National Institute for Health and Care Excellence

NICE COVID-19 rapid guideline: managing COVID-19

[K] Evidence reviews for COVID-19 Associated Pulmonary Aspergillosis (CAPA) – Effectiveness and Safety of Treatments

NICE guideline NG191

December 2021

Guideline version (Final)

Disclaimer

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Contents

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 evidence review is the last of four reviews about the diagnosis and management of CAPA in hospitalised COVID-19 patients. This review aims to evaluate the effectiveness and safety of the various antifungal treatments for treating suspected or confirmed CAPA.

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 questions for this evidence review are:

1. What is the effectiveness and safety of the various antifungal treatments for treating suspected or confirmed CAPA?1a. When should treatment be started?

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.

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 10 full text references were obtained and assessed for relevance.

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

1 study is included in this review (Bartoletti 2020). A summary of the included study and its quality assessment is shown in appendices D and E. Meta-analysis was not undertaken for this review as only one study was identified. Therefore no forest plots were produced.

Study characteristics

Study characteristic	Bartoletti 2020
Location and setting	Multicentre study at 4 ICUs across 3 major hospitals in Bologna, Italy
Study design	Prospective cohort study
No. of patients (N)	30 hospitalised adult patients with COVID-19 and CAPA
Follow-up	30 days
Age (years)	Median age 63 (IQR 57 to 70)
Gender (% female)	24 males (80%) 6 females (20%)
Baseline characteristics	Key comorbidities included (n, %): • Hypertension (16, 59%) • Obesity (10, 37%) • Chronic kidney disease (6, 20%) • Diabetes mellitus (5, 17%) • Chronic steroid treatment (5, 17%) • COPD (4, 13%)
COVID-19 infection	All patients included in the study were confirmed to have COVID-19 diagnosed by RT-PCR
CAPA infection	Invasive pulmonary aspergillosis was defined according to the following: Patients admitted to the ICU with pulmonary infiltrates who had at least 1 of the following: • Serum GM index more than 0.5; or • BAL GM index more than 1.0; or • Positive Aspergillus BAL culture or cavitating infiltrate (not attributed to

Study characteristic	Bartoletti 2020
	another cause) in the area of the pulmonary infiltrate A total of 108 hospitalised COVID-19 patients were screened for CAPA according to the following protocol: • Bronchoalveolar lavage (BAL) performed on ICU admission (0–2 days • BAL performed at day 7 (±2 days) from the first day of mechanical ventilation • BAL performed if the patient showed evidence of clinical disease progression, [defined by either (1) worsening of fever or (2) increases in respiratory secretions or deterioration in respiratory status after a period of clinical stability] Of the 108 patients screened, 30 met the above criteria for probable CAPA.
Inclusion criteria	1. Age >18 years 2. ICU admission 3. Requiring mechanical ventilation 4. With CAPA
Main exclusion criteria	1. Early (<48 hours) ICU discharge 2. ICU admission for reasons other than acute respiratory distress syndrome (ARDS)
Other notes	Of the 30 patients identified to have probable CAPA, 13 were treated with voriconazole. An additional 3 patients were treated with a different antifungal. Altogether, it is not clear which treatments (if any) were received by the 17 patients with probable CAPA who did not receive voriconazole. Furthermore, the dosage, duration of treatment and date of initiation of therapy with voriconazole are not detailed.

Results

Review question: What is the effectiveness and safety of the various antifungal treatments for treating suspected or confirmed CAPA? When should treatment be started?

What is the evidence informing this conclusion?

Evidence comes from one cohort study (Bartoletti 2020) that compared the survival outcomes of people hospitalised with COVID-19 and CAPA, who had, or did not have, treatment with voriconazole.

Publication status

The study referenced in this review was a full publication that had been peer-reviewed.

Study characteristics

Bartoletti 2020 was a prospective, multicentre cohort study that aimed to describe the incidence and outcomes of CAPA in a larger cohort of people hospitalised with COVID-19 and receiving mechanical ventilation. A total of 108 people with COVID-19 that were treated in hospitals in Bologna, Italy, between February and March 2020 were screened for CAPA using bronchoalveolar lavage (BAL). Of these, 30 people were identified as having COVID-19 and CAPA.

What are the main results?

Of the 30 people who were identified as having COVID-19 and CAPA, 13 were treated with voriconazole, an antifungal therapy. Another 3 patients were treated with a different antifungal therapy, and the study authors do not state what treatment the remaining 14 patients received. Survival at 10, 20, and 30 days after ICU admission was captured for the 30 people with COVID-19 and CAPA, and differences were noted between the group of patients that were treated with voriconazole (n=13) vs. those not treated with voriconazole (n=17). At the end of the 30 days, 7 patients were still alive in each group.

Our confidence in the results

The certainty of the evidence for differences in survival between voriconazole treated CAPA patients vs. CAPA patients not treated with voriconazole was rated as very low, due to the small sample size, serious risk of confounding and imprecision.

The study found that there was no statistically significant difference in survival between CAPA patients treated with voriconazole compared with those not treated with voriconazole at 10, 20, and 30 days after ICU admission. However, the study was not powered to detect a difference for this outcome.

Study authors do not provide baseline characteristics for patients by treatment group, nor do they explain the methods used to assign patients to treatment groups. Since it is unclear if the patients treated with voriconazole are different from patients not treated with voriconazole with regards to characteristics that might impact their survival, there is a serious risk of confounding.

Conclusion

There was low quality evidence from one cohort study (Bartoletti 2020) reporting on possible treatments for CAPA.

The study showed that, in people with COVID-19 and CAPA, there were no statistically significant differences in survival for those treated with voriconazole compared with those not treated with voriconazole, at 10, 20, and 30 days from ICU admission.

Evidence to decision

Benefits and harms

The panel considered that there are risks from inappropriate use of antifungal agents, including antifungal resistance and adverse drug effects. The panel concluded that the harms of antifungal therapies used for CAPA outweigh the benefits in people who do not have evidence of invasive pulmonary aspergillosis. The panel agreed that antifungal treatments for CAPA should not be offered unless CAPA has been diagnosed or there is clinical suspicion of CAPA and a local multidisciplinary team including infection specialists (for example, medical microbiologists or infectious disease specialists) support starting treatment.

Certainty of the evidence

The panel reviewed evidence on the effectiveness of treatments for people with CAPA. A review of the evidence only found one study available that directly investigates the effect of a specific treatment for patients with CAPA, and the panel agreed that the certainty of the evidence was very low. The study did not present evidence on when antifungal treatments for CAPA should be started.

The panel decision was based on their experience and prior knowledge of the clinical use of antifungal agents and when treatment with these agents should be started. They also drew on expertise about antifungal resistance when making this recommendation.

Values and preferences

The panel were not aware of any systematically collected data on people's preferences and values.

The panel agreed that it was likely that people would not want to take a treatment with no known benefits but well-established side effects in situations when there is a low suspicion of CAPA.

Resources

No formal analysis of resource impact has been carried out. However, it is possible that this recommendation will result in a reduction in the use of antifungals when there is low clinical suspicion or before investigations take place.

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

Equity

This recommendation is not expected to cause inequity in any subgroups. Since CAPA is most likely to affect those with the most severe COVID-19 infections, the panel noted that subgroups with disproportionately high incidence of severe COVID-19 infection may be most affected by CAPA.

The panel recognised that the effectiveness and safety of antifungals may differ in pregnant women and children but that there was no evidence in this area.

No other equity issues were identified.

Acceptability

While there was no systematically collected evidence about acceptability, the panel acknowledged that not giving antifungal treatment until CAPA is diagnosed or testing is underway may mean treatment is started later, or not at all, for some people. They acknowledged that clinicians treating people who are hospitalised with COVID-19 will seek to improve people's health outcomes as much as possible, and that families and carers of people who are hospitalised with COVID-19 would be likely to want to ensure that appropriate measures are taken to support people.

Feasibility

This recommendation may reflect usual practice in some centres. For others it may require adjustments to practice which should be feasible to implement, as this recommendation seeks to ensure appropriate practice and potentially reduce over prescribing**.**

References

Chong, W. H., & Neu, K. P. (2021a). Incidence, diagnosis and outcomes of COVID-19-associated pulmonary aspergillosis (CAPA): a systematic review. The Journal of hospital infection, 113, 115–129. https://doi.org/10.1016/j.jhin.2021.04.012

Chong, W. H., Saha, B. K., Ananthakrishnan Ramani, & Chopra, A. (2021b). State-of-the-art review of secondary pulmonary infections in patients with COVID-19 pneumonia. Infection, 49(4), 591–605. https://doi.org/10.1007/s15010-021-01602-z

Bartoletti, M., Pascale, R., Cricca, M., Rinaldi, M., Maccaro, A., Bussini, L., Fornaro, G., Tonetti, T., Pizzilli, G., Francalanci, E., Giuntoli, L., Rubin, A., Moroni, A., Ambretti, S., Trapani, F., Vatamanu, O., Ranieri, V. M., Castelli, A., Baiocchi, M., Lewis, R., … PREDICO study group (2020). Epidemiology of invasive pulmonary aspergillosis among COVID-19 intubated patients: a prospective study. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America, ciaa1065. Advance online publication. https://doi.org/10.1093/cid/ciaa1065

Verweij, P. E., Gangneux, J. P., Bassetti, M., Brüggemann, R., Cornely, O. A., Koehler, P., Lass-Flörl, C., van de Veerdonk, F. L., Chakrabarti, A., Hoenigl, M., European Confederation of Medical Mycology, International Society for Human and Animal Mycology, European Society for Clinical Microbiology and Infectious Diseases Fungal Infection Study Group, & ESCMID Study Group for Infections in Critically Ill Patients (2020). Diagnosing COVID-19-associated pulmonary aspergillosis. *The Lancet. Microbe*, *1*(2), e53–e55. https://doi.org/10.1016/S2666-5247(20)30027-6

Appendices

Appendix A: PICO table

Question: What is the effectiveness and safety of the various antifungal treatments for treating suspected or confirmed CAPA? When should treatment be started?

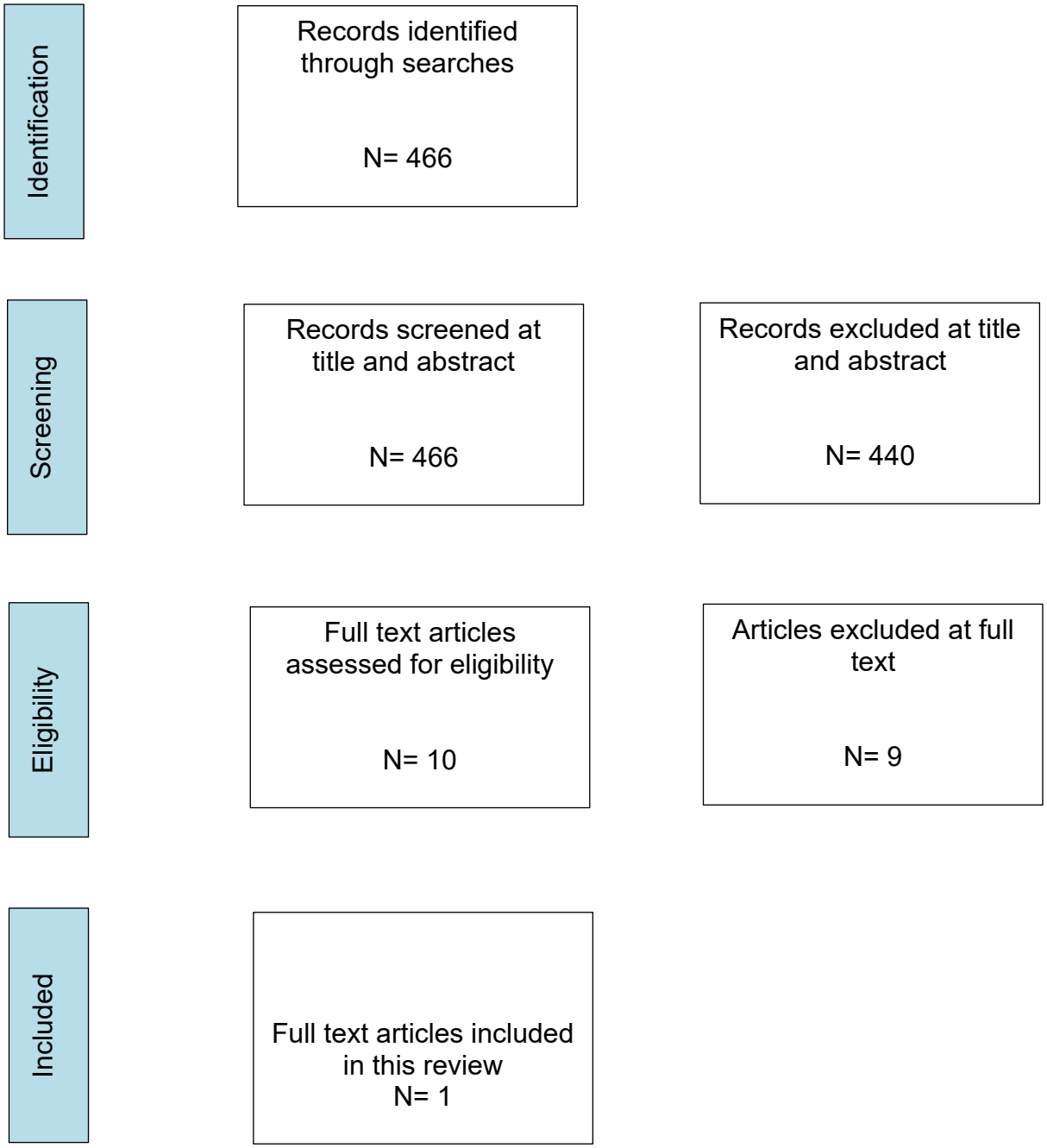
Criteria	Notes
Population	Adults, young people and children who are critically ill and have or, as part of their acute illness, have had confirmed COVID-19, and who have diagnosed or suspected CAPA.
Interventions	Voriconazole Isavuconazole Liposomal amphotericin B Posaconazole Echinocandins (e.g., caspofungin, anidulafungin) Amphotericin b deoxycholate Treatments may be of any duration.
Comparators	Standard care alone (standard care is usually voriconazole), standard care plus placebo, placebo. The interventions listed will not be compared with each other, with the exception of voriconazole.
Outcomes	Those marked with an * are critical outcomes • All-cause mortality (n/N)* (at any time point) • Duration of invasive mechanical ventilation (IMV) (days)* • Ventilator-free or organ support-free days (organ support includes use of vasopressors and renal replacement therapy) • ICU length of stay (days) • Number of patients experiencing one or more serious adverse events (n/N)* • Number of patients experiencing one or more adverse events (n/N)

	The definitions of mechanical ventilation, non-invasive ventilation and other forms of respiratory support such as high flow nasal oxygen (HFNO) therapy or continuous positive airway pressure or non-invasive bilevel ventilation may differ across the studies. In the context of UK practice the following definitions should be considered: **Advanced respiratory support:** Invasive mechanical ventilation, bilevel positive airway pressure (BiPAP) via translaryngeal tube or tracheostomy, continuous positive airway pressure (CPAP) via translaryngeal tube, or extracorporeal respiratory support) **Non-invasive ventilation:** includes HFNO, CPAP, CPAP via tracheostomy, and non-invasive bilevel ventilation. Note: oxygen via (low flow) nasal cannulae or face mask does not fall within the categories above.
Settings	Any settings for people who are critically ill
Subgroups	Studies (or arms of studies) will be subgrouped for critical outcomes depending on what criteria were used to start treatment: • Results of diagnostic tests showing proven CAPA vs lower levels of certainty. • Clinical features (e.g. refractory fever, worsening respiratory status, haemoptysis, pleural friction rub, chest pain). Other subgroups of interest will be investigated where data is sufficient: • Adults > 50 years • Children <12 years of age • Gender • Ethnic background • Pregnant women • Comorbidities (chronic obstructive pulmonary disease, hypertension, diabetes, coronary heart disease, chronic kidney disease, cancer, cerebral vascular disease, obesity).
Study types	The search will look for: • Systematic review of randomised controlled trials (RCTs) • RCTs

	If no systematic reviews or RCT evidence is available progress to: • non-randomised controlled trials • systematic reviews of non-randomised controlled trials • cohort studies with a control group • interrupted time series studies Preprints will be considered as part of the evidence review.
Countries	Any
Timepoints	From 2020 onwards
Other exclusions	The scope sets out what the guideline 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
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)	Data not reported in an extractable format
Campochiaro, Corrado, Della-Torre, Emanuel, Cavalli, Giulio et al. (2020) Efficacy and safety of tocilizumab in severe COVID-19 patients: a single-centre retrospective cohort study. European Journal of Internal Medicine 76: 43-49	Study does not contain a relevant intervention
Chong, Woon H and Neu, Kristoffer P (2021) The Incidence, Diagnosis, and Outcomes of COVID-19-associated Pulmonary Aspergillosis (CAPA): A Systematic Review. The Journal of hospital infection	Study does not contain a relevant intervention
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	Study does not contain a relevant intervention
Dimopoulos, George, Almyroudi, Maria-Panagiota, Myrianthefs, Pavlos, Rello, Jordi (2021) COVID-19-associated pulmonary aspergillosis (CAPA). Journal of Intensive Medicine	Comparator in study does not match that specified in protocol
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	Comparator in study does not match that specified in protocol
Lahmer, Tobias, Kriescher, Silja, Herner, Alexander et al. (2021) Invasive pulmonary aspergillosis in critically ill patients with severe COVID-19 pneumonia: Results from the prospective AspCOVID-19 study. PloS one 16(3): e0238825	Comparator in study does not match that specified in protocol
NCT04707703 (2021) Isavuconazole for the Prevention of COVID-19-associated Pulmonary Aspergillosis. https://clinicaltrials.gov/show/NCT04707703	Study does not contain a relevant intervention
Paramythiotou, Elisabeth, Dimopoulos, George, Koliakos, Nikolaos et al. (2021) Epidemiology and Incidence of COVID-19-Associated Pulmonary Aspergillosis (CAPA) in a Greek Tertiary Care Academic Reference Hospital. Infect Dis Ther 10(3): 1779-1792	Comparator in study does not match that specified in protocol

Appendix D: Data extraction

Bartoletti, 2020

Bibliographic Reference	Bartoletti, Michele; Pascale, Renato; Cricca, Monica; Rinaldi, Matteo; Maccaro, Angelo; Bussini, Linda; Fornaro, Giacomo; Tonetti, Tommaso; Pizzilli, Giacinto; Francalanci, Eugenia; Giuntoli, Lorenzo; Rubin, Arianna; Moroni, Alessandra; Ambretti, Simone; Trapani, Filippo; Vatamanu, Oana; Ranieri, Vito Marco; Castelli, Andrea; Baiocchi, Massimo; Lewis, Russell; Giannella, Maddalena; Viale, Pierluigi; PREDICO study, group; Epidemiology of invasive pulmonary aspergillosis among COVID-19 intubated patients: a prospective study.; Clinical infectious diseases : an official publication of the Infectious Diseases Society of America; 2020

Study details

Trial registration (if reported)	Prospective, multicentre study in adult patients with microbiologically confirmed COVID-19 receiving mechanical ventilation.
Study start date	22-Feb-2020
Study end date	19-May-2020
Aim of the study	Describe the incidence and outcome of CAPA in a larger cohort of ventilated patients with COVID19; and evaluate the prognostic impact of different aspergillosis case definitions in this setting.
Country/geographical location	Bologna, Italy
Population description	Patients with RT-PCR confirmed COVID-19 hospitalised from 22 Feb 2020 through to 20 April 2020 in 4 ICUs from 3 hospitals in Bologna, IT
Inclusion criteria	(1) Age >18 years, (2) ICU admission, (3) requiring mechanical ventilation
Exclusion criteria	(1) Early (<48 hours) ICU discharge, (2) ICU admission for reasons other than acute respiratory distress syndrome [ARDS]
Intervention dosage (loading)	Not reported
Intervention dosage (maintenance)	Not reported
Intervention scheduled duration	Not reported
Intervention actual duration	Not reported
Intervention route of administration	Not reported
Comparator (where applicable)	N/A

Methods for population selection/allocation	Not reported
Methods of data analysis	Survival analysed via Kaplan Meier curves
Attrition/loss to follow-up	Not reported
Source of funding	No external funding
Study limitations (Author)	"Although this study was not designed to address this point in explorative analysis, an interesting trend toward higher survival (Figure 4) or reduced BAL GM index was observed. Unfortunately, the relatively low sample size prevents any firm conclusions on antifungal treatment."
Study limitations (Reviewer)	Selection bias - unclear why patients received or didn't receive voriconazole; characteristics of voriconazole-treated patients (vs others) are not reported

Study arms

Voriconazole (N = 13)

Probable CAPA patients who were treated with voriconazole

No voriconazole (N = 17)

Probable CAPA patients who were not treated with voriconazole

Characteristics

Study-level characteristics

Characteristic	Study (N = 30)
Age (years) Median (IQR)	63 (57 to 70)
Gender (male) Male No of events	n = 24; % = 80
Level of respiratory support (n (%)) # Patients requiring mechanical ventilation No of events	n = 30; % = 100
Obesity No of events	n = 10; % = 37

Characteristic	Study (N = 30)
Hypertension No of events	n = 16; % = 59
Diabetes mellitus No of events	n = 5; % = 17
COPD No of events	n = 4; % = 13
Chronic kidney disease No of events	n = 6; % = 20
Chronic steroid treatment No of events	n = 5; % = 13
Hydroxychloroquine No of events	n = 28; % = 93
Azithromycin No of events	n = 9; % = 30
Lopinavir No of events	n = 12; % = 40
Darunavir No of events	n = 2; % = 7
remdesivir No of events	n = 3; % = 10
Tocilizumab No of events	n = 22; % = 73
corticosteroids No of events	n = 18; % = 60
Days of mechanical ventilation (days) Median (IQR)	13 (7 to 23)
ICU length of stay (days) Median (IQR)	16 (9 to 27)

Outcomes

Survival

Outcome	Voriconazole, , N = 13	No voriconazole (N = 17)
10-Day Survival No of events	n = 12	n = 11
20-Day Survival No of events	n = 8	n = 10
30-Day Survival No of events	n = 7	n = 7

Kaplan-Meier survival curves for 30-day mortality from ICU admission

Appendix E: Risk of bias

Critical appraisal - ROBINS Risk of BIAS

10-day survival

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes *(Patient survival may have been impacted by factors other than the intervention (voriconazole))*
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	No information
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably no *(Survival analysis using a Kaplan-Meier comparison is appropriate for comparing the mortality in two patient groups; however this does not control for all the important confounding domains.)*
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 *(No confounding domains were measured or controlled for in respect to the analysis of the effect of the intervention (voriconazole))*
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	No *(No post-intervention variables were measured or controlled for in respect to the analysis of the effect of the intervention (voriconazole))*
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 *(No confounding domains were measured or controlled for in the analysis of survival benefit from the intervention (voriconazole))*

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Critical *(There is a significant potential for confounding in the effectiveness of the intervention (voriconazole). Patient-specific factors may have played an important role in the difference in survival between the voriconazole-treated patients vs non-voriconazole-treated patients.)*
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 information *(No information is provided around how patients were selected for the treatment (voriconazole).)*
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?	No information
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?	No information
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 information
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	No information
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	No information
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	No information

Section	Question	Answer
	outcome or risk of the outcome?	
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	No information
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?	No information
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?	No information
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	No information
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 information
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low *(While the study does not state the protocol for the administration of the intervention, the intervention was administered by physicians to patients while the patients were being cared for in the ICU. Therefore, there is unlikely to be deviations from the intended interventions.)*
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes *(Outcome (mortality) data was available for all n=30 patients with likely CAPA in the study)*
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No

Section	Question	Answer
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No information
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	No information
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	No
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Probably yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	Yes
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	Low
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?	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?	Yes
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected,	Yes

Section	Question	Answer
	on the basis of the results, from different subgroups?	
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Serious
Overall bias	Directness	Directly applicable

20-day survival

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes *(Patient survival may have been impacted by factors other than the intervention (voriconazole))*
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	No information
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably no *(Survival analysis using a Kaplan-Meier comparison is appropriate for comparing the mortality in two patient groups; however this does not control for all the important confounding domains.)*
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 *(No confounding domains were measured or controlled for in respect to the analysis of the effect of the intervention (voriconazole))*
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	No *(No post-intervention variables were measured or controlled for in respect to the analysis of the effect of the intervention (voriconazole))*
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

Section	Question	Answer
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 *(No confounding domains were measured or controlled for in the analysis of survival benefit from the intervention (voriconazole))*
1. Bias due to confounding	Risk of bias judgement for confounding	Critical *(There is a significant potential for confounding in the effectiveness of the intervention (voriconazole). Patient-specific factors may have played an important role in the difference in survival between the voriconazole-treated patients vs non-voriconazole-treated patients.)*
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 information *(No information is provided around how patients were selected for the treatment (voriconazole).)*
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?	No information
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?	No information
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 information
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	No information
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	No information

Section	Question	Answer
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	No information
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?	No information
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?	No information
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	No information
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 information
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low *(While the study does not state the protocol for the administration of the intervention, the intervention was administered by physicians to patients while the patients were being cared for in the ICU. Therefore, there is unlikely to be deviations from the intended interventions.)*

Section	Question	Answer
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes *(Outcome (mortality) data was available for all n=30 patients with likely CAPA in the study)*
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No information
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	No information
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	No
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Probably yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	Yes
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	Low
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?	Yes

Section	Question	Answer
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?	Yes
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?	Yes
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Serious
Overall bias	Directness	Directly applicable

30-day survival

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes *(Patient survival may have been impacted by factors other than the intervention (voriconazole))*
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	No information
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably no *(Survival analysis using a Kaplan-Meier comparison is appropriate for comparing the mortality in two patient groups; however this does not control for all the important confounding domains.)*
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 *(No confounding domains were measured or controlled for in respect to the analysis of the effect of the intervention (voriconazole))*
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	No *(No post-intervention variables were measured or controlled for in respect to*

Section	Question	Answer
		the analysis of the effect of the intervention (voriconazole))
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 *(No confounding domains were measured or controlled for in the analysis of survival benefit from the intervention (voriconazole))*
1. Bias due to confounding	Risk of bias judgement for confounding	Critical *(There is a significant potential for confounding in the effectiveness of the intervention (voriconazole). Patient-specific factors may have played an important role in the difference in survival between the voriconazole-treated patients vs non-voriconazole-treated patients.)*
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 information *(No information is provided around how patients were selected for the treatment (voriconazole).)*
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?	No information
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?	No information
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 information

Section	Question	Answer
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	No information
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	No information
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	No information
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?	No information
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?	No information
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	No information
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 information
4. Bias due to deviations from	Risk of bias judgement for deviations from intended interventions	Low *(While the study does not state the protocol for the administration of the*

Section	Question	Answer
intended interventions		*intervention, the intervention was administered by physicians to patients while the patients were being cared for in the ICU. Therefore, there is unlikely to be deviations from the intended interventions.)*
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes *(Outcome (mortality) data was available for all n=30 patients with likely CAPA in the study)*
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No information
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	No information
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	No
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Probably yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	Yes
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	Low

Section	Question	Answer
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?	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?	Yes
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?	Yes
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Serious
Overall bias	Directness	Directly applicable

Appendix F: Forest Plots

No forest plots have been produced for this review.

Appendix G: GRADE profiles

Voriconazole compared to no voriconazole for People hospitalised with COVID-19 and with CAPA

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With no voriconazole	With voriconazole		Risk with no voriconazole	Risk difference with voriconazole
10-Day Survival											
30 (1 observational study)	very serious[a]	not serious[b]	not serious[c]	very serious[d]	none	Very low	11/17 (64.7%)	12/13 (92.3%)	**RR 1.43** (0.97 to 2.10)	647 per 1,000	**278 more per 1,000** (from 19 fewer to 712 more)
20-Day Survival											
30 (1 observational study)	very serious[a]	not serious[b]	not serious[c]	very serious[d]	none	Very low	10/17 (58.8%)	8/13 (61.5%)	**RR 1.05** (0.58 to 1.88)	588 per 1,000	**29 more per 1,000** (from 247 fewer to 518 more)
30-Day Survival											
30 (1 observational study)	very serious[a]	not serious[b]	not serious[c]	very serious[d]	none	Very low	7/17 (41.2%)	7/13 (53.8%)	**RR 1.31** (0.61 to 2.79)	412 per 1,000	**128 more per 1,000** (from 161 fewer to 737 more)

CI: confidence interval; **RR:** risk ratio

Explanations

a. The study was not originally designed to measure the effectiveness of voriconazole in people hospitalized with COVID-19 and CAPA. As such, the study authors did not provide details on the characteristics of the subset of patients treated with voriconazole, compared to the subset of patients not treated with voriconazole. It is also not made clear what the 'other' therapies were. Therefore, there is a strong likelihood that other factors (aside from the treatment with voriconazole) may have influenced the difference in 10-day survival between patients treated with voriconazole vs. other therapies.
b. There was only one study available that measured the effectiveness of a treatment for people hospitalized with COVID-19 and CAPA
c. The study focused on people hospitalized with COVID-19 and CAPA, so the evidence is relevant
d. The confidence interval for this outcome includes the possibility that there is no difference in survival between people with CAPA treated with voriconazole vs people with CAPA not treated with voriconazole. Furthermore, this outcome is based on a single study with a total of only 30 patients. Therefore, there are very serious issues with imprecision in this outcome.

Appendix H: Recommendations for research

Question	**What are the clinical and cost effectiveness, and the safety, of specific antifungal treatments for treating suspected or confirmed COVID-19-associated pulmonary aspergillosis (CAPA), and the optimal treatment duration? When should treatment be started, stopped or modified?**
Population	Adults, young people and children who are critically ill and have, or have had, COVID-19 as part of their acute illness and have probable or diagnosed CAPA. Subgroups of particular interest: children and young people, pregnant women, ethnicity, immunosuppression, and subgroups who have higher rates of COVID-19.
Intervention(s)	Voriconazole, isavuconazole, liposomal amphotericin B, posaconazole, echinocandins (for example, caspofungin, anidulafungin) and amphotericin B deoxycholate
Comparator(s)	Standard care (usually voriconazole)
Outcomes	• all-cause mortality (at any time during treatment) • number of people having 1 or more serious adverse events • number of days without respiratory or organ support (organ support includes use of vasopressors and renal replacement therapy) • length of stay in intensive care • number of people having 1 or more adverse events • treatment duration • timing of starting treatment

	• need for treatment modification • length of hospital stays • need for and duration of invasive mechanical ventilation • need for switching, starting or restarting antifungal treatment

Question	**What are the views, preferences and experiences of people with COVID-19-associated pulmonary aspergillosis (CAPA), and their families or carers, on: available tests for diagnosing CAPA and available treatments for CAPA?**
Population	People who have been diagnosed with and treated for CAPA, and their families or carers. Subgroups of particular interest include young people and children, and pregnant women.
Intervention(s)	Tests for diagnosing CAPA and treatments for CAPA
Comparator(s)	People who have been diagnosed with, and had treatment for, CAPA in hospital
Outcomes	Not specified