identified, which is highly relevant to the reviews being undertaken on CAPA (Verweij et al., 2021). In addition to the evidence review, relevant information from this document was presented to the panel and considered when making recommendations. This is reflected in the Evidence to Decision section supporting the recommendations.

This evidence review only aims to describe current investigations for CAPA and review does not aim to evaluate or test the accuracy or performance of the diagnostics and as such, risk of bias assessment was conducted at study level, not at outcome level.

The frequency of test usage (common and uncommon) is defined by the absolute number of participants who are prescribed each investigation. Outcomes where the numbers of participants exceeded 300 people were defined as common investigations as they constituted 10% of the overall study population.

Summary of included studies

A literature search for CAPA identified 466 references (see appendix B for full details). These references were screened using their titles and abstracts and 26 full text references were obtained and assessed for relevance.

22 studies were excluded. Details of the excluded studies are in appendix C.

4 studies are included in this evidence summary (2 systematic reviews – Chong 2021a and Dimopoulos 2021; 2 primary studies – Meawed 2021 and van Grootveld 2021). Chong 2021b included 19 studies in their review and all studies were evaluated as part of this review. Dimopoulous 2021 included 31 cohort studies in their systematic review, however only 8 studies were used in this evidence review due to overlap with Chong 2021a. A summary of the included studies and their quality assessment is shown in appendices D and E. Results from studies were combined, but the data was cross-sectional and not comparative. Therefore, no forest plots were produced.

Study characteristics

Study characteristic	Chong 2021a*	Dimopoulos 2021*	Meawed 2021	van Grootveld 2021
Location and setting	Belgium, Denmark, France, Germany, Italy, Mexico, Netherlands, Pakistan, Spain, Switzerland	Austria, Brazil, Belgium, China, Denmark, France, Germany, Ireland, Italy, Netherlands, Pakistan, Spain, Switzerland, UK, USA	Egypt	The Netherlands
Study design	Systematic review (19 studies)	Systematic review (8/31 studies in the systematic were used in this evidence review)	Cross-sectional study	Cohort study
No. of patients (N)	1494	1272	197	63

Study characteristic	Chong 2021a*	Dimopoulos 2021*	Meawed 2021	van Grootveld 2021
Follow-up	NA	NA	NA	NA
Age (years)	Range 36 - 97	Range 55 - 73	Range 51 - 79	Range 57 -71
Gender (% male)	80%	34%	60%	73%
Baseline characteristics	This review included 19 cohort studies. Most participants were males who were hospitalised with varying severity of COVID-19 and CAPA disease. A total of 23.8% of CAPA patients had EORTC/MSG** host risk factors and the diagnosis of probable, possible, or putative CAPA was made as per different diagnostic criteria (AspICU**, EORTC/MSG**, Modified AspICU-DB**, CAPA-ECMM**)	This review included evidence from 8/31 studies in the Dimopoulos systematic review (n=1272) with probable-possible CAPA diagnosis and confirmed COVID-19. Participants had varying co-morbidities (for example, diabetes, cardiovascular disease, chronic lung disease and hypertension.	Participants were critically ill with COVID-19 and were admitted to ICU as part of their clinical management. 197 participants were included in this study. Most of the participants were male and had a host of underlying disease such as hypertension (62.4%) and diabetes (56.3%). All participants were treated with antibiotics, steroids and tocilizumab for COVID-19 and all participants died by the end of the study collection period.	Participants included in this study were critically ill with confirmed COVID-19. Most participants were male. Participants presented with different comorbidities (for example chronic pulmonary disease, diabetes, malignant neoplasm). All participants were invasively ventilated in ICU and received vasoactive drugs.
COVID-19 infection	Confirmed SARS-CoV-2 infection with RT-PCR	Confirmed SARS-CoV-2 infection with RT-PCR	Confirmed SARS-CoV-2 infection with RT-PCR	Confirmed SARS-CoV-2 infection with RT-PCR
CAPA infection	Participants have suspected CAPA.	Participants have suspected CAPA.	Participants have suspected CAPA.	Participants have suspected CAPA.

Study characteristic	Chong 2021a*	Dimopoulos 2021*	Meawed 2021	van Grootveld 2021
Inclusion criteria	(1) observational studies that described the incidence, clinical characteristics, biomarkers, and outcomes of invasive pulmonary aspergillosis in hospitalised adults with COVID-19 infections. (2) studies where the diagnosis of CAPA was made using several well-established diagnostic criteria that had been described in the current literature involving AspICU, CAPA-ECMM**, Modified AspICU**, Modified AspICU-DB**, IAPA** or EORTC/IFICG** and EORTC/MSG**. (3) studies in which the diagnosis of COVID-19 was made by reverse transcriptase-polymerase chain reaction (RT-PCR) in all cases from respiratory tract specimens that included nasal and pharyngeal swabs, sputum, endotracheal aspirates and bronchoalveolar lavages. (4) articles published between 1st	Not reported	All participants admitted to ICU with COVID-19 and microbial superinfection between October 2020 and April 2021	All participants hospitalised with COVID-19 and admitted to ICU between April 2020 and May 2020

Study characteristic	Chong 2021a*	Dimopoulos 2021*	Meawed 2021	van Grootveld 2021
	January 2020 and 20th March 2021 in peer-reviewed journals			
Main exclusion criteria	(1) Studies that did not meet or described specific diagnostic criteria for CAPA diagnosis, that could represent colonization or had coexisting bacterial and/or (non-Aspergillus) fungal microorganisms simultaneously identified from the lower respiratory tract specimens and/or blood cultures. (2) Studies with fewer than 18 patients (defined as case series) and/or case reports. (3) Studies involving COVID-19 patients of less than 18 years of age. (4) Studies where pulmonary aspergillosis was concurrently diagnosed with other micro-organisms such as bacteria and/or viruses from similar	Not reported	Not reported	Not reported

Study characteristic	Chong 2021a*	Dimopoulos 2021*	Meawed 2021	van Grootveld 2021
	respiratory tract cultures. (5) Studies describing aspergillosis obtained from non-respiratory tract cultures.			
Other notes	Diagnostic criteria used to categorise patients in this review are: AspICU, Modified AspICU-DB**, Modified AspICU-G**, EORTC/MSG** and ECMM**.	Diagnostic criteria used to categorise patients in this review are: AspICU**, Modified AspICU-DB**, Modified AspICU-G**, EORTC/MSG** and ECMM**.	Diagnostic criteria used to categorise patients not reported. Mortality rate was 100% for this study indicative of the presence of nosocomial infections in the ICU.	Diagnostic criteria used to categorise patients in this review are: AspICU**, EORTC/MSG** and ECMM**.

*Please note that individual microbiological testing prevalence was collected by NICE, and the studies report on overall figures for each test category.

<u>Abbreviations:**</u> **AspICU:** Aspergillosis Intensive Care Unit algorithm; **AspICU-DB:** Aspergillosis Intensive Care Unit-Dutch/Belgian algorithm; **AspICU-G** Aspergillosis Intensive Care Unit-German algorithm; **EORTC:** European Organization for Research and Treatment of Cancer; **CAPA:** COVID-19 associated pulmonary aspergillosis; **CAPA-ECMM:** COVID-19 associated pulmonary aspergillosis/European Confederation of Medical Mycology; **EORTC/IFICG:** European Organization for Research and Treatment of Cancer/ Invasive Fungal Infections Cooperative Group; **EORTC/MSG:** European Organization for Research and Treatment of Cancer/ Mycoses Study Group; **IAPA:** Influenza associated pulmonary aspergillosis; **ICU:** Intensive Care Unit.

Results

Review question: What tests should be carried out to confirm a diagnosis of CAPA?

This review aimed to determine the diagnostic tests that should be used to diagnose CAPA in people with COVID-19. The evidence highlighted the range of tests that are used in clinical practice.

What is the evidence informing this conclusion?

Evidence comes from 2 systematic reviews that evaluate different diagnostic investigations for people with COVID-19 and suspected CAPA (Chong 2021 and Dimopoulos 2021). A further 2 studies were included in this evidence review to supplement the findings of the included systematic reviews: a cross-sectional study (Meawed 2021) and a cohort study (van Grootveld 2021).

Publication status

All included studies were full publications (Chong 2021, Dimopoulos 2021, Meawed 2021 and van Grootveld 2021).

Study characteristics

Study participant numbers ranged from 63 people (van Grootveld 2021) to 1494 people (Chong 2021b). The average age of participants ranged from 62 to 63 years. The proportion of male participants ranged from 34% to 80% of the study population. All participants had a wide range of underlying comorbidities (for example, hypertension, diabetes, chronic pulmonary disease, cardiovascular disease, and active malignancies).

Most participants (94%; n= 2829/3026) were hospitalised and admitted to ICU with severe COVID-19 and only 6% had moderate COVID-19 (197/3026). Disease severity was mostly scored against the WHO Clinical Progression Scale.

What are the main results?

The evidence described the use of bronchoalveolar lavage (BAL), endotracheal aspirates (ETA), serum, non-directed bronchial lavage (NBL) and sputum to diagnose

CAPA. The different microbiological investigations performed on each sample (such as tissue culture, galactomannan and beta-d-glucan biomarker levels, PCR) were also described in the literature.

CT imaging, serum assays (galactomannan (GM) and beta-d-glucan (BDG)), ETA culture and BAL are commonly used to support CAPA diagnosis. Further BAL sample investigations such as microscopy, culture, GM, BDG and PCR are also commonly used to support CAPA diagnosis.

The evidence shows that sputum sampling, NBL and ETA investigations like GM, BDG and PCR are not as commonly used to diagnose CAPA, as their prevalence was relatively low when compared to that of CT imaging, BAL, and serum assays.

The findings of this review are consistent with existing recommendations on diagnosing CAPA (Verweij et al. 2021). The Verweij et al. 2021 report states that bronchoscopy alongside BAL is recommended to diagnose CAPA and states that ETA and sputum should not be relied on solely to diagnose CAPA.

Narrative summary of results

The following results were calculated from the primary studies included in the systematic reviews and subsequent primary studies identified in the search.

CT imaging

Twenty-two studies reported that 770/1607 (48%) of participants had undergone a CT imaging investigation to support CAPA diagnosis.

Serum galactomannan

Twenty-two studies reported that 957/1227 (78%) of participants had undergone a serum galactomannan investigation to support CAPA diagnosis.

Serum beta-D-glucan

Nine studies reported that 636/1566 (41%) of participants had undergone a serum beta-d-glucan investigation to support CAPA diagnosis.

Endotracheal aspirate culture

Fourteen studies reported that 370/1059 (35%) of a participants had undergone a endotracheal aspirate microscopy investigation to support CAPA diagnosis.

Endotracheal aspirate Beta-d glucan

Four studies reported that 52/383 (14%) of participants had undergone a endotracheal aspirate beta-d-glucan investigation to support CAPA diagnosis.

Endotracheal Aspirate PCR

10 studies reported that 127/1558 (8%) of patients had undergone an endotracheal aspirate PCR investigation to support CAPA diagnosis.

Non-directed Bronchial Lavage Culture

Eight studies reported that 217/744 (29%) of participants had undergone a non-directed bronchial lavage culture investigation to support CAPA diagnosis.

Non-directed Bronchial Lavage Galactomannan

Five studies reported that 78/344 (23%) of participants had undergone a non-directed bronchial lavage galactomannan investigation to support CAPA diagnosis.

Non-directed Bronchial Lavage PCR

Seven studies reported that 66/692 (10%) of participants had undergone a non-directed bronchial lavage PCR investigation to support CAPA diagnosis.

Bronchoalveolar Lavage Microscopy

Two studies reported that 16/73 (22%) of participants had undergone a bronchoalveolar lavage microscopy investigation to support CAPA diagnosis.

Bronchoalveolar Lavage Culture

Twenty-two studies reported that 572/1589 (36%) of participants had undergone a bronchoalveolar lavage culture investigation to support CAPA diagnosis.

Bronchoalveolar Lavage Galactomannan

Eighteen studies reported that 518/1159 (45%) of participants had undergone a bronchoalveolar lavage galactomannan investigation to support CAPA diagnosis.

Bronchoalveolar Lavage PCR

Fifteen studies reported that 540/1418 (38%) of participants had undergone a bronchoalveolar lavage PCR investigation to support CAPA diagnosis.

Sputum

Six studies reported that 241/564 (43%) of participants had undergone a sputum investigation to support CAPA diagnosis.

Our confidence in the results

GRADE could not be conducted on the results of this review because the results were descriptive rather than analytical.

There were some concerns about risk of bias due to unclear reporting of participant eligibility criteria in all studies (Chong 2021b, Dimopoulous 2021, Meawed 2021 and van Grootveld 2021). There was also insufficient information to assess the data collection and data analysis methods used in Chong 2021b and Dimopoulous 2021 and as such, risk of bias was rated as high for both studies.

The two systematic reviews contained studies from international centres and as such, there may have been differences in standard of care as well as diagnostic investigations and assessment criteria. As such, there is risk of the evidence being indirect to the UK context.

Although Chong 2021b defined clear eligibility criteria to limit the heterogeneity, studies are heterogeneous with epidemiological, clinical, and methodological diversity, meaning that it may not be possible to generalise the results.

Conclusion

The review has found that CT imaging, serum assays of biomarkers, ETA culture and BAL are the most common investigations for diagnosing CAPA.

The findings of this review are consistent with current recommendations on diagnosing CAPA.

References

Chong, W.H. and Neu, K.P., 2021a. The incidence, diagnosis, and outcomes of COVID-19-associated pulmonary aspergillosis (CAPA): a systematic review. *Journal of Hospital Infection*

Chong, W.H., Saha, B.K., Ramani, A. and Chopra, A., 2021b. State-of-the-art review of secondary pulmonary infections in patients with COVID-19 pneumonia. *Infection*, pp.1-15.

Dimopoulos, G., Almyroudi, M.P., Myrianthefs, P. and Rello, J., 2021. COVID-19-associated pulmonary aspergillosis (CAPA). *Journal of Intensive Medicine*.

Koehler, P., Bassetti, M., Chakrabarti, A., Chen, S.C., Colombo, A.L., Hoenigl, M., Klimko, N., Lass-Flörl, C., Oladele, R.O., Vinh, D.C. and Zhu, L.P., 2020. Defining and managing COVID-19-associated pulmonary aspergillosis: the 2020 ECMM/ISHAM consensus criteria for research and clinical guidance. *The Lancet Infectious Diseases*.

Meawed, T.E., Ahmed, S.M., Mowafy, S.M., Samir, G.M. and Anis, R.H., 2021. Bacterial and fungal ventilator associated pneumonia in critically ill COVID-19 patients during the second wave. *Journal of infection and public health*, *14*(10), pp.1375-1380.

van Grootveld, R., van Paassen, J., de Boer, M.G., Claas, E.C., Kuijper, E.J., van Der Beek, M.T. and LUMC-COVID-19 Research Group, 2021. Systematic screening for COVID-19 associated invasive aspergillosis in ICU patients by culture and PCR on tracheal aspirate. *Mycoses*, *64*(6), pp.641-650.

Verweij, P.E., Brüggemann, R.J., Azoulay, E., Bassetti, M., Blot, S., Buil, J.B., Calandra, T., Chiller, T., Clancy, C.J., Cornely, O.A. and Depuydt, P., 2021.

Taskforce report on the diagnosis and clinical management of COVID-19 associated pulmonary aspergillosis. *Intensive Care Medicine*, pp.1-16.

Evidence to decision

Benefits and harms

The panel were presented with information from a taskforce report by Verweij et al. on diagnosing and managing CAPA that prevalence of CAPA in people being treated in ICU was between 0% and 33% (the average across included studies was 9.3%). They discussed that this prevalence included possible as well as probable and proven CAPA, and was therefore likely to be an overestimation. The panel agreed that in their experience, prevalence of CAPA is low, and so testing for CAPA should only take place if there is clinical suspicion of the condition.

The panel were also presented with evidence from 2 systematic reviews (Chong 2021 and Dimopoulos 2021), and 2 primary studies (Meawed 2021 and van Grootveld 2021). The panel discussed the most common types of diagnostic tests and also referred to the taskforce report by Verweij et al.

The evidence showed that a range of different diagnostic test types are conducted to confirm CAPA diagnosis. The panel agreed that some of the common tests for diagnosing CAPA, for example bronchoalveolar lavage (BAL), are invasive and so the risks of carrying out the test should be considered against the benefit of a potential diagnosis.

The evidence described the frequency of diagnostic tests that are used to investigate CAPA. It showed that bronchoalveolar lavage (BAL) is one of the most commonly used diagnostic tests for diagnosing CAPA. Of the studies included, 55% of people had a BAL carried out, with further investigations on the sample (for example culture, galactomannan and PCR). The panel noted that BAL is carried out in intensive care units in people who are critically ill and invasively mechanically ventilated to investigate infectious lung disease.

The taskforce report discussed by the panel, recommends bronchoscopy with BAL, stating that it is the most important tool to diagnose invasive pulmonary aspergillosis, including in people who are critically ill and have, or have had, COVID-19 as part of their acute illness. The panel acknowledged that BAL is an invasive procedure that is

not risk-free and may not be feasible to carry out in all patients, particularly in patients who remain on non-invasive ventilation.

The reviewed studies and the taskforce report also reported that other tests such as endotracheal aspirates, serological assays for beta-D-glucan and galactomannan (fungal biomarkers) are used to diagnose CAPA. Overall, the panel agreed that there are variations in the sensitivity and specificity of diagnostic tests, but that BAL may perform most favourably for the diagnosis of CAPA.

The panel concluded that BAL is the preferred diagnostic approach for investigating a CAPA diagnosis, but the risks and harms from carrying out the procedure need to be carefully assessed and other tests should be used alongside BAL or if BAL is not possible.

The panel discussed that, in their experience, a diagnosis of CAPA should usually be made as part of a multidisciplinary team with input from infection specialists, for example medical microbiologists or infectious disease specialists.

The panel agreed that the approach for diagnosing CAPA in children and young people should be the same as the approach for adults, however the levels of serum biomarkers may be different.

Certainty of the evidence

It was not possible to apply GRADE to the outcomes in this review, because the outcomes were descriptive rather than analytical.

The panel agreed that the studies were at moderate to high risk of bias due to high heterogeneity between study participants and variations in local practice in study centres. The panel agreed that the evidence informing the taskforce report by Verweij et al on diagnosing and managing CAPA was sparse.

Based on the evidence, the panel agreed that it was not possible to identify with certainty which tests, and in which order, should be used to diagnose CAPA. They also agreed that it would not be possible to determine the best diagnostic tests to request when CAPA was suspected. The panel agreed that unless CAPA was suspected clinically, further investigations for CAPA should not be carried out. They

agreed with the taskforce report that a BAL is likely to be the most accurate test for diagnosing CAPA based on the evidence of comparisons of diagnostic tests in IPA more broadly.

Values and preferences

The panel considered that some of the diagnostic tests for CAPA, for example a bronchoscopy or BAL, may involve clinical risk or patient discomfort and some people may be apprehensive about having it done. Therefore these tests should be carried out following an appropriate multidisciplinary discussion and decision on the clinical suspicion of CAPA. They suggested that the risks and patient experience may be different if the person is already on invasive mechanical ventilation. The panel suggested that people's preferences and values should be considered as part of the shared-decision making process with the patients and their families

The panel were not aware of any systematically collected data on preferences and values of people in relation to the different investigations that are used to diagnose CAPA.

Resources

The panel discussed the need for timely testing and diagnostics to investigate CAPA. Since BAL is a commonly used diagnostic test for the assessment of pulmonary aspergillosis, it is not expected that this recommendation will lead to significant changes in resource utilisation. One of the recommendations advises against investigation when suspicion is low, so has potential for savings in resource use from unnecessary procedures.

Cost-effectiveness was not assessed as part of the evidence review.

Equity

The panel noted that there was no information reported on pregnant women or children aged 17 and under, but that assessments should take place in the same way for all people who are critically ill because of current or previous COVID-19.

No other equity issues were identified.

Acceptability

The panel discussed that, in their experience, there are few issues with acceptance of BAL as a diagnostic tool for CAPA among people who are critically ill and have, or have had, COVID-19 as part of their acute illness. However, the panel noted that in some cases, people may reject BAL or bronchoscopy as it may cause some discomfort.

Feasibility

The panel were not aware of any systematically collected evidence about feasibility. They agreed that testing for CAPA only in cases where there is a clinical suspicion of CAPA should be feasible, especially where it results in a reduction in testing.

The panel identified several potential barriers to feasibility. They noted that while BAL is recommended to diagnose CAPA, a wait is required for the results of BAL to become available. The panel noted that bronchoscopy may not always be feasible to carry out in patients with suspected CAPA. The panel addressed these feasibility concerns by ensuring that other diagnostic tests for CAPA were also included in the recommendation.

Appendices

Appendix A: PICO table

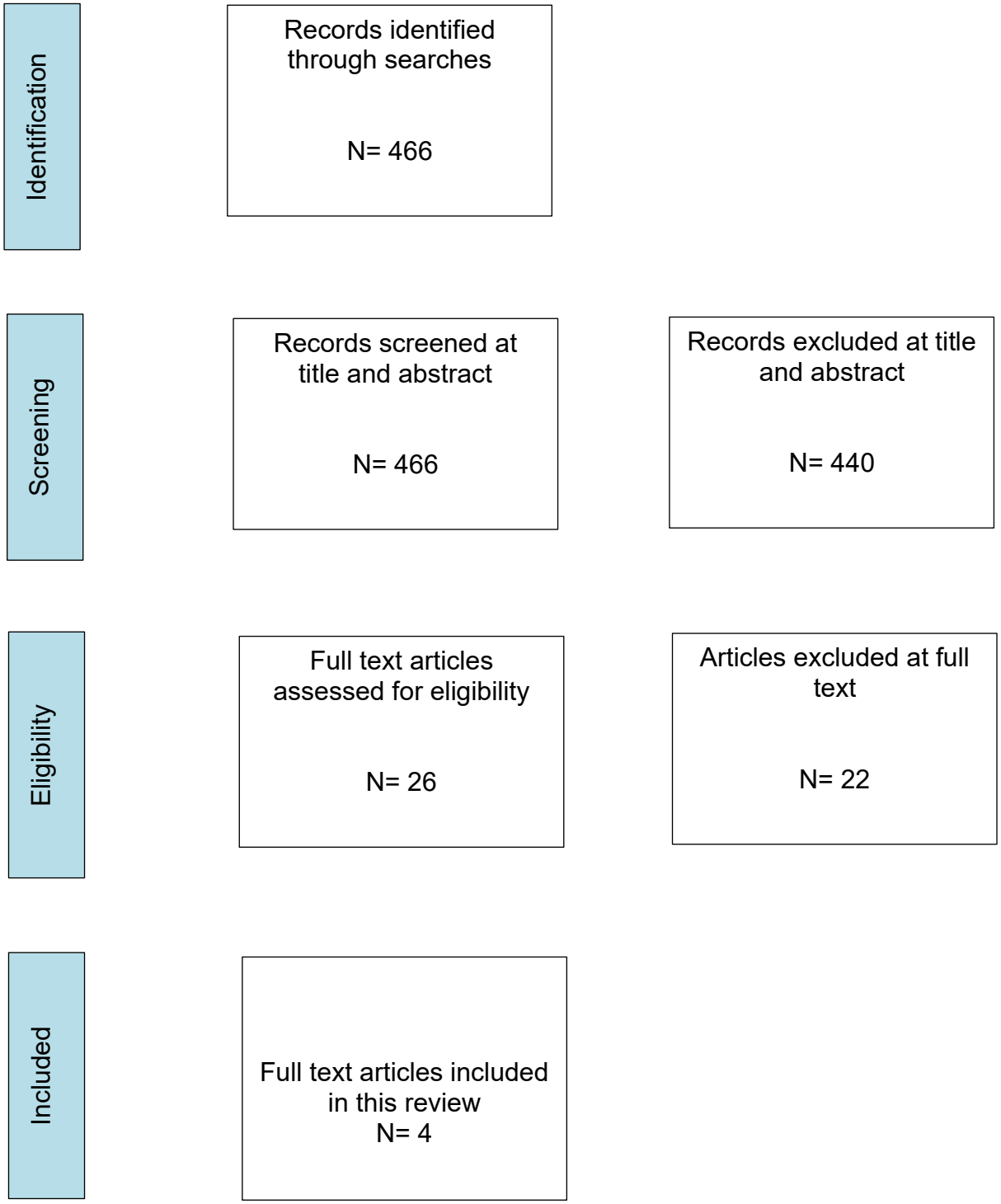
Question: What tests should be carried out to confirm a diagnosis of CAPA?

Criteria	Notes
Population	Adults, young people and children who are critically ill and have or, as part of their acute illness, have had confirmed COVID-19, and who have suspected CAPA.
Diagnostic tests	• Imaging evidence of invasion (i.e. CT) • Serological evidence of invasion (blood galactomannan or lateral flow) • Histological evidence of invasion (biopsy) • Evidence of airway colonisation (tracheal aspirate, NBL, sputum etc.) • Evidence of lung colonisation (BAL micro/culture/galactomannan) Tests may be used in combination.
Target condition	COVID-19 associated pulmonary aspergillosis (CAPA)
Outcomes	Frequency of tests being used for diagnosis of CAPA where CAPA is suspected. Tests recommended for use in diagnosing CAPA by guidance or consensus.
Settings	Any settings for people who are critically ill
Subgroups	• People who are already receiving antifungal treatment for CAPA vs people who are not receiving antifungal treatment for CAPA. • Corticosteroid therapy vs no corticosteroid therapy for COVID-19. • Immune competence at baseline (all groups with immune incompetence vs others. Immune incompetence can be defined as people with neutropenia, people undergoing chemotherapy, or people with inborn or acquired immunodeficiency).

Study types	• Cohort studies • Cross-sectional studies • Guidance documents • Systematic reviews of included study designs.
Countries	Any
Timepoints	From 2020 onwards
Other exclusions	The scope sets out what the guidelines will and will not include (exclusions). Further exclusions specific to this guideline include: • non-English language papers, studies that are only available as abstracts, and narrative reviews • animal studies • editorials, letters, news items, case reports and commentaries, conference abstracts and posters • theses and dissertations
Equality issues	Sex, age, ethnicity, religion or beliefs, people with a learning disability and disabled people, socioeconomic status, people who are pregnant or breastfeeding, people whose first language isn't English, people who are homeless, refugees, asylum seekers, migrant workers and people who are homeless.

Appendix B: Literature search strategy/Data source

PRISMA flowchart



Search history methods

The searches for the effectiveness evidence were run on 12 10 2021. The following databases were searched: Central Register of Controlled Trials (Wiley), Cochrane Database of Systematic Reviews (Wiley), Embase (Ovid), MEDLINE ALL (Ovid), NICE Evidence Search and the World Health Organisation Covid-19 database. Full search strategies for each database are provided in Appendix B. Pre-prints were searched via EPPI reviewer v5.

A NICE information specialist conducted the searches. The MEDLINE strategy was quality assured by a trained NICE information specialist and all translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the 2016 PRESS Checklist.

Search design and peer review

This search was developed in compliance with Appendix L of NICE's manual on developing guidelines.

A NICE information specialist conducted the literature searches for the evidence review. The searches were run on 12/10/2021. This search report is compliant with the requirements of PRISMA-S.

The MEDLINE strategy below was quality assured (QA) by a trained NICE information specialist. All translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the 2016 PRESS Checklist.

The principal search strategy was developed in MEDLINE (Ovid interface) and adapted, as appropriate, for use in the other sources listed in the protocol, taking into account their size, search functionality and subject coverage.

NICE's approach to retrieving preprints has evolved throughout the pandemic:

- Prior to 20th April 2020 MedRxiv and BioRxiv were searched directly.
- From 20th April 2020 an automated process was used to download the entire MedRxiv and BioRxiv COVID-19 and SARS-COV-2 collection into EPPI Reviewer 5 and update the results daily. Individual topic searches were

conducted within EPPI Reviewer to get round the limitations of the native search functionality in MedRxiv and BioRxiv.
- From 19th August 2021, results from additional preprint servers were added to the EPPI Reviewer database on a weekly basis. The additional results were sourced from the aggregator sites Europe PMC and the NIH Office of Portfolio Analysis COVID-19 database. These sites index multiple preprint servers, including Arxiv, MedRxiv, BioRxiv, Research Square, SSRN and preprints.org. The NIH database is pre-sifted for COVID-19 related references. Europe PMC is broader, and so we initially used their stock strategy to narrow the results down to a subset that were related to COVID-19. References added to the aggregator sites from the 10th August 2021 were downloaded, but searches of these sources were not backdated further.

Review management

The search results were managed in EPPI-Reviewer v5. Duplicates were removed in EPPI-R5 using a two-step process. First, automated deduplication is performed using a high-value algorithm. Second, manual deduplication is used to assess 'low-probability' matches. All decisions made for the review can be accessed via the deduplication history.

Limits and restrictions

English language limits were applied in adherence to standard NICE practice and the review protocol.

The search was limited from 2020 to date as defined in the review protocol.

Search filters

- Covid-19 filter

The development of NICE's main database search strategy for Covid-19 is covered in: Levay P and Finnegan A (2021) The NICE COVID-19 search strategy for Ovid MEDLINE and Embase: developing and maintaining a strategy to support rapid guidelines. MedRxiv preprint. https://doi.org/10.1101/2021.06.11.21258749

- Systematic reviews filters

The MEDLINE SR filter was "Health-evidence.ca Systematic review search filter" from Lee et al. (2012). The standard NICE modifications were used: pubmed.tw added; systematic review.pt added from MeSH update 2019.

The Embase SR filter was “Health-evidence.ca Systematic review search filter” from Lee et al. (2012). The standard NICE modifications were used: pubmed.tw added to line medline.tw.

Lee, E. et al. (2012) An optimal search filter for retrieving systematic reviews and meta-analyses. *BMC Medical Research Methodology,* 12(1), 51.

- RCT filters

The MEDLINE RCT filter was McMaster Therapy – Medline - “best balance of sensitivity and specificity” version. The standard NICE modifications were used: randomized.mp changed to randomi?ed.mp.
Haynes RB et al. (2005) Optimal search strategies for retrieving scientifically strong studies of treatment from Medline: analytical survey. *BMJ*, 330, 1179-1183.
The Embase RCT filter was McMaster Therapy – Embase “best balance of sensitivity and specificity” version.
Wong SSL et al. (2006) Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. *Journal of the Medical Library Association*, 94(1), 41-47.

Main search – Databases

Database	Date searched	Database platform	Database segment or version	No. of results downloaded
MEDLINE ALL	12/10/21	Ovid	Ovid MEDLINE(R) ALL 1946 to October 11, 2021	170
Embase	12/10/21	Ovid	Embase 1974 to 2021 October 11	167
Cochrane - Cochrane Database of Systematic Reviews	12/10/21	Wiley	Cochrane Database of Systematic Reviews Issue 10 of 12, October 2021	0
Cochrane - CENTRAL	12/10/21	Wiley	*Cochrane* Central Register of Controlled Trials Issue 10 of 12, October 2021	4

MedRxiv/BioRxiv/Europe PMC/NIH Portfolio Preprints [EPPI review]	12/10/21	Wiley	pre-prints v3 09:29	12
WHO Covid-19 Database	12/10/21	N/A	N/A	0 (Searched but nothing unique found)
NICE Evidence Search	12/10/21	N/A	N/A	0 (Searched but nothing unique found)

Search strategy history

Database name: MEDLINE ALL

1 SARS-CoV-2/ or COVID-19/ (112571)

2 (corona* adj1 (virus* or viral*)).ti,ab,kw,kf. (4214)

3 (CoV not (Coefficien* or "co-efficien*" or covalent* or Covington* or covariant* or covarianc* or "cut-off value*" or "cutoff value*" or "cut-off volume*" or "cutoff volume*" or "combined optimi?ation value*" or "central vessel trunk*" or CoVR or CoVS)).ti,ab,kw,kf. (64038)

4 (coronavirus* or 2019nCoV* or 19nCoV* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or SARSCoV2* or "SARS-CoV2*" or "severe acute respiratory syndrome*" or COVID*2).ti,ab,kw,kf. (196275)

5 or/1-4 (201655)

6 limit 5 to yr="2020-Current" (188328)

7 (6 and english.lg.) not (letter or historical article or comment or editorial or news or case reports).pt. not (Animals/ not humans/) (138128)

8 exp Aspergillosis/ (17174)

9 aspergill*.ti,ab,kw,kf. (56403)

10 CAPA.ti,ab,kw,kf. (538)

11 azole-resist*.ti,ab,kw,kf. (1672)

12 or/8-11 (60368)

13 7 and 12 (170)

Database name: Embase

1 exp severe acute respiratory syndrome coronavirus 2/ or coronavirus disease 2019/ or experimental coronavirus disease 2019/ (161779)

2 (corona* adj1 (virus* or viral*)).ti,ab,kw. (3898)

3 (CoV not (Coefficien* or co-efficien* or covalent* or covington or covariant* or covarianc* or "cut-off value*" or "cutoff value*" or "cut-off volume*" or "cutoff volume*" or "combined optimi?ation value*" or "central vessel trunk" or CoVR or CoVS)).ti,ab,kw. (56317)

4 (coronavirus* or 2019nCoV* or 19nCoV* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or SARSCoV2* or "SARS-CoV2*" or "severe acute respiratory syndrome*" or COVID*2).ti,ab,kw. (198000)

5 or/1-4 (212228)

6 limit 5 to yr="2020-Current" (197095)

7 (6 and english.lg.) not (letter or editorial or conference).pt. not (nonhuman/ not human/) not "case report".sh. not medline*.db. (89410)

8 exp aspergillosis/ (28021)

9 aspergill*.ti,ab,kw. (71121)

10 CAPA.ti,ab,kw. (689)

11 azole-resist*.ti,ab,kw. (2043)

12 or/8-11 (80048)

13 7 and 12 (167)

14 (conference abstract or conference paper or conference proceeding or "conference review").pt. (4991938)

15 13 not 14 (167)

Database name: Cochrane Database of Systematic Reviews / Central Register of Controlled Trials

#1 MeSH descriptor: [SARS-CoV-2] this term only 479

#2 MeSH descriptor: [COVID-19] this term only 657

#3 (corona* near/1 (virus* or viral*)):ti,ab,kw 262

#4 (CoV NOT (Coefficien* or "co-efficient" or “co-efficiency” or “co-efficiencies” or covalent* or Covington* or covariant* or covarianc* or "cut-off value" or "cut-off values" or "cutoff value" or "cutoff values" or "cut-off volume" or "cut-off volumes" or "cutoff volume" or "cutoff volumes" or "combined optimisation value" or "combined optimisation values" or "combined optimization value" or "combined optimization values" or "central vessel trunk" or "central vessel trunks" or CoVR or CoVS)):ti,ab,kw 528

#5 (coronavirus* or 2019nCoV* or 19nCoV* or "2019 novel" or Ncov* or "n-cov" or "SARS-CoV-2" or "SARSCoV-2" or SARSCoV2* or "SARS-CoV2" or "severe acute respiratory syndrome" or "severe acute respiratory syndromes" or covid19 or covid-19 or covid):ti,ab,kw 7869

#6 {or #1-#5} with Cochrane Library publication date Between Jan 2020 and Dec 2021, in Cochrane Reviews 43

#7 {or #1-#5} with Publication Year from 2020 to 2021, in Trials 7644

#8 #6 OR #7 7687

#9 MeSH descriptor: [Aspergillosis] explode all trees 148

#10 aspergill*:ti,ab,kw 882

#11 CAPA:ti,ab,kw 140

#12 azole-resist*:ti,ab,kw 22

#13 {or #9-#12} 1038

#14 #8 and #13 4

Database name: Pre-print - medRxiv and bioRxiv/ Europe PMC/NIH Portfolio

These were searched via EPPI reviewer v5 using filters Title and Abstract HAS ALL and AND Title and Abstract HAS ANY.

Search term Aspergill*

Database name: World Health Organisation Covid-19 database

This was searched by using search term Aspergill*

Database name: NICE Evidence Search

This was searched by using search terms Aspergill*

Appendix C: Excluded studies at full text screening

Study	Reason for exclusion
Almyroudi, Maria Panagiota and Dimopoulos, George (2020) Covid-19 associated aspergillosis. Pneumon 33(2): 1-4	- Not a relevant study design *Non-systematic review*
Apostolopoulou, Anna, Esquer Garrigos, Zerelda, Vijayvargiya, Prakhar et al. (2020) Invasive Pulmonary Aspergillosis in Patients with SARS-CoV-2 Infection: A Systematic Review of the Literature. Diagnostics (Basel, Switzerland) 10(10)	- Study does not report any of the factors of interest specified in the protocol *There is no extractable data reported*
Borman, Andrew M, Palmer, Michael D, Fraser, Mark et al. (2020) COVID-19-Associated Invasive Aspergillosis: Data from the UK National Mycology Reference Laboratory. Journal of clinical microbiology 59(1): e02136-20-	- Study is covered in included systematic review
Charalampous, Themoula, Medina Adela, Alcolea-Medina, Snell Luke, B et al. Application of respiratory metagenomics for COVID-19 patients on the intensive care unit to inform appropriate initial antimicrobial treatment and rapid detection of nosocomial transmission. medrxiv preprint	- Not a relevant study design *Evaluation of diagnostics testing*
Chauvet, Paul, Mallat, Jihad, Arumadura, Clothilde et al. (2020) Risk Factors for Invasive Pulmonary Aspergillosis in Critically Ill Patients With Coronavirus Disease 2019-Induced Acute Respiratory Distress Syndrome. Critical care explorations 2(11): e0244	- Study is covered in included systematic review
Chong, Woon Hean; Saha, Biplab K; Neu, Kristoffer P (2021) Comparing the clinical characteristics and outcomes of COVID-19-associate pulmonary aspergillosis (CAPA): a systematic review and meta-analysis. Infection	- More recent systematic review included that covers the same topic *Included Chong review covers the same studies in this review and contains extractable data on diagnostics*
Eibschutz, Liesl S, Rabiee, Behnam, Asadollahi, Shadi et al. (2021) FDG-PET/CT of COVID-19 and Other Lung Infections. Seminars in nuclear medicine	- Not a relevant study design *Review of case series and reports (not cohort studies)*
Hoenigl, Martin, Egger, Matthias, Boyer, Johannes et al. (2021) Serum Lateral Flow assay with digital reader for the diagnosis of invasive pulmonary aspergillosis: A two-centre mixed cohort study. Mycoses 64(10): 1197-1202	- Not a relevant study design *Study is evaluating diagnostic tests*
Jenks, Jeffrey D; Nam, Hannah H; Hoenigl, Martin (2021) Invasive aspergillosis in critically ill patients: Review of definitions and diagnostic approaches. Mycoses 64(9): 1002-1014	- Review article but not a systematic review
Kariyawasam Ruwandi, M., Dingle Tanis, C., Kula Brittany, E. et al. COVID-19 Associated Pulmonary Aspergillosis: Systematic Review and Patient-Level Meta-Analysis. medrxiv preprint	- Study does not report any of the factors of interest specified in the protocol *Assesses the various diagnostic criteria and applies to case reports and cohort study data.*
Koehler, Philipp, Bassetti, Matteo, Chakrabarti, Arunaloke et al. (2021) Defining and managing COVID-19-associated pulmonary aspergillosis: the 2020 ECMM/ISHAM consensus criteria for	- Study is covered in included systematic review

Study	Reason for exclusion
research and clinical guidance. The Lancet. Infectious diseases 21(6): e149-e162	
Koehler, Philipp; Cornely, Oliver A; Kochanek, Matthias (2021) Bronchoscopy safety precautions for diagnosing COVID-19 associated pulmonary aspergillosis-A simulation study. Mycoses 64(1): 55-59	- Not a relevant study design *Simulation model for BAL, does not report frequency of BAL use*
Mortezaee, V., Saraee, S.A.S., Ghazanfari, M. et al. (2020) Invasive aspergillosis in COVID-19: A review study and recommendations for diagnostic approaches. Journal of Mazandaran University of Medical Sciences 30(184): 169-178	-Study does not report any of the factors of interest specified in the protocol *Study is a review but does not report extractable data on people with aspergillus infection*
Patrucco, Filippo, Airoldi, Chiara, Falaschi, Zeno et al. (2021) Mycotic infection prevalence among patients undergoing bronchoalveolar lavage with search of SARS-CoV-2 after two negative nasopharyngeal swabs. Journal of breath research 15(4)	- Not a relevant study design *Study is evaluating diagnostic tests*
Prattes, Juergen; Koehler, Philipp; Hoenigl, Martin (2021) COVID-19 associated pulmonary aspergillosis: regional variation in incidence and diagnostic challenges. Intensive care medicine: 1-2	- Not a relevant study design *A comment piece.*
Roman-Montes, Carla M, Martinez-Gamboa, Areli, Diaz-Lomelí, Paulette et al. (2021) Accuracy of galactomannan testing on tracheal aspirates in COVID-19-associated pulmonary aspergillosis. Mycoses 64(4): 364-371	- Not a relevant study design *Evaluates diagnostic tests*
Rothe, K., Feihl, S., Schneider, J., Wallnöfer, F., Wurst, M., Lukas, M., Treiber, M., Lahmer, T., Heim, M., Dommasch, M. and Waschulzik, B., 2021. Rates of bacterial co-infections and antimicrobial use in COVID-19 patients: a retrospective cohort study in light of antibiotic stewardship. *European Journal of Clinical Microbiology & Infectious Diseases*, *40*(4), pp.859-869.	-Study does not report any of the factors of interest specified in the protocol *Study does not report extractable data on people with aspergillus infection*
Taton, Olivier, Bondue, Benjamin, Knoop, Christiane et al. (2020) Role of the Bronchoalveolar Lavage in Noncritically Ill Patients during the SARS-CoV-2 Epidemic. Pulmonary Medicine 2020: 9012187	- Does not contain a population of people with CAPA *Evaluates BAL in COVID-19 not CAPA*
Van Biesen, Stefaan, Kwa, David, Bosman, Robert J et al. (2020) Detection of Invasive Pulmonary Aspergillosis in COVID-19 with Non-directed Bronchoalveolar Lavage. American journal of respiratory and critical care medicine	- Not a relevant study design *A letter*
Versyck, Maaike, Zarrougui, Wafa, Lambiotte, Fabien et al. (2021) Invasive pulmonary aspergillosis in COVID-19 critically ill patients: Results of a French monocentric cohort. Journal de mycologie medicale 31(2): 101122	- Study is covered in included systematic review
Verweij, Paul E, Gangneux, Jean-Pierre, Bassetti, Matteo et al. (2020) Diagnosing COVID-19-associated pulmonary aspergillosis. The Lancet Microbe 1(2): e53-e55	- Not a relevant study design *A comment piece*

Study	Reason for exclusion
White, P Lewis; Price, Jessica S; Backx, Matthijs (2021) Evaluation of the Performance of the Associates of Cape Cod STAT Assay for the Diagnosis of Invasive Fungal Disease in Critical-Care Patients with COVID-19. Journal of clinical microbiology 59(9): e0086921	- Not a relevant study design *Study is a case control*

Appendix D: Evidence tables

Chong, 2021

Bibliographic Reference	Chong, Woon H; Neu, Kristoffer P; The Incidence, Diagnosis, and Outcomes of COVID-19-associated Pulmonary Aspergillosis (CAPA): A Systematic Review.; The Journal of hospital infection; 2021

Study details

Study design	Systematic review
Aims/ review questions	This systematic review aimed to examine and discuss the incidence of CAPA, clinical characteristics, diagnostic criteria, biomarkers, and associated outcomes based on the literature available
Search date	31-Mar-2021
Country/ Geographical location	Belgium, Denmark, France, Germany, Italy, Mexico, Netherlands, Pakistan, Spain, Switzerland
Setting(s)	Hospitalised patients with COVID-19 and CAPA (ICU/ward-based)
Population description	This review included 19 cohort studies with participants' ages ranging from 36 to 97 years old. Most participants were males who were hospitalised with varying severity of COVID-19 and CAPA disease. A total of 23.8% of CAPA patients had EORTC host risk factors and the diagnosis of probable, possible, or putative CAPA was made as per different diagnostic criteria (AspICU, EORTC/MSG, Modified AspICU-DB, CAPA-ECMM)
Inclusion criteria	(1) observational studies that described the incidence, clinical characteristics, biomarkers, and outcomes of invasive pulmonary aspergillosis in hospitalized adults with COVID-19 infections. (2) articles where the diagnosis of CAPA was made using several well-established diagnostic criteria that had been described in the current literature involving AspICU, CAPA-ECMM, Modified AspICU, Modified AspICU-DB, influenza-associated pulmonary aspergillosis (IAPA) criteria or European Organization for Research and Treatment of Cancer/ Invasive Fungal Infections Cooperative Group and EORTC/MSG. (3) studies in which the diagnosis of COVID-19 was made by reverse transcriptase-polymerase chain reaction (RT-PCR) in all cases from respiratory tract specimens that included nasal and pharyngeal swabs, sputum, ETA and BAL. (4) articles published between 1st January 2020 and 20th March 2021 in peer-reviewed journals

Exclusion criteria	(1) articles that did not meet or described specific diagnostic criteria for CAPA diagnosis, that could represent colonization or had coexisting bacterial and/or (non-Aspergillus) fungal microorganisms simultaneously identified from the LRT specimens and/or blood cultures. (2) articles with fewer than 18 patients (defined as case series) and/or case reports. (3) articles involving COVID-19 patients of less than 18 years of age. (4) articles where pulmonary aspergillosis was concurrently diagnosed with other micro-organisms such as bacteria and/or viruses from similar respiratory tract cultures. (5) articles describing aspergillosis obtained from non-respiratory tract cultures.
Intervention/test/approach	Investigations for confirming CAPA diagnosis
Comparator (where applicable)	NA
Searching methods	A literature search was performed through Pubmed and Web of Science databases for articles published, using the keywords of “coronavirus disease 2019 (COVID-19),” “severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2),” “COVID-19- associated pulmonary aspergillosis (CAPA),” “fungal infections,” “secondary infections,” “fungal pneumonia,” “mycosis,” “Aspergillosis,” “Aspergillus,” and “invasive pulmonary aspergillosis (IPA).” All specified keywords were combined using the “OR” operator and “AND” operator for searching the literature. Moreover, to detect additional studies, any cited references were reviewed to identify relevant literature that met our inclusion criteria.
Methods of data analysis	Two researchers (W.C. and K.N.) independently screened the titles and abstracts and reviewed the full texts of articles to identify studies that evaluated the incidence, clinical characteristics, diagnostic criteria, biomarkers and associated outcomes of hospitalized COVID-19 patients diagnosed with CAPA. Any disagreements were resolved by discussion. The extracted data from full texts of included studies were added into a standardised Excel (Microsoft Corporation) form.
Methods to investigate heterogeneity	Not reported
Risk of bias assessment	Risk of bias was assessed using the Newcastle-Ottawa Scale. Two researchers performed this assessment of the included studies, and any disagreements were resolved by discussion.
Summary of findings	Not reported
Source of funding	None
Study limitations (Author)	Not reported

Study limitations (Reviewer)	There is high heterogeneity between the included studies in terms of participant numbers, CAPA incidence and COVID-19 pandemic context. There are also some studies included that combine diagnostics and do not provide extractable data for quantification and analysis.
Other details	Diagnostic criteria included in this review are: AspICU, Modified AspICU-DB, Modified AspICU-G, EORTC/MSG and ECMM

Characteristics

Study-level characteristics

Characteristic	Study (N = 1462)
Age Range	36 to 97
Male No of events	n = 921; % = 63
AspICU No of events	n = 20; % = 1.42
Modified AspICU-DB No of events	n = 919; % = 62.8
Modified AspICU-G No of events	n = 45; % = 3.1
EORTC/MSG No of events	n = 8; % = 0.48
IAPA No of events	n = 321; % = 22
CAPA-ECMM No of events	n = 149; % = 10.2

Outcomes

Diagnostic

Outcome	Study (N = 1462)
Bronchoalveolar Lavage (BAL)	n = 1144; % = 78

Outcome	Study (N = 1462)
No of events	
Endotracheal Aspirates (ETA) No of events	n = 158; % = 10.5
Bronchial Aspirates (BAS) No of events	n = 153; % = 11
Sputum No of events	n = 7; % = 0.5

Dimopoulos, 2021

Bibliographic Reference	Dimopoulos, George, Almyroudi, Maria-Panagiota, Myrianthefs, Pavlos, Rello, Jordi; COVID-19-associated pulmonary aspergillosis (CAPA); Journal of Intensive Medicine; 2021

Study details

Study design	Systematic review
Aims/ review questions	This review aimed to identify differences in the incidence, pathophysiology, diagnosis, and treatment of CAPA.
Search date	31-Jan-2021
Country/ Geographical location	Austria, Brazil, Belgium, China, Denmark, France, Germany, Ireland, Italy, Netherlands, Pakistan, Spain, Switzerland, UK, USA
Setting(s)	Hospitalised patients with CAPA and COVID-19
Population description	This review included evidence from 31 studies (n=2409) with probable-possible CAPA diagnosis and confirmed COVID-19. Participants had varying co-morbidities (for example, diabetes, cardiovascular disease, chronic lung disease, hypertension)
Inclusion criteria	Not reported
Exclusion criteria	Not reported
Intervention/test/approach	Diagnostic investigations use to confirm CAPA diagnosis
Comparator (where applicable)	NA
Searching methods	Data for this work were identified by searches of MED- LINE, PubMed using the search string “(Aspergill ”) AND (“in-vasive ”OR “infection ”OR “case ”OR “patient ”OR “report ”) AND (“COVID ∗ ”OR “corona ”), AND (“SARS-CoV-2 ”) AND (“Aspergill ∗ ”), AND (“aspergill ∗ ”) AND (guideline OR treatment OR therapy OR diagnosis). Only articles published in English until January 31, 2021 were included.

Methods of data analysis	Not reported
Methods to investigate heterogeneity	Not reported
Risk of bias assessment	Not reported
Summary of findings	Different diagnostic strategies are necessary to differentiate between fungal disease progression and COVID-19 disease. The usefulness of imaging techniques in diagnosing CAPA is limited, however, the usage of sue bronchoscopy and tissue sampling adds value to the diagnostic process.
Source of funding	None
Study limitations (Author)	Not reported
Study limitations (Reviewer)	The eligibility criteria for studies in this review were not clear and as such, there is wide variation between the studies included and participant numbers. The authors did not make note of how this heterogeneity is accounted for in their review and neither did they reveal more details about included studies that could help with determining heterogeneity.
Other details	Patient clinical characteristics not reported

Outcomes

Diagnostics for CAPA

Outcome	**Study (N = 1272)**
Serum galactomannan (GM) No of events	n = 37; % = 1.54
Serum beta-d-glucan (BDG) No of events	n = 37; % = 1.54
Bronchoscopy No of events	n = 85; % = 3.5

Meawed, 2021

Bibliographic Reference	Meawed, Takwa E; Ahmed, Sherweet M; Mowafy, Sherif M S; Samir, Ghada M; Anis, Reham H; Bacterial and fungal ventilator associated pneumonia in critically ill COVID-19 patients during the second wave.; Journal of infection and public health; 2021; vol. 14 (no. 10); 1375-1380

Study details

Study design	Cross-sectional study

Trial registration (if reported)	Not reported
Study start date	01-Oct-2020
Study end date	30-Apr-2021
COVID-19 prevalence at the time of the study	Higher prevalence (for example during peak of first wave)
Aim of the study	This study aimed to assess bacterial and fungal superinfection in mechanically ventilated COVID-19 patients admitted to ICUs during the second wave.
Country/ Geographical location	Egypt
Study setting	Hospitalised patients with COVID-19 in ICU
Population description	Participants were critically ill with COVID-19 and were admitted to ICU as part of their clinical management. 197 participants were included in this study with ages ranging from 54 - 79 years old. Most of the participants were male (59.9%) and had underlying disease. Most participants had hypertension (62.4%) and diabetes (56.3%). All participants were treated with antibiotics, steroids and tocilizumab for COVID-19 and all participants died by the end of the study collection period.
Inclusion criteria	Not reported
Exclusion criteria	Not reported
Intervention/test/approach	Patients who were admitted to ICU with COVID-19 and investigated for bacterial/fungal superinfection
Comparator (where applicable)	NA
Methods for population selection/allocation	All patients who were admitted to ICU with COVID-19 and microbial superinfection and their records were collected.
Methods of data analysis	All results were analysed using IBM SPSS 23.0 (SPSS Inc., Chicago, USA). Categorical data were presented as frequency and percentage, whereas continuous data were presented as mean ±standard deviation (SD). Odds ratios (ORs) with 95% confidence intervals (95%CI) were calculated for each significant variable based on univariate logistic regression. Significance was indicated by probability (P-value) ≤0.05
Attrition/loss to follow-up	NA
Summary of findings	Bacterial and fungal superinfections in ventilator-associated pneumonia are serious causes of mortality that require urgent and careful management to ensure better outcomes for patients
Source of funding	None
Study limitations (Author)	A significant limitation of this study includes the fact that there were no participants in a control group to evaluate treatment and diagnosis course against. Moreover, the death of all patients included in this study limited the amount of or

	analysis or exploration that could be conducted to determine further outcomes and risk factors.
Study limitations (Reviewer)	The lack of clear eligibility criteria for this study and the lack of a control group makes it difficult to fully determine the results and their impact. Although clear descriptions of microbiological testing and methods are described, there is insufficient evidence on the frequency of testing and periods of testing throughout the patient's admission, which is a factor that can help with understanding the clinical pathway of patients and the value of diagnostics/interventions.
Other details	22 patients presented with aspergillus following sampling

Characteristics

Study-level characteristics

Characteristic	**Study (N = 197)**
Age Mean (SD)	65 (14.3)
Male No of events	n = 118; % = 59.9
Female No of events	n = 79; % = 40.1
Obesity No of events	n = 37; % = 18.8
Diabetes No of events	n = 111; % = 56.3
Hypertension No of events	n = 123; % = 62.4
Hypothyroidism No of events	n = 51; % = 25.9
Chest disease No of events	n = 88; % = 44.7
Heart disease No of events	n = 34; % = 17.3
Kidney disease No of events	n = 43; % = 21.9

Outcomes

Diagnostics

Outcome	Study (N = 197)
Sputum No of events	n = 197; % = 100
Endotracheal aspirates (ETA) No of events	n = 197; % = 100

van Grootveld, 2021

Bibliographic Reference	van Grootveld, Rebecca; van Paassen, Judith; de Boer, Mark G J; Claas, Eric C J; Kuijper, Ed J; van der Beek, Martha T; Systematic screening for COVID-19 associated invasive aspergillosis in ICU patients by culture and PCR on tracheal aspirate.; Mycoses; 2021; vol. 64 (no. 6); 641-650

Study details

Trial registration (if reported)	Not reported
Study start date	01-Apr-2020
Study end date	11-May-2020
COVID-19 prevalence at the time of the study	Higher prevalence (for example, during peak of first wave)
Aim of the study	This study aimed to assess the value of different diagnostic tests and optimise the diagnostic workflow
Country/ Geographical location	The Netherlands
Study setting	Adult patients hospitalised with COVID-19 and admitted to ICU
Population description	Participants included in this study were critically ill with confirmed COVID-19. Most participants were male, with ages ranging from 57-71 years. Participants presented with different comorbidities (for example, chronic pulmonary disease, diabetes, malignant neoplasm). All participants were invasively ventilated in ICU and received vasoactive drugs.
Inclusion criteria	All participants who were admitted to ICU with critical COVID-19 illness between 1st April 2020 and 11th May 2020.
Exclusion criteria	Not reported
Intervention/test/approach	Evaluating different investigations for the diagnosis of CAPA

Comparator (where applicable)	NA
Methods for population selection/allocation	Data from the laboratory information system about bacterial culture, SARS-CoV-2 PCR, aspergillus cultures, PCR, and galactomannan results for the study period. Once patients were identified the clinical data was obtained from electronic patients' records.
Methods of data analysis	Categorical variables were described as numbers and percentages. Continuous variables were described as median and interquartile ranges. Patients with positive and negative aspergillus culture, PCR or galactomannan results were compared with the Mann Whitney U-test for numerical data and Chi-square test or Fischer's exact test for categorical data depending on sample size. A p-value of less than 0.05 was considered statistically significant. All statistical analyses were performed with SPSS statistics (version 25.0)
Attrition/loss to follow-up	Not applicable
Summary of findings	Positive culture, molecular detection and or antigen detection of aspergillus species do not equal infection. Until we understand the clinical relevance of aspergillus species detected in respiratory samples of COVID-19 patients, minimally invasive screening by tracheal aspirate is a feasible method to monitor patients. Positive screening results should be an indication to perform bronchoalveolar lavage to rule out upper airway colonisation.
Source of funding	Not reported
Study limitations (Author)	The authors noted that the electronic patient records were sometimes insufficient in providing a full clinical picture of the patient and their management as such, some information may be missing from analysis and data collection
Study limitations (Reviewer)	More information on testing timings and thresholds for requesting further investigation could have helped fill in the gaps between some of the outcomes reported by the study (for example, time to positivity, concordance of PCR and TA).
Other details	None

Characteristics

Study-level characteristics

Characteristic	Study (N = 63)
Age Median (IQR)	62 (57 to 71)
Male No of events	n = 46; % = 73

Characteristic	Study (N = 63)
Chronic pulmonary disease or asthma No of events	n = 17; % = 27
Diabetes No of events	n = 15; % = 23.8
Malignant neoplasm No of events	n = 5; % = 7.9
Organ transplant No of events	n = 2; % = 3.2

Outcomes

Diagnostics for CAPA

Outcome	Study (N = 63)
Bronchoalveolar Lavage (BAL) No of events	n = 35; % = 55.6
Bronchoalveolar culture CAPA positive No of events	n = 2; % = 5.7
Bronchoalveolar PCR positive aspergillus No of events	n = 3; % = 8.6
Bronchoalveolar Galactomannan positive No of events	n = 2; % = 5.7
Tracheal Aspirates Culture No of events	n = 63; % = 100

Appendix E: Risk of bias

Chong, 2021

Bibliographic Reference	Chong, Woon H; Neu, Kristoffer P; The Incidence, Diagnosis, and Outcomes of COVID-19-associated Pulmonary Aspergillosis (CAPA): A Systematic Review.; The Journal of hospital infection; 2021

Critical appraisal – ROBIS Tool

Section	Question	Answer
Study eligibility criteria	Did the review adhere to pre-defined objectives and eligibility criteria?	Probably yes
Study eligibility criteria	Were the eligibility criteria appropriate for the review question?	Probably yes
Study eligibility criteria	Were eligibility criteria unambiguous?	Probably yes
Study eligibility criteria	Were all restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?	Probably no
Study eligibility criteria	Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	Probably no
Study eligibility criteria	Concerns regarding specification of study eligibility criteria	Unclear
Identification and selection of studies	Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	Probably yes
Identification and selection of studies	Were methods additional to database searching used to identify relevant reports?	No information
Identification and selection of studies	Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Yes
Identification and selection of studies	Were restrictions based on date, publication format, or language appropriate?	Yes
Identification and selection of studies	Were efforts made to minimise error in selection of studies?	Probably yes
Identification and selection of studies	Concerns regarding methods used to identify and/or select studies	Unclear
Data collection and study appraisal	Were efforts made to minimise error in data collection?	No information
Data collection and study appraisal	Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Probably no
Data collection and study appraisal	Were all relevant study results collected for use in the synthesis?	Probably yes

Section	Question	Answer
Data collection and study appraisal	Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Probably yes
Data collection and study appraisal	Were efforts made to minimise error in risk of bias assessment?	Probably yes
Data collection and study appraisal	Concerns regarding methods used to collect data and appraise studies	Unclear
Synthesis and findings	Did the synthesis include all studies that it should?	Probably yes
Synthesis and findings	Were all pre-defined analyses reported or departures explained?	No information
Synthesis and findings	Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	Yes
Synthesis and findings	Was between-study variation (heterogeneity) minimal or addressed in the synthesis?	No information
Synthesis and findings	Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	No information
Synthesis and findings	Were biases in primary studies minimal or addressed in the synthesis?	No information
Synthesis and findings	Concerns regarding the synthesis and findings	High
Overall study ratings	Overall risk of bias	Moderate
Overall study ratings	Applicability as a source of data	Partially applicable

Dimopoulos, 2021

Bibliographic Reference	Dimopoulos, George, Almyroudi, Maria-Panagiota, Myrianthefs, Pavlos, Rello, Jordi; COVID-19-associated pulmonary aspergillosis (CAPA); Journal of Intensive Medicine; 2021

Critical appraisal – ROBIS Tool

Section	Question	Answer
Study eligibility criteria	Did the review adhere to pre-defined objectives and eligibility criteria?	No information
Study eligibility criteria	Were the eligibility criteria appropriate for the review question?	No information
Study eligibility criteria	Were eligibility criteria unambiguous?	No information
Study eligibility criteria	Were all restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?	Probably no

Section	Question	Answer
Study eligibility criteria	Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	No information
Study eligibility criteria	Concerns regarding specification of study eligibility criteria	High
Identification and selection of studies	Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	Probably yes
Identification and selection of studies	Were methods additional to database searching used to identify relevant reports?	No information
Identification and selection of studies	Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Probably yes
Identification and selection of studies	Were restrictions based on date, publication format, or language appropriate?	Probably no
Identification and selection of studies	Were efforts made to minimise error in selection of studies?	No information
Identification and selection of studies	Concerns regarding methods used to identify and/or select studies	Unclear
Data collection and study appraisal	Were efforts made to minimise error in data collection?	No information
Data collection and study appraisal	Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	No
Data collection and study appraisal	Were all relevant study results collected for use in the synthesis?	Probably yes
Data collection and study appraisal	Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	No information
Data collection and study appraisal	Were efforts made to minimise error in risk of bias assessment?	No information
Data collection and study appraisal	Concerns regarding methods used to collect data and appraise studies	Unclear
Synthesis and findings	Did the synthesis include all studies that it should?	Probably yes
Synthesis and findings	Were all pre-defined analyses reported or departures explained?	No information
Synthesis and findings	Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	Probably yes
Synthesis and findings	Was between-study variation (heterogeneity) minimal or addressed in the synthesis?	No
Synthesis and findings	Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Probably no
Synthesis and findings	Were biases in primary studies minimal or addressed in the synthesis?	No

Section	Question	Answer
Synthesis and findings	Concerns regarding the synthesis and findings	High
Overall study ratings	Overall risk of bias	High
Overall study ratings	Applicability as a source of data	Partially applicable

Meawed, 2021

Bibliographic Reference	Meawed, Takwa E; Ahmed, Sherweet M; Mowafy, Sherif M S; Samir, Ghada M; Anis, Reham H; Bacterial and fungal ventilator associated pneumonia in critically ill COVID-19 patients during the second wave.; Journal of infection and public health; 2021; vol. 14 (no. 10); 1375-1380

Critical appraisal - JBI Critical Appraisal Checklist

Section	Question	Answer
Assessment questions	Were the criteria for inclusion in the sample clearly defined?	Yes
Assessment questions	Were the study subjects and the setting described in detail?	No
Assessment questions	Was the exposure measured in a valid and reliable way?	No
Assessment questions	Were objective, standard criteria used for measurement of the condition?	Unclear
Assessment questions	Were confounding factors identified?	No
Assessment questions	Were strategies to deal with confounding factors stated?	No
Assessment questions	Were the outcomes measured in a valid and reliable way?	Unclear
Assessment questions	Was appropriate statistical analysis used?	Unclear
Overall bias and directness	Risk of bias judgment	High
Overall bias and directness	Directness	Indirectly applicable

van Grootveld, 2021

Bibliographic Reference	van Grootveld, Rebecca; van Paassen, Judith; de Boer, Mark G J; Claas, Eric C J; Kuijper, Ed J; van der Beek, Martha T; Systematic screening for COVID-19 associated invasive aspergillosis in ICU patients by culture and PCR on tracheal aspirate.; Mycoses; 2021; vol. 64 (no. 6); 641-650

Critical appraisal - ROBINS-I Tool

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Probably yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No information
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Probably yes
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	No information
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	No information
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Not applicable
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	No information
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	No information
1. Bias due to confounding	Risk of bias judgement for confounding	Serious
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable

Section	Question	Answer
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	No information
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	No
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Moderate
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Probably yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	No information
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	No information
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Moderate
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Not applicable
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	Probably no
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	Probably yes
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	Probably yes
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	No
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Probably no
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No information
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No information

Section	Question	Answer
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	No information
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	No information
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Probably no
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	No information
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	No information
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	Probably yes
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	No
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Probably no
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Moderate
Overall bias	Risk of bias judgement	Serious
Overall bias	Directness	Partially Applicable

Appendix F: Forest Plots

No forest plots have been produced for this review.

Appendix G: GRADE profiles

GRADE summaries have not been carried out for this review.

Appendix I: Recommendations for research

Question	**In people with suspected COVID-19-associated pulmonary aspergillosis (CAPA), what are the most accurate tests for diagnosing the infection and when should they be done?**
Population	Adults, young people and children who are critically ill and have, or have had, COVID-19 as part of their acute illness, and suspected CAPA. Subgroups of particular interest include young people and children, and pregnant women.
Diagnostic tests	Any methods used to diagnose pulmonary aspergillosis (for example, CT imaging, testing of bronchoalveolar lavage, non-bronchoscopic lavage, endotracheal aspirate, sputum samples, serum assays)
Reference standard	Lung biopsy or postmortem diagnosis
Outcomes	• sensitivity and specificity • positive and negative likelihood ratios
Analysis	Optimal time of diagnostic testing