Defining and managing COVID-19-associated pulmonary aspergillosis: the 2020 ECMM/ISHAM consensus criteria for research and clinical guidance

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Sabine Kuster

Background

- Viral pneumonia increases susceptibility to superinfections
- Many patient could not be classified using EORTC criteria
- Reports of COVID-19-associated pulmonary aspergillosis (CAPA) raised concerns about additional mortality
- Viral infections cause direct damage to the airway epithelium, hamper ciliary clearance and lead to immune dysfunction or dysregulation
- Diagnosis of CAPA is challenging

CAPA characteristics and host factors

- Mortality is 16-25% higher in patients with CAPA
- Classical host factors are absent
- Unclear whether SARS-CoV-2 itself is the main risk factor for CAPA, or whether additional risk factors, such as corticosteroid therapy, further increases the risk for disease progression.

Imaging

- Many atypical signs of COVID-19 pneumonia can mimic IPA and vice versa, therefore, radiology alone is not sufficient to define CAPA.
- Multiple pulmonary nodules or lung cavitation should prompt investigation for IPA.
- Halo sign without mycological evidence is not sufficient to define CAPA

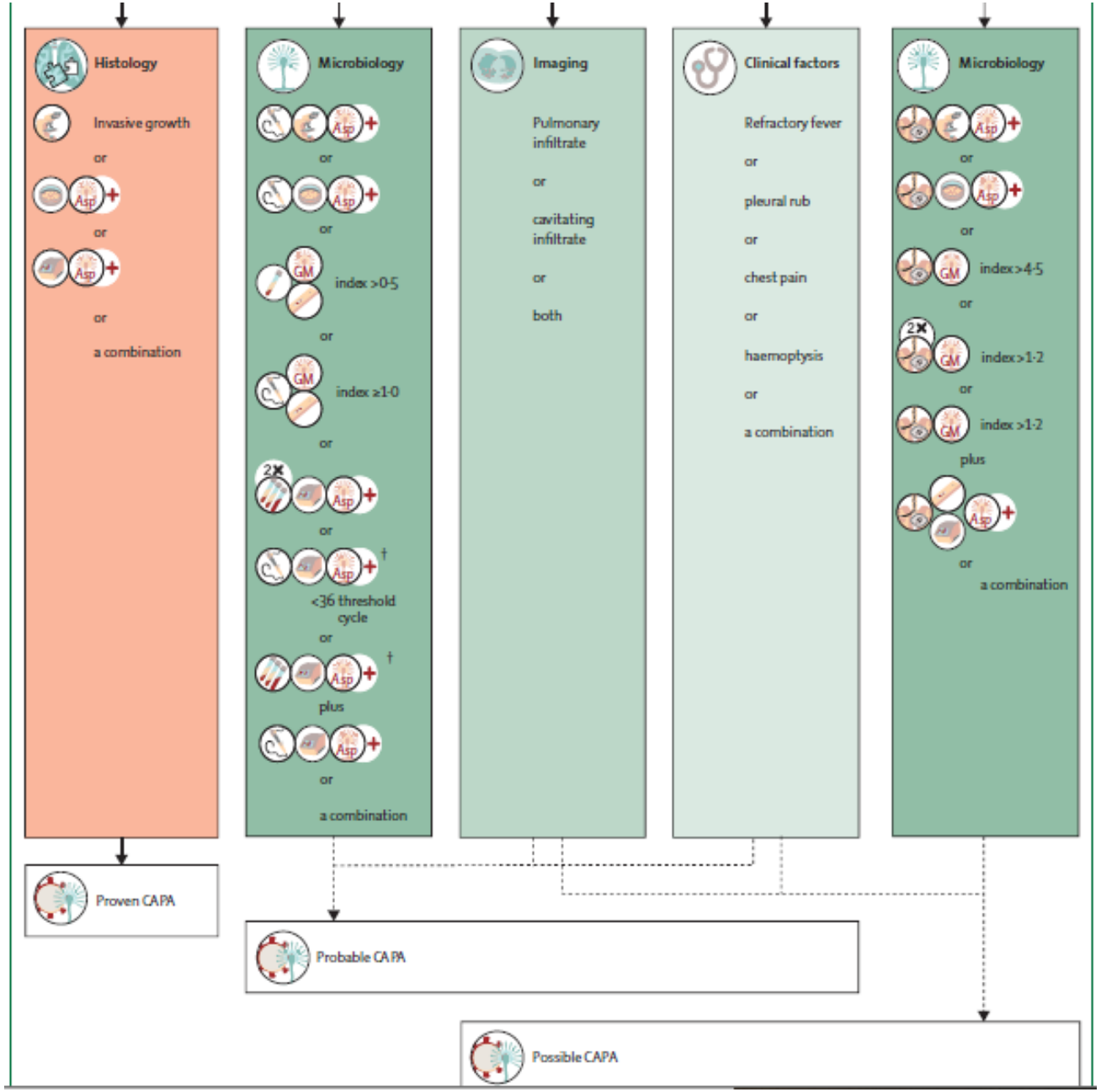
Mycological evidence

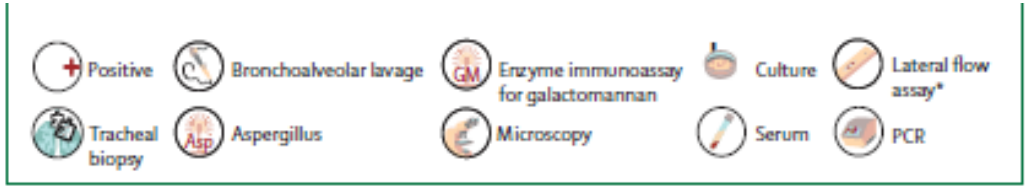
	Pros	Cons	Comments related to CAPA
Lung biopsy	Provides proof of IPA	Risk of sampling error; scarcely used due to high risk of complications	CT-guided biopsies post mortem have been used as alternative to autopsy[29]
Bronchoscopy with bronchoalveolar lavage	Allows visualisation of lesions (eg, plaques); bronchoalveolar lavage well validated for the diagnosis of IPA and IAPA; validated specimen for aspergillus antigen test (eg, enzyme immunoassay and lateral flow assay) and PCR; targeted sampling possible	Aerosol generation and contamination of surfaces	In some centres, use is decreased because of risk of nosocomial transmission and SARS-CoV-2 infection of health-care workers;[31,39] SARS-CoV-2 infectiousness correlates with PCR-signal strength, which can be used as guidance on when it's safe to perform bronchoscopy[32–33]
Non-bronchoscopic lavage	Obtains material from lower respiratory tract; technique validated for diagnosis of ventilator-associated pneumonia; closed-system sampling	Not fully validated for IPA diagnosis; not fully validated for aspergillus antigen and PCR detection; non-targeted sampling	Suggested as alternative to bronchoalveolar lavage to diagnose CAPA; small number of validation studies[32,34]
Tracheal aspirate	Easy to obtain in patients who are intubated	Less representative of lower respiratory tract than is bronchoalveolar lavage; not validated for biomarker detection	Often positive in patients with COVID-19 who are critically ill but can represent upper airway colonisation
Sputum	Easy to obtain in most patients	Less representative of lower respiratory tract than is bronchoalveolar lavage; not validated for biomarker detection	Often positive in patients with COVID-19 who are critically ill but can represent upper airway colonisation
Serum	Highly indicative for IPA (galactomannan, lateral flow assay, and PCR); validated specimen for galactomannan, lateral flow assay, (1–3)-β-D-glucan, and PCR; easy to obtain	Variable performance in non-neutropenic patients; (1–3)-β-D-glucan not pathogen specific	Commonly negative in CAPA, including proven cases[32]

CAPA=COVID-19-associated invasive pulmonary aspergillosis. IAPA=influenza-associated pulmonary aspergillosis. IPA=invasive pulmonary aspergillosis.

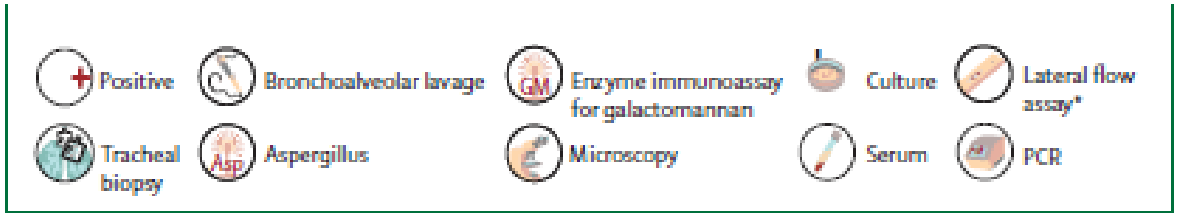
Table 1: Pros and cons of diagnostic procedures and their samples in patients with COVID-19

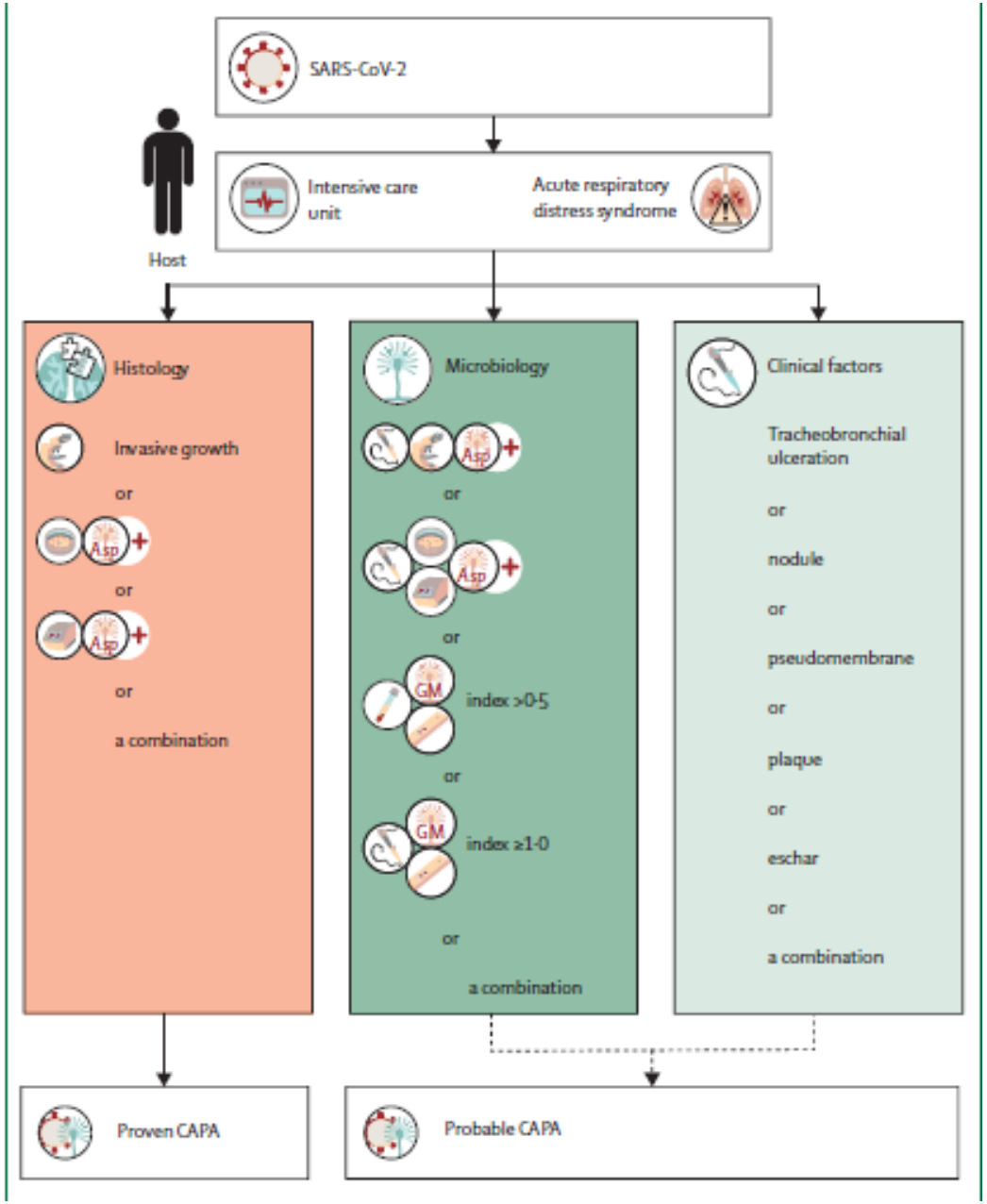
Defining and diagnosing CAPA (pulmonary form)





Defining and diagnosing CAPA (tracheobronchial form)





Guidance on clinical management of CAPA

- Any of the following findings can trigger diagnostic interventions:
  - Refractory fever > 3 days or new fever after a period of defervescence > 48h during appropriate antibiotic therapy
  - Worsening respiratory status
  - Haemoptysis
  - Pleural friction rub or chest pain
- Screning with serum galactomannan assay should be considered three times per week

Treatment

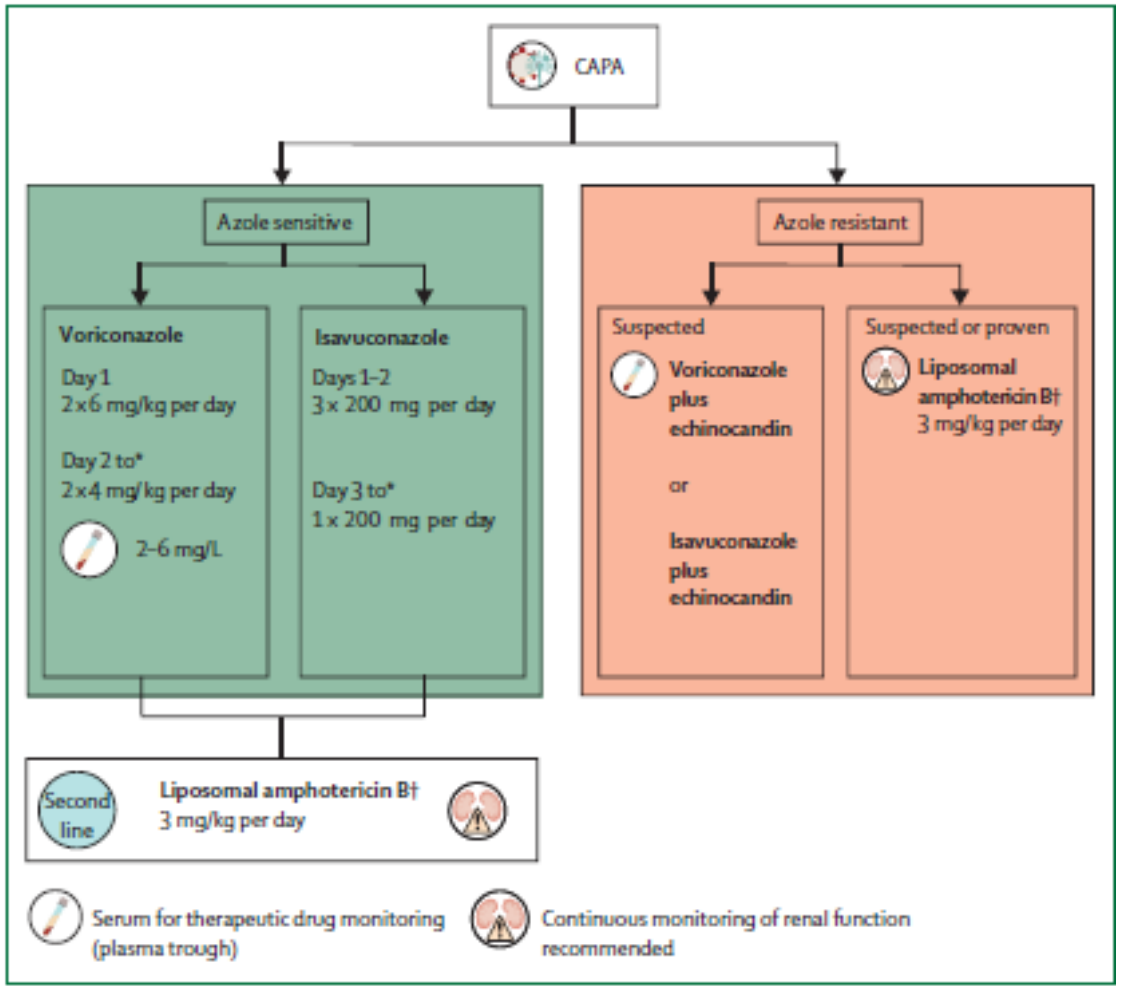


Figure 3: **Recommended treatment for CAPA**
CAPA=COVID-19-associated pulmonary aspergillosis. *The optimal duration is unknown, but the expert panel suggests 6–12 weeks as a treatment course. In immunocompromised patients (eg, with haematological malignancy or receiving immunosuppressive therapy), longer treatment might be necessary. †Salvage therapy: caspofungin 70 mg loading dose on the first day followed by 50 mg/day. If body weight is more than 80 kg, then 70 mg loading dose on the first day followed by 70 mg/day.

Conclusions

- Consensus definitions for CAPA enable to homogeneously classify patients in registries and interventional clinical trials but also help to facilitate clinical management.

Mögliche Implikationen für den klinischen Alltag

- Häufigeres Screening mittels Galactomannan aus dem Serum?
- Wöchentliches Screening (Trachealsekret/Sputum) mit Kultur, Aspergillus PCR und Galactomannan?
- Allenfalls zusätzlich Beta-D-Glucan aus dem Serum?
- Bei positiver Kultur aus respiratorischem Material vermehrt BAL und/oder CT-Verlaufskontrolle?

Lateral Flow Assay