Peer review comments – CAPA

Managing COVID-19 rapid guideline (NG191)

Peer review organisations

For a list of stakeholders invited to comment on COVID-19 guidance as part of the targeted peer review, please see the targeted peer review stakeholder list on the NICE website.

For this topic, the following stakeholder organisations were also invited to comment:

- Aspergillosis Trust
- British Thoracic Society
- Royal College of Pathologists
- UK Clinical Mycology Network
- AMR National Pharmacy and Prescribing

Overarching category	Guideline section	Theme of comments	Action taken
General comments	Recommendations [Diagnostic and Treatment]	Reviewers agreed with the requirement for the new recommendations and the areas discussed [when to suspect CAPA, how to diagnose CAPA, how to treat CAPA, and key evidence gaps for further research].	No action necessary

Date of completion: 15/12/2021

General comments	Recommendations [Diagnostic and Treatment]	Regarding references to 'local protocols' and 'multidisciplinary teams' (MDTs): 2 reviewers wrote that deferring to local protocols may be insufficient as many Trusts do not have specialist mycologists. 1 reviewer also questioned whether MDTs would all be in the same hospital or not. Another reviewer requested clarification around which 'infection specialists' should be included in the MDTs.	Where possible, we have clarified the objectives of local protocols and the composition of multidisciplinary teams.
General comments	Recommendations [Diagnostic and Treatment]	2 reviewers wrote that the guidelines are too vague to be helpful to clinicians. Their comments suggested that recommendations should be made more specific and directive.	No further actions were possible, as this is due to the uncertain nature of the evidence supporting the CAPA guideline.
General comments	Recommendations [Diagnostic and Treatment]	A reviewer from the RCPCH wrote that the management of CAPA in paediatric patients should be consistent with the management of CAPA in adults, except for in the following ways: (1) the values of serum biomarkers, (2) the choice of antifungal and (3) antifungal dosing. Suggested to reference the ESCMID/ECMM guideline (Warris, Clin Microbiol Inf 2019)	We have expanded on information in the 'Evidence to Decision' section of relevant recommendations around CAPA diagnosis and treatment to reflect these considerations. We have ensured that research recommendations reflect evidence gaps re: CAPA diagnosis and treatment in children and young people. No link to the ESCMID/ECMM guideline has been added as this pertains to IPA, not CAPA and is therefore outside the scope of this review. Experts agreed that CAPA may have different clinical features from other invasive pulmonary aspergillosis and require its own specific diagnostic criteria and approach to management. Therefore, the decision was made to only consider evidence directly related to CAPA.
General comments	Recommendations [Diagnostic]	4 reviewers agreed with the recommendations around diagnosing CAPA and the evidence on which those recommendations were based	No action necessary

Suggested amendment to recommendation	Info Box Recommendations - Diagnostic Rec #1 Evidence Summary - Risk Factors	2 reviewers suggested that the focus for suspecting/diagnosing CAPA should be on invasively mechanically ventilated patients and that recommendations should be oriented around explaining triggers for suspicion of CAPA. 2 reviewers suggested that clinicians should consider immunosuppression when deciding when to suspect CAPA. Together, these reviewers suggested that 'invasive mechanical ventilation' and 'immunosuppression' be highlighted as an important risk factor for CAPA in (1) the evidence summary for CAPA risk factors, (2) the info box, and (3) recommendations around when to suspect CAPA.	We did not make any changes as the existing language appropriately describes the lack of clarity on risk factors for COVID. The panel had already discussed that evidence that 'invasive mechanical ventilation' is associated with CAPA is likely to be confounded. The evidence reviewed in this guideline did not show a significant association between long-term immunosuppresants and CAPA.
Suggested amendment to recommendation	Diagnostic Rec #2	1 reviewer suggested that a screening strategy may be relevant if CAPA prevalence is moderate to high in some centres [>10%]. Another reviewer suggested that since there are no specific signs or symptoms of CAPA, the recommendation could also be oriented around a screening strategy in a defined population in the ICU.	No action taken as screening was not in the scope of this review.
Question	Diagnostic Rec #2	1 reviewer asked about informed consent for patients receiving a bronchoscopy for CAPA	No action taken as informed consent was assumed.
Clarification	Evidence Summary - Diagnosis	One reviewer noted minor errors in language re: diagnostic options for CAPA - • Diagnostic assays can only 'support' diagnosis of CAPA • Gold standard for diagnosing/ 'confirming' IPA is culture + histopathology of a normal sterile tissue sample • CT chest scan cannot be used to confirm CAPA • Throughout the plain language summary, 'confirm' needs to be changed to 'support'	Changed 'confirm' to 'support' throughout evidence profile and elsewhere in the guideline, where appropriate.
Concern	Recommendations - Diagnostic Rec #3	Regarding recommendation of bronchoalveolar lavage (BAL): 1 reviewer was concerned that the recommendation was too strongly worded and could lead to increase in BALs without appropriate consideration of risk to patients. Another reviewer	The panel agreed that BAL is an important tool in diagnosing CAPA, and that combining it with other diagnostic tests will increase certainty.

		pointed out that BAL is not feasible in a significant cohort of patients.	We clarified the recommendation to state that a range of tests should be used to increase the likelihood of a confident diagnosis or if BAL is not possible, but that BAL should be used if possible.
Concern / Suggested amendment to recommendation	Diagnostic Rec #4	3 reviewers detailed their concerns with this recommendation and suggested changes: • Waiting for susceptibility test result for cultured aspergillus isolate in patient with indication for antifungal therapy will lead to an inappropriate delay in effective treatment (48-72hour based on standard lab practice). • Whilst susceptibility testing should be undertaken to guide definitive therapy, empiric anti-aspergillosis treatment should not be delayed until these results are available. • Suggest instead that a sample off treatment should be sent – and that if Aspergillus is cultured treatment can be started pending sensitivity results – but that sensitivity results should then inform a rationalization of treatment. • Recommendation should be to commence treatment whilst awaiting resistance information and make changes accordingly	Removed the requirement to obtain an antifungal resistance test result before starting treatment from recommendation, and added text to the evidence to decision to clarify that treatment may be started before the results are received, based on clinician judgement.
Clarification / Suggested amendment to recommendation	Diagnostic Rec #5	2 reviewers requested that 'timely test result' for CAPA diagnostic tests be described [eg, how many days]	No action taken. The panel chose not to put forward a specific timeframe, as this should be decided and implemented locally.
General Comments	Recommendations [Treatment]	Reviewers agreed with the treatment recommendations, including sections related to benefits and harms, acceptability and rationale.	No action taken

Concern	Treatment Rec #2	2 reviewers were concerned that the study referenced in the treatment recommendations [Bartoletti 2021] was under-powered and that the evidence was at risk of serious bias.	No changes were made as the limitations of the evidence had already been identified by the panel. As such, the guideline does not recommend a specific treatment based on this evidence.
Clarification / Suggested amendment to recommendation	Research Recommendations	Reviewers emphasised the need to address evidence gaps around the treatment and management of CAPA in pregnant people and children.	Ensured that pregnant people, children and young people were included in ‘subgroups of particular interest’ in research recommendations re: CAPA.