Διάγνωση CAPA

Covid Associated Pulmonary Aspergillosis

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

Philipp Koehler, Matteo Bassetti, Arunaloke Chakrabarti, Sharon C A Chen, Arnaldo Lopes Colombo, Martin Hoenigl, Nikolay Klimko, Cornelia Lass-Flörl, Rita O Oladele, Donald C Vinh, Li-Ping Zhu, Boris Böll, Roger Brüggemann, Jean-Pierre Gangneux, John R Perfect, Thomas F Patterson, Thorsten Persigehl, Jacques F Meis, Luis Ostrosky-Zeichner, P Lewis White, Paul E Verweij, Oliver A Cornely, on behalf of the European Confederation of Medical Mycology, the International Society for Human and Animal Mycology, the Asia Fungal Working Group, the INFOCUS LATAM/ISHAM Working Group, the ISHAM Pan Africa Mycology Working Group, the European Society for Clinical Microbiology and Infectious Diseases Fungal Infection Study Group, the ESCMID Study Group for Infections in Critically Ill Patients, the Interregional Association of Clinical Microbiology and Antimicrobial Chemotherapy, the Medical Mycology Society of Nigeria, the Medical Mycology Society of China Medicine Education Association, Infectious Diseases Working Party of the German Society for Haematology and Medical Oncology, and Association of Medical Microbiology and Infectious Disease Canada

Faculty of Medicine (P Koehler MD, B Böll MD, Prof O A Cornely MD, T Persigehl MD) **and Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases** (P Koehler, Prof O A Cornely), **University of Cologne, Cologne, Germany; Department I of Internal Medicine, European Excellence Center for Medical Mycology (ECMM)** (P Koehler, B Böll, Prof O A Cornely) **and Department of Radiology** (T Persigehl), **University Hospital Cologne, Cologne, Germany; Infectious Diseases Clinic, Department of Health Sciences, University of Genoa, Genoa, Italy** (Prof M Bassetti MD); **Policlinico San Martino Hospital, Genoa, Italy** (Prof M Bassetti); **Department of Medical Microbiology, Postgraduate Institute of Medical Education and Research, Chandigarh, India** (Prof A Chakrabarti MD); **Centre for Infectious Diseases and Microbiology Laboratory Services, Institute of Clinical Pathology and Medical Research, New South Wales Health Pathology, Sydney, NSW, Australia** (Prof S C A Chen MD); **Department of Infectious Diseases, Westmead Hospital, Sydney, NSW, Australia** (Prof S C A Chen); **School of Medicine, University of Sydney, Sydney, NSW, Australia** (Prof S C A Chen); **Escola**

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

- COVID-19-associated pulmonary aspergillosis is proposed to be defined as possible, probable, or proven on the basis of sample validity and thus diagnostic certainty.
- Recommended first-line therapy is either voriconazole or isavuconazole.
- If azole resistance is a concern, then liposomal amphotericin B is the drug of choice.

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- Decrease of T-cell populations, is observed in patients with COVID-19, especially in patients with severe disease.
- Decline of lymphocyte counts can be accompanied by defective function.
- Severe lymphopenia has been established as a factor predicting the risk of invasive mould disease in patients with haematological malignancies.

J Infect 2019

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- Patients with CAPA might not have host factors and typical radiological features.
- Obtaining mycological evidence of airway invasive aspergillosis in pts with COVID-19, is complicated by decreased use of diagnostic bronchoscopy, which is necessary to protect health-care workers from aerosol exposure and the low sensitivity of detection of circulating galactomannan in serum.
- Detection of *aspergillus* in specimens of the upper respiratory tract, such as sputum or tracheal aspirate, often does not distinguish between *aspergillus* colonisation and invasive disease.

Host factors

- Unclear whether severe SARS-CoV-2 infection itself is the main risk factor for CAPA, or whether additional risk factors, such as corticosteroid therapy, further increase the risk for disease progression.
- In the study by Bartoletti and colleagues, most patients received anti-interleukin (IL)-6 treatment with tocilizumab, as well as corticosteroids.
- Corticosteroid use was more frequent in patients who did not survive.
- Dexamethasone treatment and anti-IL-6-directed strategies might, however, also result in an increased susceptibility to superinfections, including IPA in patients with severe COVID-19.

Imaging

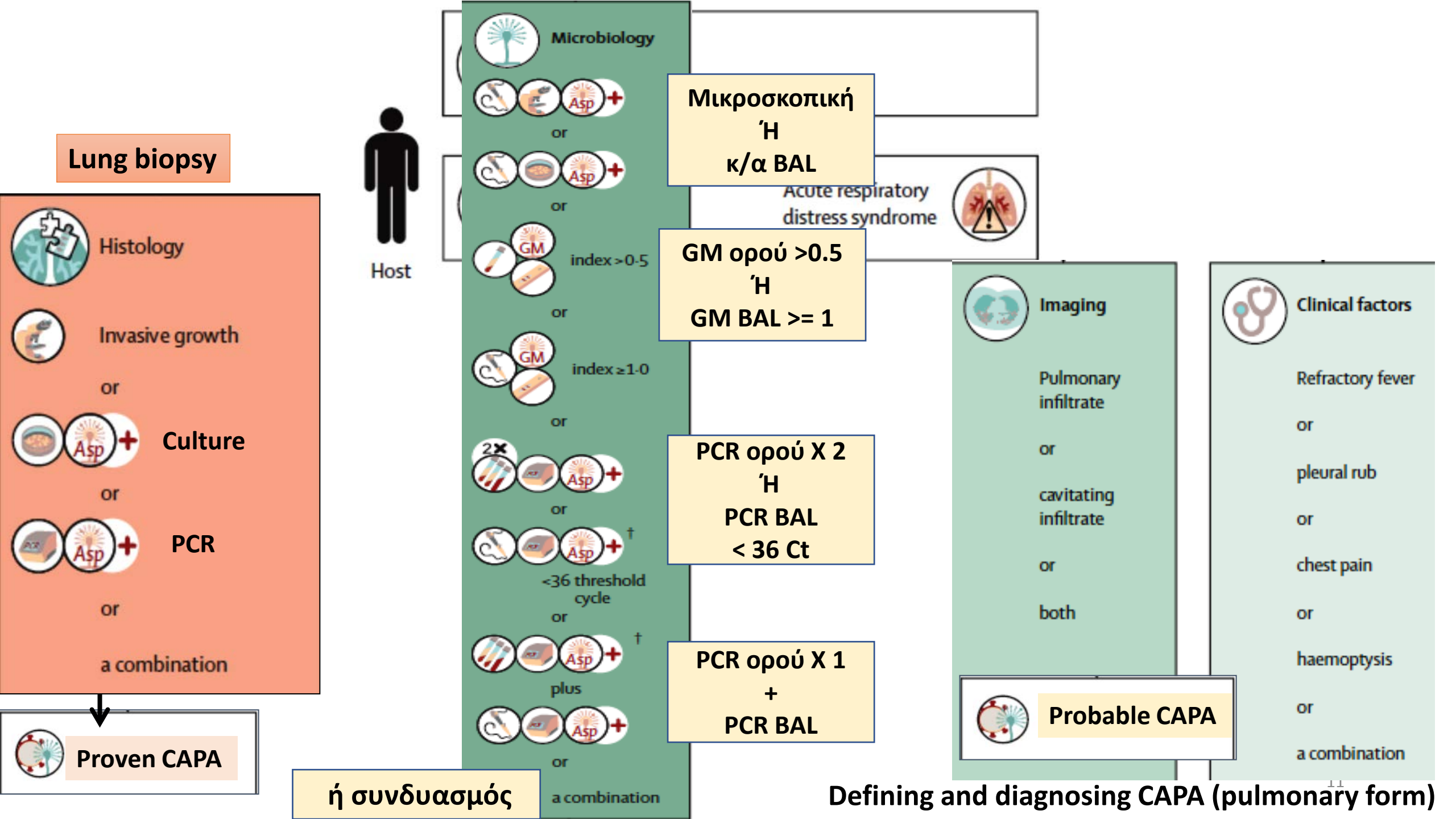
- Use of imaging as a reliable criterion for a case definition of CAPA is debatable, since similar features can be caused by COVID-19 alone.
- Multiple pulmonary nodules or lung cavitation should prompt thorough investigation for IPA, as they are rarely seen with COVID-19 alone.
- Frequently observed radiological features of IPA, such as the halo sign, are not sufficient to define CAPA without mycological evidence.
- This feature is insufficient because the halo sign suggests local infarction, and an intrinsic part of severe COVID-19 is in-situ thrombosis due to endotheliopathy.

Mycological evidence

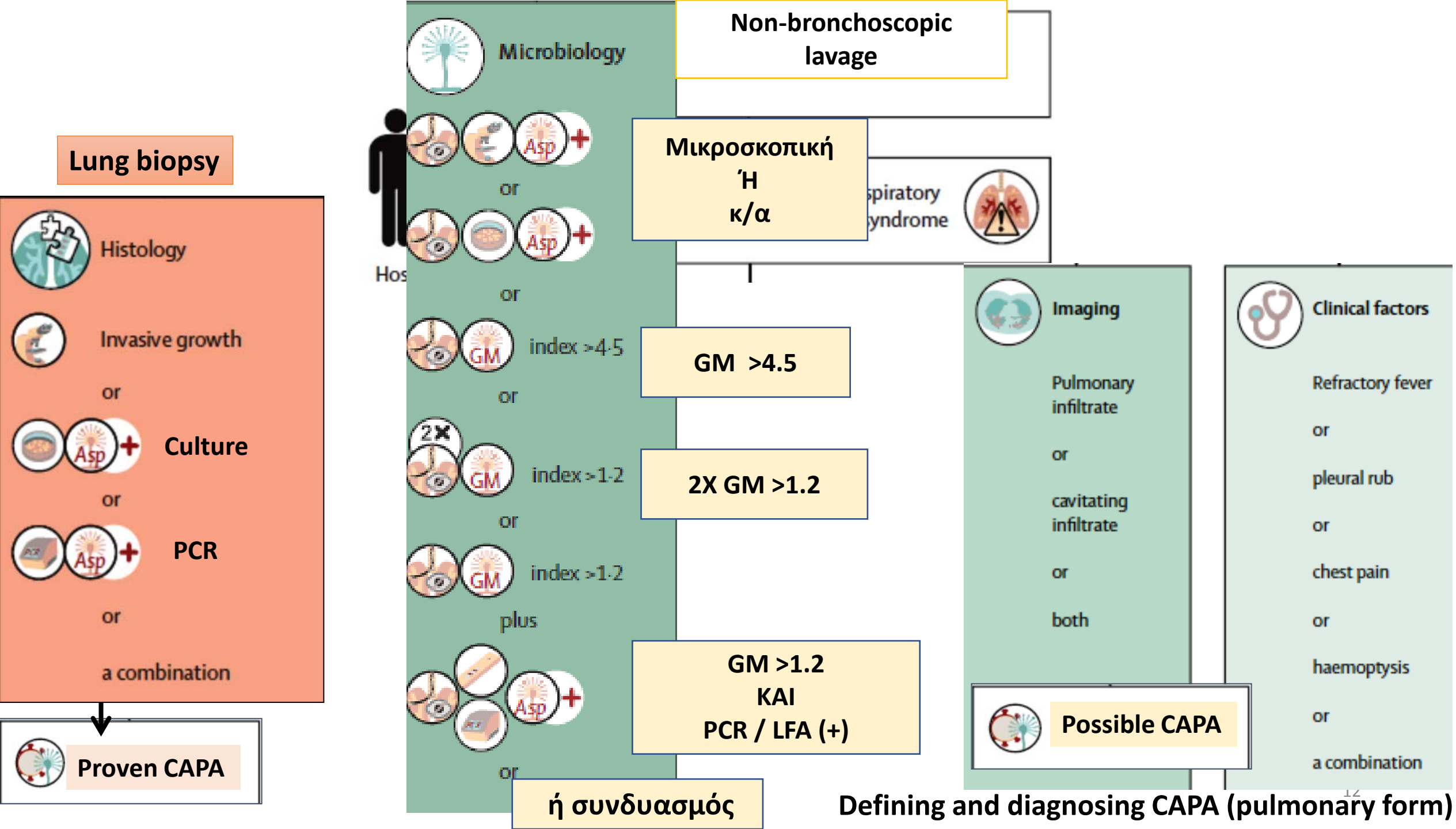
- For diagnosis of IPA, bronchoalveolar lavage fluid and lung biopsy samples are the specimens of choice.
- Tissue culture and tissue microscopy showing invasive growth of septate fungal hyphae of primarily sterile specimens represent the diagnostic gold standard in proving infection.
- Biopsies are high-risk procedures in this patient population and, therefore, are avoided by many clinicians.
- Detection of galactomannan in BAL fluid is highly indicative of IPA, as the antigen is released during active fungal growth.
- Detection of galactomannan in BAL does not prove tissue invasion, and the likelihood of infection is increased if circulating galactomannan is detected.
- The diagnostic yield of serum galactomannan is low in CAPA as, at best, 20% of patients positive results, and proven CAPA cases have been reported with negative serum galactomannan!!!

Mycological evidence

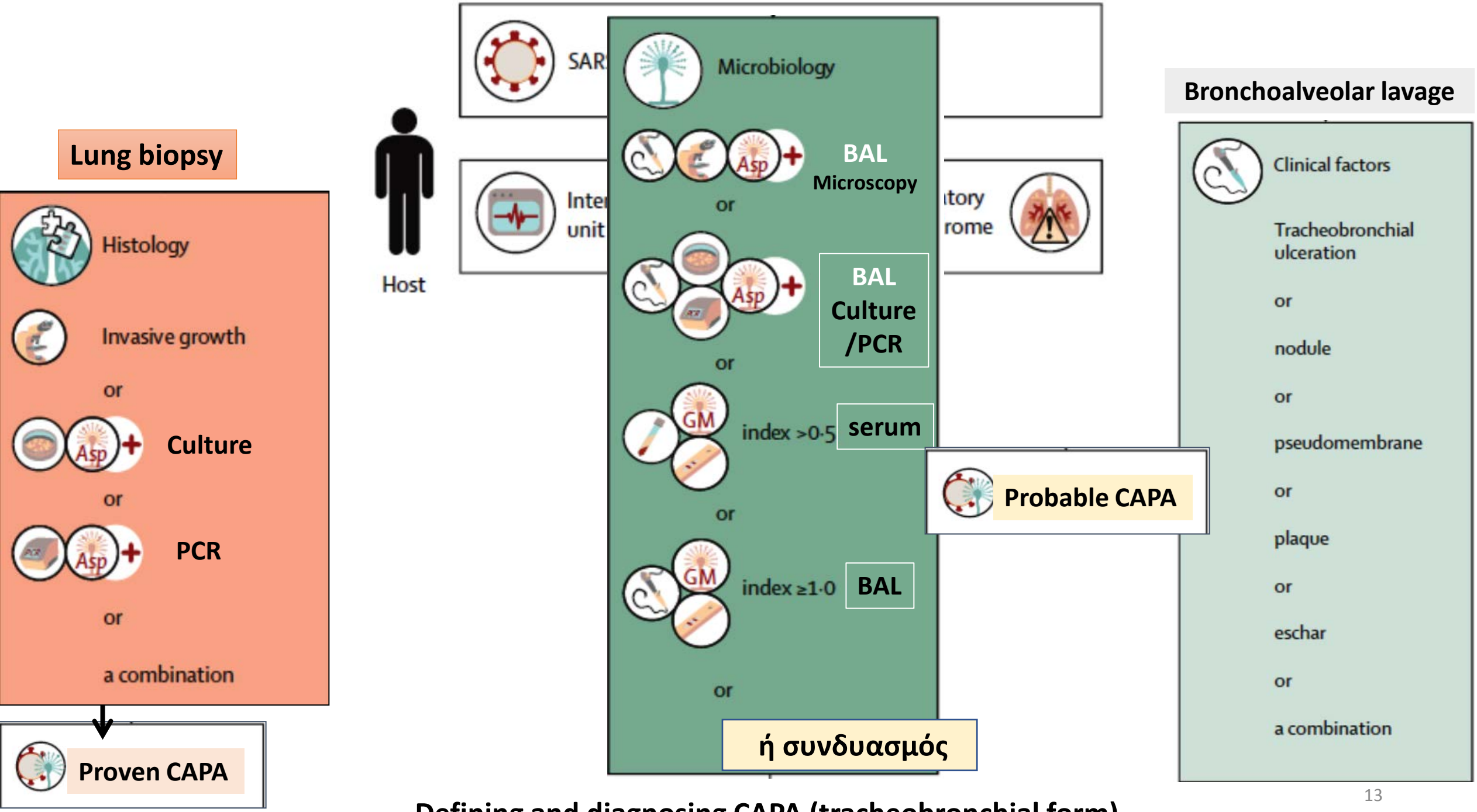
- Use of not only galactomannan but also another biomarker, namely (1–3)-β-D-glucan, for serum screening might be beneficial.
- Two consecutive results for serum (1–3)-β-D-glucan might, therefore, increase suspicion of invasive aspergillosis, although (1–3)-β-D-glucan is not specific for aspergillosis and other causes of elevated serum concentration of (1–3)-β-D-glucan need to be excluded.
- In 2020, *aspergillus* PCR was included in consensus guidelines for defining IFD, with the requirement of two positive results providing sufficient specificity to confirm a diagnosis.
- *Aspergillus* PCR data have been evaluated most extensively in adults with haematological malignancies and stem-cell transplantation, and results might not be transferable to patients in ICUs.



Defining and diagnosing CAPA (pulmonary form)

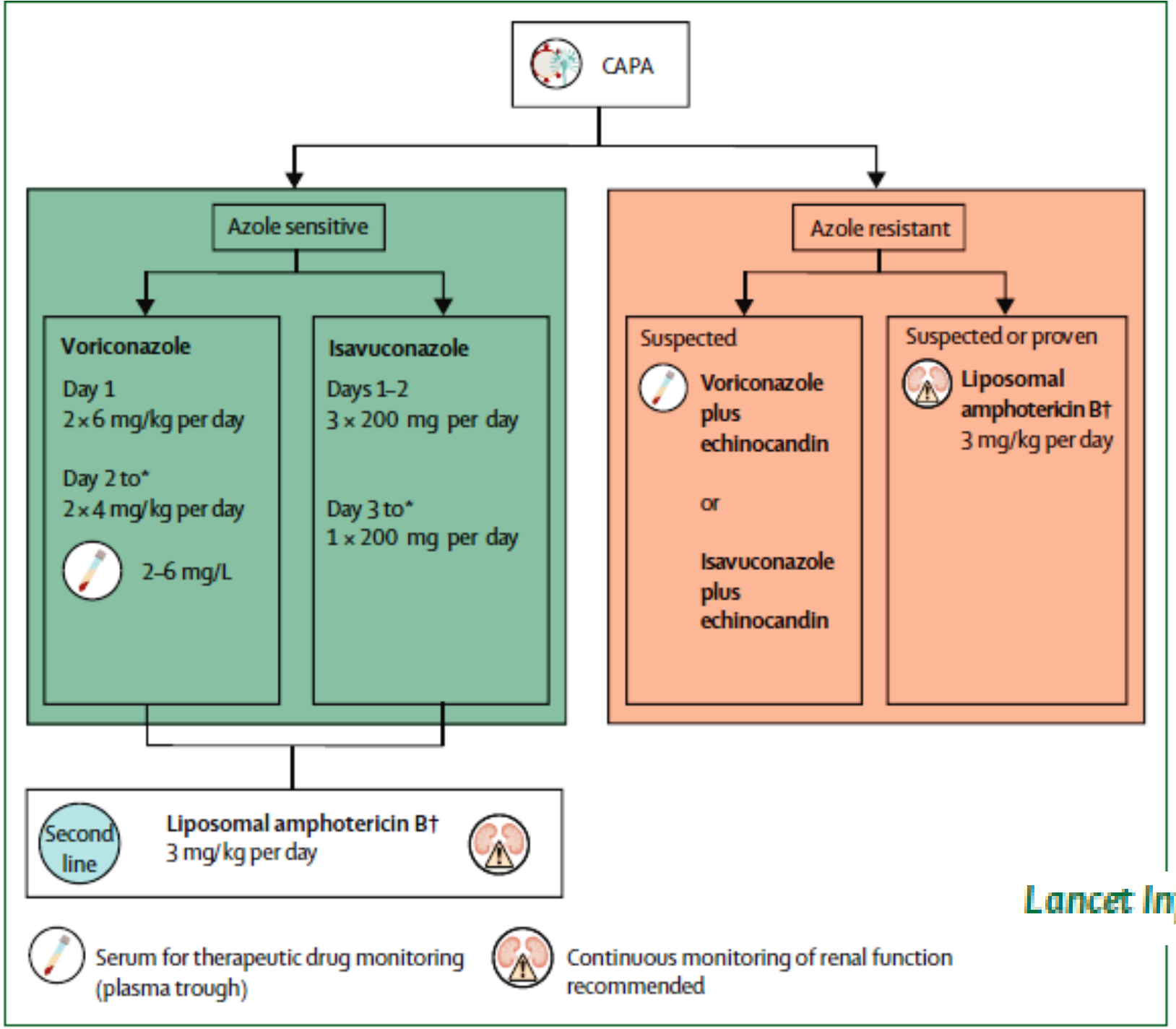


Defining and diagnosing CAPA (pulmonary form)



Defining and diagnosing CAPA (tracheobronchial form)

Προτεινόμενη θεραπεία για CAPA



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What is the likelihood that patients fulfilling diagnostic criteria for CAPA have invasive aspergillosis?

Open Forum Infectious Diseases

MAJOR ARTICLE

Coronavirus Disease 2019-Associated Pulmonary Aspergillosis: Reframing the Debate

Cornelius J. Clancy[1,2] and M. Hong Nguyen[1,3]

[1]University of Pittsburgh, Division of Infectious Diseases, Pittsburgh, Pennsylvania, USA, [2]VA Pittsburgh Healthcare System, Pittsburgh, Pennsylvania, USA, [3]University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA

MAY 2022

Coronavirus Disease 2019-Associated Pulmonary Aspergillosis

- Pulmonary aspergillosis is well recognized among patients with severe coronavirus disease 2019 (COVID-19).
- CAPA has been reported in ~5%– 10% of critically ill COVID-19 patients.
  - Incidence varies widely (0%–33%) across hospitals,
  - Most cases are unproven, and
  - CAPA definitions and clinical relevance are debated.
- Discrepancies between studies may reflect differences in local epidemiology, environmental factors, treatment of COVID-19, thresholds for testing, disease definitions, diagnostic criteria, and patient populations.

Diagnosing Coronavirus Disease 2019-Associated Pulmonary Aspergillosis

- CAPA definitions are based on a combination of clinical and host factors, imaging findings, and mycologic test results in critically ill patients with COVID-19.
- Across guidelines, the major driver of diagnosis is detection of *Aspergillus* in respiratory tract samples by methods such as culture, galactomannan (GM) detection, or polymerase chain reaction (PCR).
- These are not definitive diagnostic tests, because they do not distinguish between colonization and disease.
- The preferred sample for testing, after respiratory tract tissue, is bronchoalveolar lavage (BAL) collected by bronchoscopy.
- Bronchoscopies of patients with COVID-19 are safe using risk-minimizing protocols, and they are now endorsed for diagnosing coinfections.

For any test, more strongly positive and repeatedly positive results increase the probability

Diagnosing Coronavirus Disease 2019-Associated Pulmonary Aspergillosis

- Respiratory samples such as sputa, bronchial and tracheal aspirates, and non-bronchoscopic BAL (NBL) are used in many CAPA studies, despite increased potential for upper airway microbial contamination and lack of validation for GM testing or *Aspergillus* PCR.
- In the absence of other positive diagnostic markers, *Aspergillus* detection in non-BAL respiratory samples is supportive of possible disease.
- Blood cultures and serum GM are insensitive for diagnosing pulmonary aspergillosis, but detection in at-risk hosts may reflect disseminated disease.
- BAL galactomannan testing is performed widely in Europe and the United States.
- *Aspergillus* PCR is commonly used in Europe but not in USA.
- BAL galactomannan as the representative CAPA diagnostic test will be used.

Coronavirus Disease 2019-Associated Pulmonary Aspergillosis

- In studies that have retrospectively applied standardized CAPA definitions, pooled incidence of CAPA in intensive care units (ICUs) was 2% to 11%.
- Only 2% of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)-infected decedents in autopsy studies published through September 2020 had histopathologic evidence of aspergillosis or other invasive mould infections;

Do Patients Diagnosed With Coronavirus Disease 2019-Associated Pulmonary Aspergillosis Have Invasive Aspergillosis?

	BAL GM Cutoff 0.5 (Sens/Spec: 85%/80%)[a]			BAL GM Cutoff 1.0 (Sens/Spec: 75%/90%)[a]			BAL GM Cutoff 1.0 (Sens/Spec: 80%/94%)[a]		
CAPA Likelihood	PPV for IPA	NPV for IPA	IPA Incidence	PPV for IPA	NPV for IPA	IPA Incidence	PPV for IPA	NPV for IPA	IPA Incidence
1%	4%	>99%	<0.1%	7%	>99%	<0.1%	12%	>99%	<0.1%
2%	8%	>99%	0.1%	13%	>99%	0.2%	**21%**	**>99%**	0.3%
3%	12%	>99%	0.5%	**19%**	**>99%**	0.5%	**32%**	**>99%**	1%
5%	**22%**	**99%**	1%	**28%**	**99%**	1%	**40%**	**99%**	2%
10%	**32%**	**98%**	3%	**45%**	**97%**	3%	**60%**	**98%**	5%
15%	**43%**	**97%**	6%	**57%**	**95%**	6%	**71%**	**96%**	9%
20%	**52%**	**96%**	9%	**65%**	**94%**	10%	**76%**	**95%**	12%

Abbreviations: BAL, bronchoalveolar lavage; CAPA, coronavirus disease 2019-associated pulmonary aspergillosis; GM, galactomannan; PPV, positive predictive value; NPV, negative predictive value; Sens, sensitivity; Spec, specificity.

CAPA has been diagnosed in 0% to 33% of critically ill COVID-19 patients in intensive care units (ICUs) at different hospitals. Optimal BAL galactomannan cutoffs for diagnosing invasive aspergillosis in patients with COVID-19 are not defined [7, 11]. Cutoffs and test performance in non-COVID-19 populations can be used to estimate positive predictive values (PPVs) and negative predictive values (NPVs) for invasive aspergillosis in ICUs with various underlying burdens of CAPA (column 1). Bolded text shows PPVs > 15% and NPVs ≥94%, representing settings in which CAPA criteria might be useful in guiding treatment decisions. PPVs ≥15%–30% may be sufficiently high to justify empiric antifungal treatment, depending on constellation of clinical findings and other data in individual patients (Table 3). NPVs are likely high enough to justify withholding antifungal treatment. Clinicians can modify calculations based on local epidemiology and knowledge of test performance.

The relationship between CAPA and IPA in critically ill patients with coronavirus disease 2019 (COVID-19) is represented by a Venn diagram.

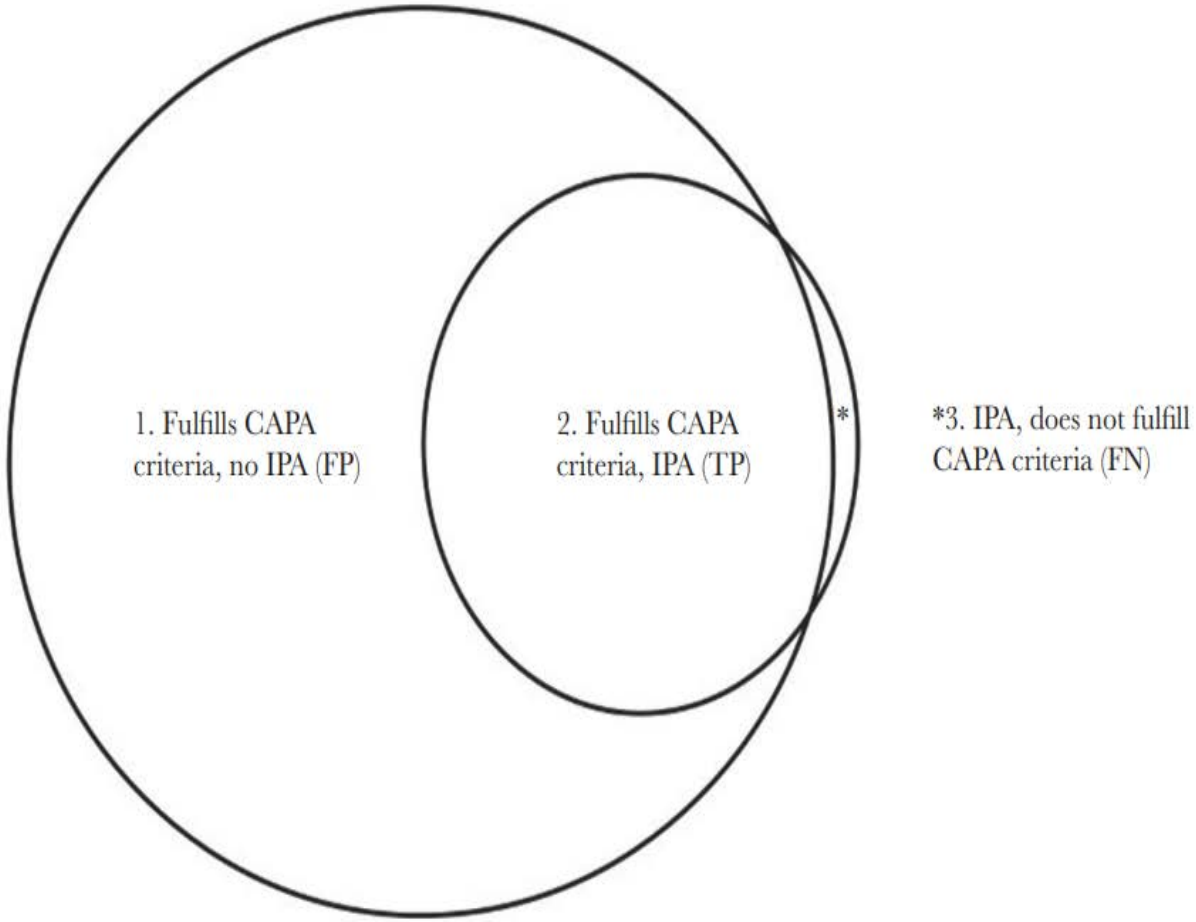

Table 2. Definitions of CAPA and Invasive Aspergillosis

Entity	Definition
CAPA	The likely presence of *Aspergillus* in the respiratory tract of patients with COVID-19, which may or may not be associated with tissue invasion and damage. It is plausible that CAPA representing respiratory tract colonization is a risk factor for development of invasive aspergillosis.
Invasive aspergillosis	Invasive *Aspergillus* infection of organs with attendant tissue damage, most commonly in the lungs, bronchi, trachea, or sinuses

Abbreviations: CAPA, coronavirus disease 2019-associated pulmonary aspergillosis; COVID-19, coronavirus. disease 2019.

Table 3. Stepwise Approach to Diagnosis and Management of CAPA

Step	Objectives	Comments
Understand local epidemiology of CAPA and aspergillosis	Use retrospective reviews and pathology/autopsy data to get rough estimate of burdens at your hospital	Pilot data for CAPA incidence locally may be useful. Historic incidence of aspergillosis in vulnerable populations (eg, transplant) and ICUs may give sense of relative local burdens
2.Define at-risk patient populations for CAPA	Use local data and review of published literature to define risk factors relevant at your hospital	Test performance, PPVs and NPVs will be most useful if testing is directed toward populations with reasonable pretest likelihoods of aspergillosis, rather than including all patients with COVID-19
3.Estimate PPVs and NPVs given approximate pretest likelihoods	Use data from steps 1 and 2 to calculate estimated PPVs and NPVs (Table 1)	Even if exact numbers are not available, it may be possible to approximate PPVs and NPVs for aspergillosis within ranges, and classify these as relatively low, medium, or high
4.Develop strategies to direct testing to at-risk populations	Engage clinical services relevant to at-risk patients to develop testing, interpretive and management protocols	Many services are involved in care of critically ill patients with COVID-19. Engagement with and buy-in from services will improve compliance with protocols and treatment recommendations. Directed testing rather than routine surveillance testing will decrease false positives for aspergillosis
5.Determine thresholds to justify antifungal treatment	Develop treatment protocols based on estimated PPVs and NPVs, using team approach	Agree among clinical and stewardship services on likelihoods of aspergillosis that justify treatment, and how much potential antifungal overtreatment you are willing to tolerate
6.Individualize decisions in each patient	Make treatment decisions for each patient by considering clinical data and case details	In each patient, clinical parameters (eg, new findings, lack of alternative diagnoses, length of stay, etc), radiography (eg, new lesions), and laboratory data (eg, higher values, repeat or multiple positive results, etc) may refine assessments of disease likelihood and need for treatment

Abbreviations: CAPA, coronavirus disease 2019-associated pulmonary aspergillosis; COVID-19, coronavirus; ICU, intensive care unit; NPV, negative predictive value; PPV, positive predictive value.

How Should Clinicians Approach the Diagnosis and Treatment of Coronavirus Disease 2019-Associated Pulmonary Aspergillosis?

- Priority subpopulations can be defined by demographic and clinical factors identified using local data and/or published studies.
- Examples of such factors might be ICU stays ≥3 days (particularly prolonged stays), receipt of tocilizumab, or other anti-interleukin-6 agents, invasive respiratory support, worsening respiratory status in absence of established etiology despite optimized COVID-19 and antibacterial treatment, new or evolving imaging findings, and tracheobronchial lesions.

How Should Clinicians Approach the Diagnosis and Treatment of Coronavirus Disease 2019-Associated Pulmonary Aspergillosis?

An example is as follows: “This mechanically ventilated patient with COVID-19 who was treated with tocilizumab has worsening respiratory status and imaging.

The work-up thus far is negative.

- ❑Positive respiratory tract galactomannan increases the likelihood of invasive aspergillosis such that I am going to treat empirically.
- ❑Negative respiratory tract galactomannan and fungal culture make invasive aspergillosis unlikely, so I am comfortable holding antifungal treatment even though the patient has some risk factors.”