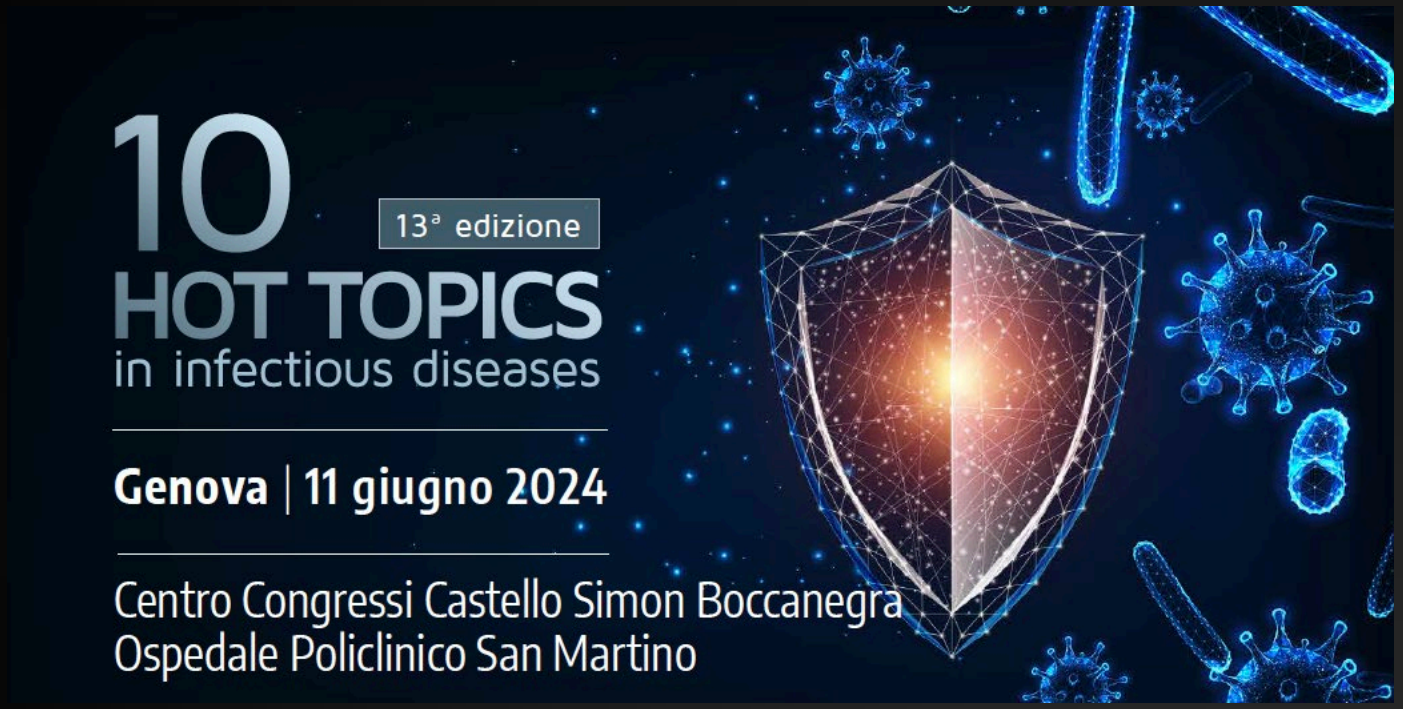

Le nuove definizioni internazionali sulle infezioni fungine e il punto sulla situazione epidemiologica

Daniele Roberto Giacobbe, MD, PhD
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Conflicts of interest

- Investigator-initiated grants from Pfizer, Shionogi, Gilead Italia, BioMérieux, Tillotts Pharma, Menarini

- Fees for speaker/advisor from Pfizer, Tillotts Pharma, Menarini, BioMérieux, GSK

Treating mould infections in the ICU

- For a clinician treating suspected mould infections in the ICU the diagnosis is unlikely to be obvious (or *proven*)

AI-generated image

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Matter of probability

"Many investigators believe that the detection of Aspergillus in the respiratory tract of a patient with significant risk factors for infection and with the appropriate clinical presentation (that is, pulmonary infiltrate) should be presumed to signify active infection, not colonization"

Crawford SW. Intensive Care Med. 1996; 22:1291-1293

"Probability theory is nothing but common sense reduced to calculation"

Pierre-SImon Laplace, 1812

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What level of probability can we accept?

AI-generated image

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What level of probability can we accept?

RESEARCH → HIGHER →  Practice

PRACTICE → LOWER →  Research

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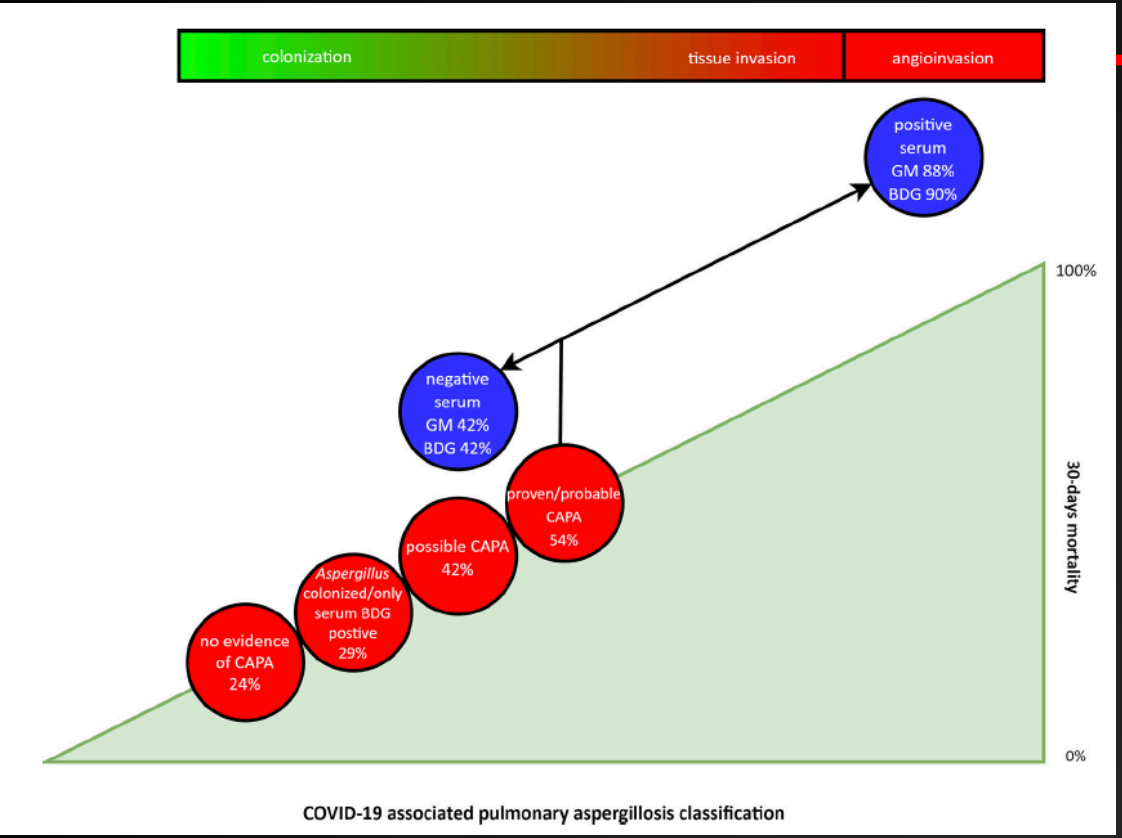

Ergun M, et al. J Clin Microbiol. 2021; 59(12):e0122921

TABLE 3 Multivariable analysis of factors associated with 90-day mortality

Model and factor	Hazard ratio (95% CI)	P^a
Model A		
Age (per 5 yrs)	1.23 (1.12–1.35)	<0.001*
Active malignant disease	1.98 (1.12–3.51)	0.019*
Results of BALF mycological tests		0.62
Negative BALF GM and negative BALF culture	Reference	
Positive BALF GM and negative BALF culture	0.90 (0.46–1.76)	0.77
Negative BALF GM and positive BALF culture	1.30 (0.41–4.14)	0.66
Positive BALF GM and positive BALF culture	1.39 (0.82–2.37)	0.22
Model B[b]		
Age (per 5 yrs)	1.27 (1.14–1.40)	<0.001*
Active malignant disease	2.02 (1.11–3.68)	0.021*
Results of BALF mycological tests		0.11
Negative BALF GM and negative BALF culture	Reference	
Positive BALF GM and negative BALF culture	1.30 (0.62–2.70)	0.49
Negative BALF GM and positive BALF culture	1.53 (0.42–5.54)	0.52
Positive BALF GM and positive BALF culture	2.53 (1.28–5.02)	0.008*

[a]*, $P < 0.05$.
[b]Model B included center as shared frailty.

Giacobbe DR, et al. J Clin Microbiol. 2022; 60(4):e0229821

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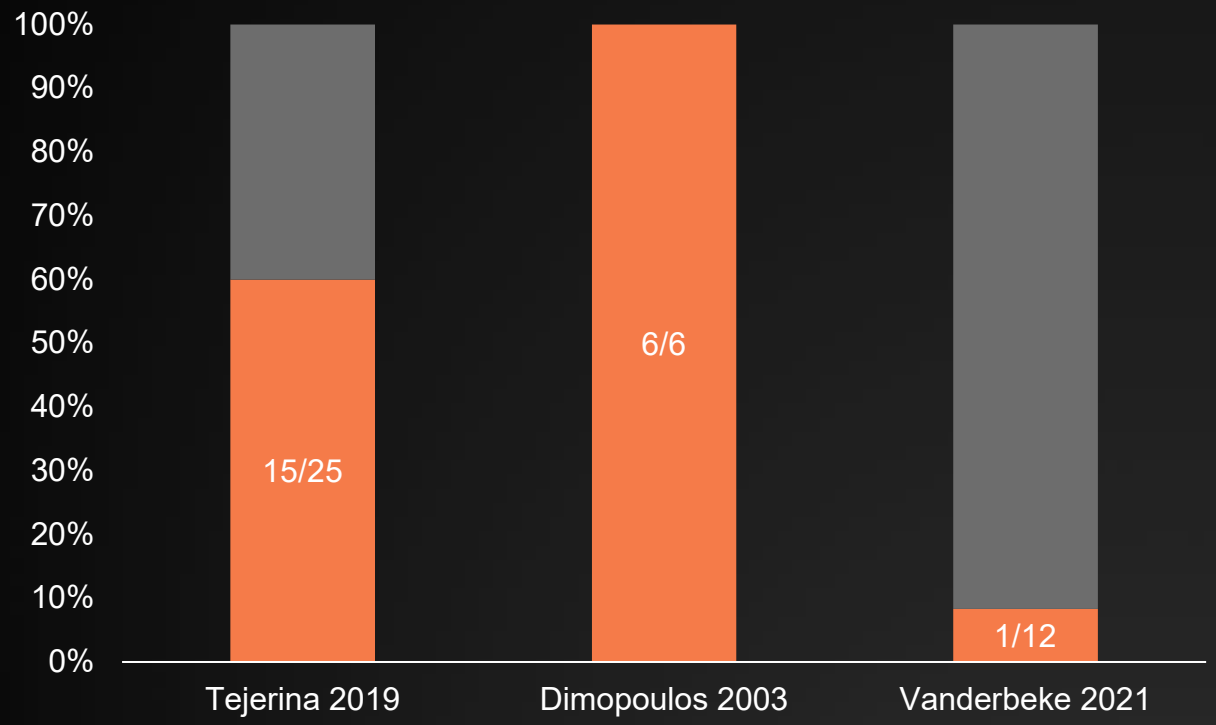
Missed diagnosis of IPA in the ICU (autopsy studies)



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Dimopoulos G, et al. J Chemother. 2003; 15(1):71-5
Vanderbeke L, et al. Am J Respir Crit Care Med. 2023; 208(3):301-311

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(Studied/proposed) risk factors for IPA in the ICU

- Neutropenia
- HSCT
- Malignancy
- COPD
- Influenza
- COVID-19
- Systemic steroids (either long or short term)
- Inhaled steroids
- Liver cirrhosis
- Organ transplantation
- AIDS
- Malnutrition
- Transfusions
- Sepsis/MOF
- Immunosuppression for systemic diseases
- Severe burns
- Post-cardiac surgery status
- Prolonged ICU stay
- Non-fungal pneumonia
- Antibiotics
- Alcoholism
- CGD
- Hemodialysis
- Congestive heart failure
- Near-drowning
- Invasive procedures
- Diabetes mellitus
- Severe bacterial infection
- Smoking
- Concentration of *Aspergillus* spores in the air
- Surgery
- Immunoparalysis

Vandewoude KH, et al. Med Mycol. 2006; 44(Supplement_1):S71-S76
Meersseman W, et al. Clin Infect Dis. 2007; 45(2):205-16
Stevens DA, et al. Immunol Invest. 2011; 40(7-8):751-66
Dimopoulos G, et al. Ann N Y Acad Sci. 2012; 1272:31-9
Bassetti M, et al. Crit Care. 2014; 18(4):458
Schauwvlieghe AFAD, et al. Lancet Respir Med. 2018; 6(10):782-792
Danion F, et al. Med Mycol. 2019; 57(Supplement_2):S94-S103
Koehler P, et al. Clin Microbiol Infect. 2019; 25(12):1501-1509
Cuenca-Estrella M, et al. J Antimicrob Chemother. 2019; 74(Suppl 2):ii9-ii
Verweij, et al. Intensive Care Med. 2020; 46(8):1524-1535
Arastehfar A, et al. J Fungi (Basel). 2020; 6(2):91
Kluge S, et al. Med Mycol. 2021; 60(1):myab064
Rouzé A, et al. Curr Opin Crit Care. 2022; 28(5):470-479

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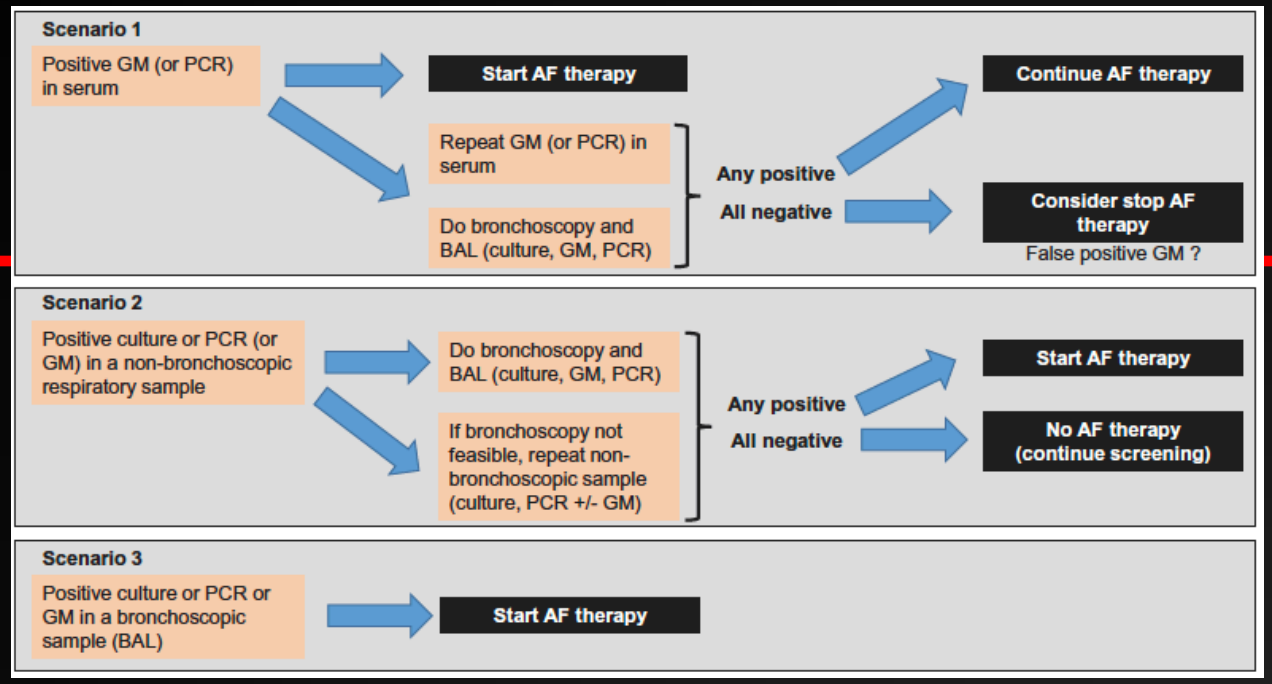
Table 2. Risk of invasive aspergillosis among patients admitted to the intensive care unit (ICU; medical, mixed or surgical).

High-risk category
Neutropenia (neutrophil count, <500 neutrophils/mm^3)
Hematological malignancy
Allogeneic bone marrow transplantation
Intermediate-risk category
Prolonged treatment with corticosteroids before admission to the ICU
Autologous bone marrow transplantation
Chronic obstructive pulmonary disease
Liver cirrhosis with a duration of stay in the ICU >7 days
Solid-organ cancer
HIV infection
Lung transplantation
Systemic diseases requiring immunosuppressive therapy
Low-risk category
Severe burns
Other solid-organ transplant recipients (e.g., heart, kidney, or liver transplant recipients)
Steroid treatment with a duration of ⩽7 days
Prolonged stay in the ICU (>21 days)
Malnutrition
Post–cardiac surgery status

"Patients who survived IAPA received antifungal therapy much earlier than those who did not (2 days after diagnosis of influenza among survivors versus 9 days among non-survivors)"

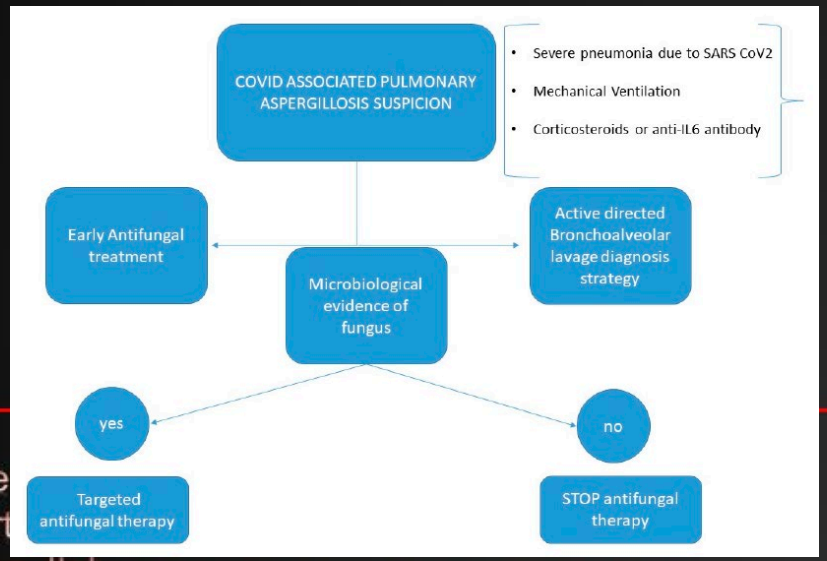
- Role of baseline risk
- Role of disease severity
- Role of lack of alternative diagnoses/response to other treatments

Meersseman W, et al. Clin Infect Dis. 2007; 45(2):205-16
Verweij PE, et al. Intensive Care Med 2020; 46(8):1524-1535
van de Veerdonk FL, et al. Am J Respir Crit Care Med 196:524–527



Is antifungal therapy indicated in patients suspected of CAPA?

Recommendations	Strength of recommendation	Quality of evidence
Antifungal therapy is **indicated** in patients with CAPA	Strong	Low
We **recommend to follow** national or international **guidelines** on antifungal therapy of invasive aspergillosis	Strong	Low
We **recommend to consider empirical therapy** for CAPA in patients in who(m) a **BAL** has been **performed** and **BAL GM/PCR** results are **pending**	Weak	Very low
In patients with a **negative BAL GM, discontinuation of empirical** antifungal **therapy** is **recommended**	Weak	Very low
Therapeutic drug monitoring (TDM) is **recommended** in critically ill CAPA patients receiving **triazole therapy**	Strong	Low



Estella A, et al. J Fungi (Basel). 2023; 9(3):288
Lamoth F. Curr Opin Infect Dis. 2022; 35:163-169
Verweij PE, et al. Intensive Care Med. 2021; 47(8):819-834

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Definitions of IPA (used in ICU patients)

EORTC/MSG (Ascioglu et al. Clin Infect Dis 2002)

EORTC/MSG plus cirrhosis, COPD, and steroids added as host factors (Meersseman et al. Am J Respir Crit Care Med 2008)

Revised EORTC/MSG (De Pauw et al. Clin Infect Dis 2008)

Revised EORTC/MSG plus ICU stay > 4 days as host factor (Eigl et al. Critical Care 2015)

Revised EORTC/MSG plus alcoholic liver cirrhosis, long stay in the intensive care unit and severe acute respiratory distress syndrome as host factors (Imbert et al. Clin Microbiol Infect 2016)

Revised EORTC/MSG with additional host factors (COPD, low dosage steroid treatment) and clinical criteria (symptoms of lower respiratory tract infection, e.g., dyspnea, pleural rub and new infiltrate without an alternative diagnosis) (Orsi et al. New Microbiol 2015)

Revised EORTC/MSG plus underlying respiratory disease as host factor and BALF GM >1.0 OD as mycological criterion (Prattes et al. Am J Respir Crit Care Med 2014)

Revised EORTC/MSG plus COPD, long-term therapy with corticosteroids, solid organ transplant, HIV infection in patients with < 200 CD4/mm^3, cirrhosis (Fortun et al. J Infect 2016)

ISHLT (Husain et al. J Heart Lung Transplant 2011)

AspICU (Blot et al. Am J Respir Crit Care Med 2012: Vandewoude et al. Critical Care 2007)

Modified AspICU with BALF GM as alternative entry criterion (Schroeder et al. Critical Care 2016)

BULPA (Bulpa et al. Eur Respir J 2007)

Clinical Infectious Diseases

MAJOR ARTICLE

Revision and Update of the Consensus Definitions of Invasive Fungal Disease From the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium

"Group 10 (IFD definitions in ICU patients) was unable to generate recommendations that preserved a level of certainty consistent with the existing definitions except for proven IFD"

Donnelly JP, et al. Clin Infect Dis. 2020; 71(6):1367-1376

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Received: 15 October 2018 | Revised: 21 October 2018 | Accepted: 5 November 2018

DOI: 10.1111/myc.12869

ORIGINAL ARTICLE

WILEY mycoses

Developing definitions for invasive fungal diseases in critically ill adult patients in intensive care units. Protocol of the FUNgal infections Definitions in ICU patients (FUNDICU) project

- Protocol developed in 2018
- WP1 including systematic review
- Consensus based on RAND-UCLA appropriateness method
- Consensus published in 2024

Bassetti M, et al. Mycoses. 2019; 62(4):310-319

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WP1

- Identification of relevant literature on the diagnostic performance of existing definitions/scores and laboratory tests for the diagnosis of IFD in critically ill patients in ICU

Bassetti M, et al. Mycoses 2019; 62:310-319

Invasive aspergillosis

Review

Performance of existing definitions and tests for the diagnosis of invasive aspergillosis in critically ill, adult patients: A systematic review with qualitative evidence synthesis ☆

M. Bassetti [a,b,*], D.R. Giacobbe [a,b], C. Grecchi [c,d], C. Rebuffi [e], V. Zuccaro [c], L. Scudeller [f], the FUNDICU investigators [1]

Bassetti M, et al. J Infect. 2020; 81:131-146

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Invasive aspergillosis

- Sufficient data for evaluating the performance of existing definitions and laboratory tests for the diagnosis of IA in critically ill patients is available only for invasive pulmonary aspergillosis
- Against histology/autopsy as reference, the AspICU definition showed a promising diagnostic performance but based on small samples and applicable only to patients with positive respiratory cultures
- Studies on laboratory tests consistently indicated a better diagnostic performance of bronchoalveolar lavage fluid (BALF) galactomannan (GM) than serum GM, and a suboptimal specificity of BALF and serum (1,3)-β-D-glucan.

Bassetti M, et al. J Infect. 2020; 81:131-146

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Invasive aspergillosis

Performance of existing definitions and tests for the diagnosis of invasive aspergillosis in critically ill, non-neutropenic, adult patients: An update including COVID-19 data ☆

Bassetti M, et al. J Infect. 2022; 85:573-607

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Invasive aspergillosis

- The updated evidence is in line with the conclusions of the original study on the better performance of BALF GM than serum GM and the suboptimal specificity of serum BDG for the diagnosis of IPA
- 55% (6/11) of included study assessed the diagnostic performance of laboratory markers for the diagnosis of COVID-19-associated pulmonary aspergillosis (CAPA), although the lack of included studies on the diagnostic performance of mycological tests against histology further precludes a firm assessment of their true accuracy for the diagnosis of CAPA
- The concept of improving diagnostic accuracy by combining classical mycological markers with PCR or other innovative tests is certainly promising, but the related evidence is still preliminary, as also testified by the heterogeneity of evaluated combinations across the few studies that met the inclusion criteria

Bassetti M, et al. J Infect. 2022; 85:573-607

Invasive candidiasis

Performance of existing clinical scores and laboratory tests for the diagnosis of invasive candidiasis in critically ill, nonneutropenic, adult patients: A systematic review with qualitative evidence synthesis

Daniele Roberto Giacobbe[1,2] | Erika Asperges[3] | Andrea Cortegiani[4,5] | Cecilia Grecchi[3] | Chiara Rebuffi[6] | Valentina Zuccaro[3] | Luigia Scudeller[7] | Matteo Bassetti[1,2] | the FUNDICU investigators

Giacobbe DR, et al. Mycoses 2022; doi: 10.1111/myc.13515. Online ahead of print

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Invasive candidiasis

- Despite the heterogeneity of study populations and IC prevalence, clinical scores constantly showed a high negative predictive value (NPV) and a low positive predictive value (PPV) for the diagnosis of IC in the target population

- Fungal antigen-based biomarkers (with most studies assessing serum beta-D-glucan) retained a high NPV similar to that of clinical scores, with a higher PPV, although the latter showed important heterogeneity across studies, possibly reflecting the targeted or untargeted use of these tests in patients with a consistent clinical picture and risk factors for IC.

Giacobbe DR, et al. Mycoses 2022; doi: 10.1111/myc.13515. Online ahead of print

PJP and other IFD

Communication

Performance of Existing Definitions and Tests for the Diagnosis of Invasive Fungal Diseases other than Invasive Candidiasis and Invasive Aspergillosis in Critically Ill, Adult Patients: A Systematic Review with Qualitative Evidence Synthesis

Daniele R. Giacobbe [1,2,*,†], Andrea Cortegiani [3,4,†], Ilias Karaiskos [5], Toine Mercier [6,7], Sofia Tejada [8,9], Maddalena Peghin [10], Cecilia Grecchi [11,12], Chiara Rebuffi [13], Erika Asperges [11], Valentina Zuccaro [11], Luigia Scudeller [14], Matteo Bassetti [1,2] and the FUNDICU investigators [‡,§]

Giacobbe DR, et al. J Fungi 2022; 2021; 7:176

PJP and other IFD

- Only two studies for PJP and no studies for other IFDs met the FUNDICU protocol criteria for inclusion in qualitative synthesis
- Currently, there is no sufficient solid data for directly evaluating the performance of existing definitions and laboratory tests for the diagnosis of PJP and other non-IA, non-IC IFDs in critically ill adult patients outside classical populations at risk.

Giacobbe DR, et al. J Fungi 2022; 2021; 7:176

Received: 15 October 2018 | Revised: 21 October 2018 | Accepted: 5 November 2018

DOI: 10.1111/myc.12869

ORIGINAL ARTICLE

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Bassetti M, et al. Mycoses. 2019; 62(4):310-319

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CONFERENCE REPORTS AND EXPERT PANEL

Invasive Fungal Diseases in Adult Patients in Intensive Care Unit (FUNDICU): 2024 consensus definitions from ESGCIP, EFISG, ESICM, ECMM, MSGERC, ISAC, and ISHAM

Matteo Bassetti[1,2*], Daniele R. Giacobbe[1,2], Christina Agvald-Ohman[3], Murat Akova[4], Ana Alastruey-Izquierdo[5,6], Sevtap Arikan-Akdagli[7], Elie Azoulay[8,9], Stijn Blot[10,11], Oliver A. Cornely[12,13,14,15], Manuel Cuenca-Estrella[5], Dylan W. de Lange[16], Francesco G. De Rosa[17], Jan J. De Waele[18], George Dimopoulos[19], Jose Garnacho-Montero[20], Martin Hoenigl[21,22,23], Souha S. Kanj[24], Philipp Koehler[12,25], Bart J. Kullberg[26], Frédéric Lamoth[27,28,29], Cornelia Lass-Flörl[30], Johan Maertens[31], Ignacio Martin-Loeches[32], Patricia Muñoz[33,34,35,36], Garyphallia Poulakou[37], Jordi Rello[38,39,40,41], Maurizio Sanguinetti[42,43], Fabio S. Taccone[44], Jean-François Timsit[45,46], Antoni Torres[47,48,49,50], Jose A. Vazquez[51], Joost Wauters[52], Erika Asperges[53], Andrea Cortegiani[54,55], Cecilia Grecchi[56], Ilias Karaiskos[57], Clément Le Bihan[58], Toine Mercier[59,60], Klaus L. Mortensen[61], Maddalena Peghin[62], Chiara Rebuffi[63], Sofia Tejada[38,41], Antonio Vena[1,2], Valentina Zuccaro[53], Luigia Scudeller[64] and Thierry Calandra[28,29] on behalf of the Study Group for Infections in Critically Ill Patients of the European Society of Clinical Microbiology and Infectious Diseases (ESGCIP), the Fungal Infection Study Group of the European Society of Clinical Microbiology and Infectious Diseases (EFISG), the European Society of Intensive Care Medicine (ESICM), the European Confederation of Medical Mycology (ECMM), the Mycoses Study Group Education and Research Consortium (MSGERC), the International Society of Antimicrobial Chemotherapy (ISAC), the International Society for Human and Animal Mycology (ISHAM), the Austrian Society for Medical Mycology (ÖGMM), the Italian Society of Anesthesia, Analgesia, Reanimation, and Intensive Care (SIAARTI), the Italian Society of Anti-Infective Therapy (SITA), and the FUNDICU Collaborators

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Bassetti M, et al. Intensive Care Med 2024; 2024; 50(4):502-515

Table 3 Research definition for proven invasive aspergillosis in non-neutropenic, adult patients in ICU

Definition of proven invasive aspergillosis
Consensus reached after two rounds of remote voting and one round of live meeting voting (93% agreement)
Proven invasive aspergillosis is defined by at least one of the following
Tissue invasion shown by histological or cytopathological evidence on a specimen obtained from a normally sterile site or the lung with biopsy or needle aspiration, combined with detection of hyphae compatible with *Aspergillus* spp. (confirmed by culture or PCR)
Recovery of *Aspergillus* spp. by culture on a specimen obtained from a normally sterile site by means of biopsy or needle aspiration, from a lesion consistent with an infectious process

ICU intensive care unit, *PCR* polymerase chain reaction

Bassetti M, et al. Intensive Care Med 2024; 2024; 50(4):502-515

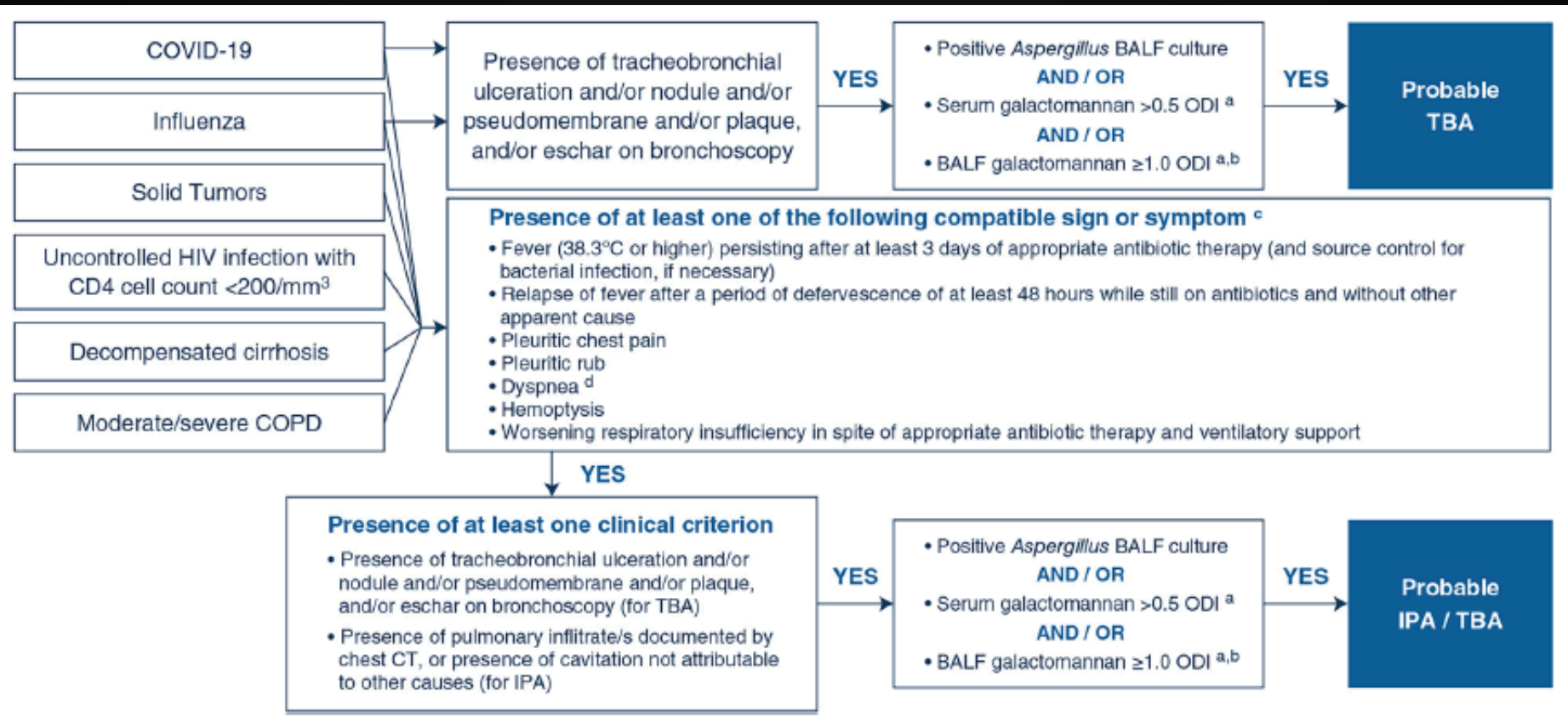

Fig. 2 Flowchart for probable IPA and probable TBA research definitions in non-neutropenic, adult patients in ICU*. *BALF* bronchoalveolar lavage fluid, *COPD* chronic obstructive pulmonary disease, *COVID-19* coronavirus disease 2019, *CT* computerized tomography, *GM* galactomannan, *HIV* human immunodeficiency virus, *ICU* intensive care unit, *IPA* invasive pulmonary aspergillosis, *ODI* optical density index, *TBA* tracheobronchial aspergillosis. *The definitions of probable IPA/TBA for research studies provided in the present document do not apply to those ICU patients fulfilling host factors as defined in the EORTC/MSGERC consensus: (i) hematology and solid organ transplant patients; (ii) prolonged use of corticosteroids; (iii) treatment with other recognized T-cell immunosuppressants; (iv) treatment with recognized B-cell immunosuppressants; (v) inherited severe immunodeficiency; (vi) acute graft-versus-host disease grade III or IV involving the gut, lungs, or liver that is refractory to first-line treatment with steroids. In these patients, the EORTC/MSGERC definitions should be used for defining IPA/TBA in research studies (for more details, see the EORTC/MSGERC consensus document [20]). [a]Platelia *Aspergillus* Ag Kit. [b]When the Platelia test is unavailable, another GM test can be used when this test was compared with the Platelia test in a well-designed study and shown to have comparable specificity to the 1.0 Platelia cut-off. [c]Compatible with the site/progression of IPA or TBA. [d]Not applicable for patients ventilated patients from more than 48 h at the time of assessment for probable IPA/TBA. TBA; applicable in the first 48 h if dyspneic at the time of initiation of ventilation

Bassetti M, et al. Intensive Care Med 2024; 2024; 50(4):502-515

Table 1 Research definition for proven invasive candidiasis in non-neutropenic, adult patients in ICU

Type of proven invasive candidiasis	Definition
Candidemia Consensus reached after two rounds of remote voting and one round of live meeting voting (100% agreement)	Proven candidemia is defined by the isolation of *Candida* spp. from at least one blood culture obtained from venipuncture (not from a catheter)
Deep-seated candidiasis Consensus reached after three rounds of remote voting and one round of live meeting voting (100% agreement)	Proven deep-seated candidiasis is defined by the identification of *Candida* spp. on specimens obtained through surgery or US-guided or CT-guided puncture from normally sterile deep sites[a] other than blood, in a patient without a suspected mucosal perforation or recent gastrointestinal or urogenital surgery that could result in contamination of the body cavity. Identification can be achieved by means of direct microscopy, culture, or histology[b] Identification of *Candida* spp. by histology defines proven disease also in presence of alterations possibly leading to contamination of the site The histological evidence of budding cells consistent with *Candida* spp. defines proven invasive candidiasis Species identification through PCR or culture is necessary for hyphae or pseudohyphae, which may be observed also for other yeasts

CT computerized tomography, *PCR* polymerase chain reaction, *US* ultrasound

[a] i.e., not skin or mucous membranes

[b] Histology is required also for defining proven pulmonary candidiasis, for the following reason: (i) the lung is not a normally sterile site; (ii) pulmonary candidiasis is an extremely rare disease entity in nonneutropenic ICU patients requiring lung biopsy for definite diagnosis. Consequently, no definition was developed for probable pulmonary candidiasis (see Table 2)

Bassetti M, et al. Intensive Care Med 2024; 2024; 50(4):502-515

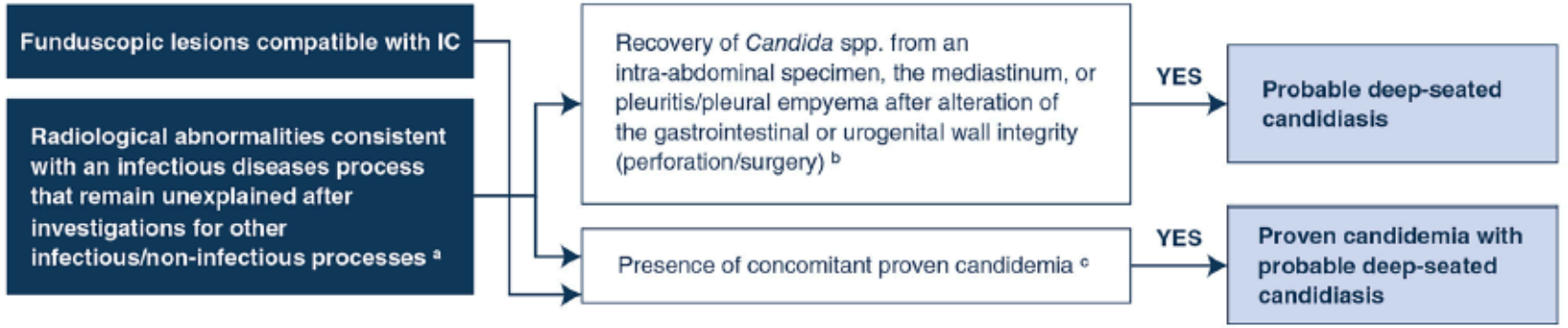

Fig. 1 Flowchart for probable deep-seated candidiasis research definition in non-neutropenic, adult patients in ICU. The definitions of probable IC provided in the present document do not apply to those ICU patients fulfilling host factors as defined in the European Organization for Research and Treatment of Cancer (EORTC) and the Mycoses Study Group Education and Research Consortium (MSGERC) consensus: (i) hematology and solid organ transplantation patients; (ii) prolonged use of corticosteroids; (iii) treatment with other recognized T-cell immunosuppressants; (iv) treatment with recognized B-cell immunosuppressants; (v) inherited severe immunodeficiency; (vi) acute graft-versus-host disease grade III or IV involving the gut, lungs, or liver that is refractory to first-line treatment with steroids. In these patients, the EORTC/MSGERC definitions should be used for defining IC in research studies (for more details, see the EORTC/MSGERC consensus document [20]). [a]Such abnormalities should be evident in deep sites where invasive candidiasis may develop either because of direct inoculation or because of previous, undetected hematogenous spread (e.g., IAC, endocarditis, osteomyelitis, arthritis, mediastinitis, meningitis; with the exclusion of the lung, for which only a proven diagnosis through histology would be considered as invasive candidiasis). The investigations carried out for excluding alternative diagnoses should be reported in detail. [b] Specimens should be obtained during surgery, puncture, or obtained from a newly inserted drain as soon as possible (no later than 24 h after placement). This mycological criterion does not apply to the isolation of *Candida* spp. from peritoneal fluid after gastrointestinal/urogenital perforation if complete source control is rapidly obtained (within 24 h from perforation and after peritoneal fluid collection). This may reflect contamination before development of invasive disease and does not define a mycological criterion for probable deep-seated candidiasis. In case of source control performed > 24 h after perforation or in case of recurrent peritonitis (e.g., anastomosis leakage), isolation of *Candida* spp. from the peritoneum (from an intra-abdominal specimen during surgery or obtained from an external drainage inserted from < 24 h) does define a mycological criterion for probable deep-seated candidiasis. The same concepts apply to Candida mediastinitis and pleuritis/pleural empyema after esophageal perforation. [c] The presence of concomitant proven candidemia can be considered as a mycological criterion for probable deep-seated candidiasis. In this case, the disease should be classified as proven IC in research studies (proven candidemia plus probable deep-seated candidiasis). *IC* invasive candidiasis, *ICU* intensive care unit

Bassetti M, et al. Intensive Care Med 2024; 2024; 50(4):502-515

Conclusion (on novel definitions)

- Difference between research and practice
- Standardization of research definitions important first step
- Possible future role of AI?
  - Improve overall gain from observational evidence
  - Issues of interpretability, hallucinations, and undetected biases

A word of caution

Real photo

AI-generated image

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AI-generated image

Prompt:

"Intensive care unit physician of the future happy to achieve a diagnosis of invasive pulmonary aspergillosis with 100% sensitivity and 100% specificity"

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Dealing with *Candida auris*

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Morbidity and Mortality Weekly Report

Candida auris Outbreak in a COVID-19 Specialty Care Unit — Florida, July–August 2020

Christopher Prestel, MD[1,2]; Erica Anderson, MPH[2]; Kaitlin Forsberg, MPH[3]; Meghan Lyman, MD[3]; Marie A. de Perio, MD[4,5]; David Kuhar, MD[1]; Kendra Edwards[6]; Maria Rivera, MPH[2]; Alicia Shugart, MA[1]; Maroya Walters, PhD[1]; Nychie Q. Dotson, PhD[2]

Clinical Infectious Diseases

CORRESPONDENCE

***Candida auris*: A Latent Threat to Critically Ill Patients With Coronavirus Disease 2019**

ELSEVIER

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Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

CMI CLINICAL MICROBIOLOGY AND INFECTION ESCMID

Letter to the Editor

Outbreak of *Candida auris* infection in a COVID-19 hospital in Mexico

Hiram Villanueva-Lozano [1,*], Rogelio de J. Treviño-Rangel [1,*], Gloria M. González [1,*], María Teresa Ramírez-Elizondo [2,3], Reynaldo Lara-Medrano [2], Mary Cruz Aleman-Bocanegra [2], Claudia E. Guajardo-Lara [4], Natalia Gaona-Chávez [2], Fernando Castilleja-Leal [3], Guillermo Torre-Amione [3], Michel F. Martínez-Reséndez [2,3,*]

Rodriguez et al. Clin Infect Dis 2021; Prestel et al. MMWR 2021; Villanueva-Lozano et al. Clin Microbiol Infect 2021

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Article

Spread of Carbapenem-Resistant Gram-Negatives and *Candida auris* during the COVID-19 Pandemic in Critically Ill Patients: One Step Back in Antimicrobial Stewardship?

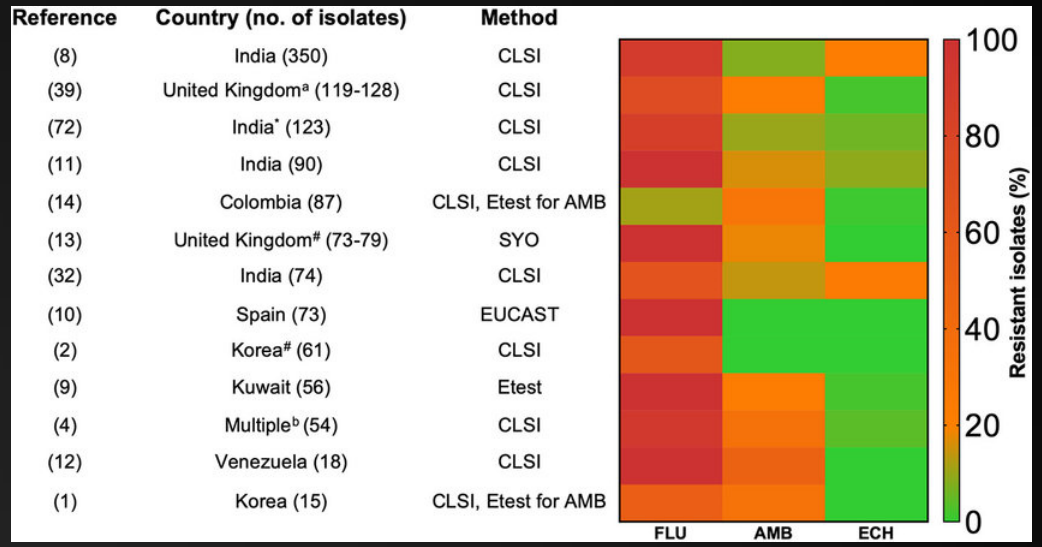
Laura Magnasco [1,*], Malgorzata Mikulska [1,2], Daniele Roberto Giacobbe [1,2], Lucia Taramasso [1], Antonio Vena [1], Chiara Dentone [1], Silvia Dettori [2], Stefania Tutino [2], Laura Labate [2], Vincenzo Di Pilato [3], Francesca Crea [4], Erika Coppo [3,4], Giulia Codda [3], Chiara Robba [5], Lorenzo Ball [3,5], Nicolo' Patroniti [3,5], Anna Marchese [3,4], Paolo Pelosi [3,5] and Matteo Bassetti [1,2]

- 118 critically ill patients with COVID-19 in 2 ICUs
- 12 colonization/infection CRPA (9 VAP, 2 BSI)
- 6 colonization/infection *C. auris* (4 candidemia)
- Mortality 42% (CRPA), 50% (*C. auris)*

Magnasco et al. Microorganisms 2021

Resistance rates

- 93% resistant to fluconazole
- 54% resistant to voriconazole
- 35% resistant to amphotericin B
- 7% resistant to echinocandins
- 6% resistant to flucytosine
- **41% resistant to ≥2 antifungal classes**



Ryan Kean, Gordon Ramage, Combined Antifungal Resistance and Biofilm Tolerance: the Global Threat of *Candida auris,* mSphere, 2019

Shawn R. Lockhart et al, Simultaneous Emergence of Multidrug-Resistant *Candida auris* on 3 Continents Confirmed by Whole-Genome Sequencing and Epidemiological Analyses, *Clinical Infectious Diseases*, January 2017

Comparative Outcomes *of Candida auris* Bloodstream Infections: A Multicenter Retrospective Case-Control Study

Samuel P. Simon,[1] Rosanna Li,[1] Michael Silver,[1] Justin Andrade,[2] Biju Tharian,[3] Lung Fu,[1] Diana Villanueva,[3] Daniel Gonzalez Abascal,[3] Ariel Mayer,[1] James Truong,[2] Nilka Figueroa,[3] Monica Ghitan,[1] Edward Chapnick,[1] and Yu Shia Lin[1]

Table 3. Unadjusted and Adjusted Outcomes

	Patients, No. (%)				
Outcome	*Candida auris* (n = 83)	Other *Candida* spp. (n = 113)	*P* Value	aOR (95% CI)	*P* Value
30-d mortality rate	25 (30.1)	44 (38.9)	.20	1.014 (.563–1.828)	.96
In-hospital mortality rate	37 (44.6)	48 (42.4)	.76	1.40 (.787–2.489)	.25
90-d mortality rate	37 (44.6)	53 (46.9)	.75	0.863 (.478–1.558)	.62
14-d clinical failure	21 (25.3)	36 (31.9)	.32	1.28 (.698–2.364)	.42
60-d microbiologic recurrence	8/67(11.9)	3/75 (4.0)	.08	4.461 (1.033–19.263)	.04
Sequelae of candidemia					
Endophthalmitis	0 (0)	2 (1.8)	.51	…	…
Persistently positive blood cultures	9 (10.8)	22 (19.5)	.10	…	…
Endocarditis (confirmed)	2 (2.4)	3 (2.7)	>.99	…	…
Endocarditis (probable)	4 (4.8)	2 (1.8)	.24	…	…

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval.

Simon et al., Clin Infect Dis 2023 Feb 8;76(3):e1436-e1443

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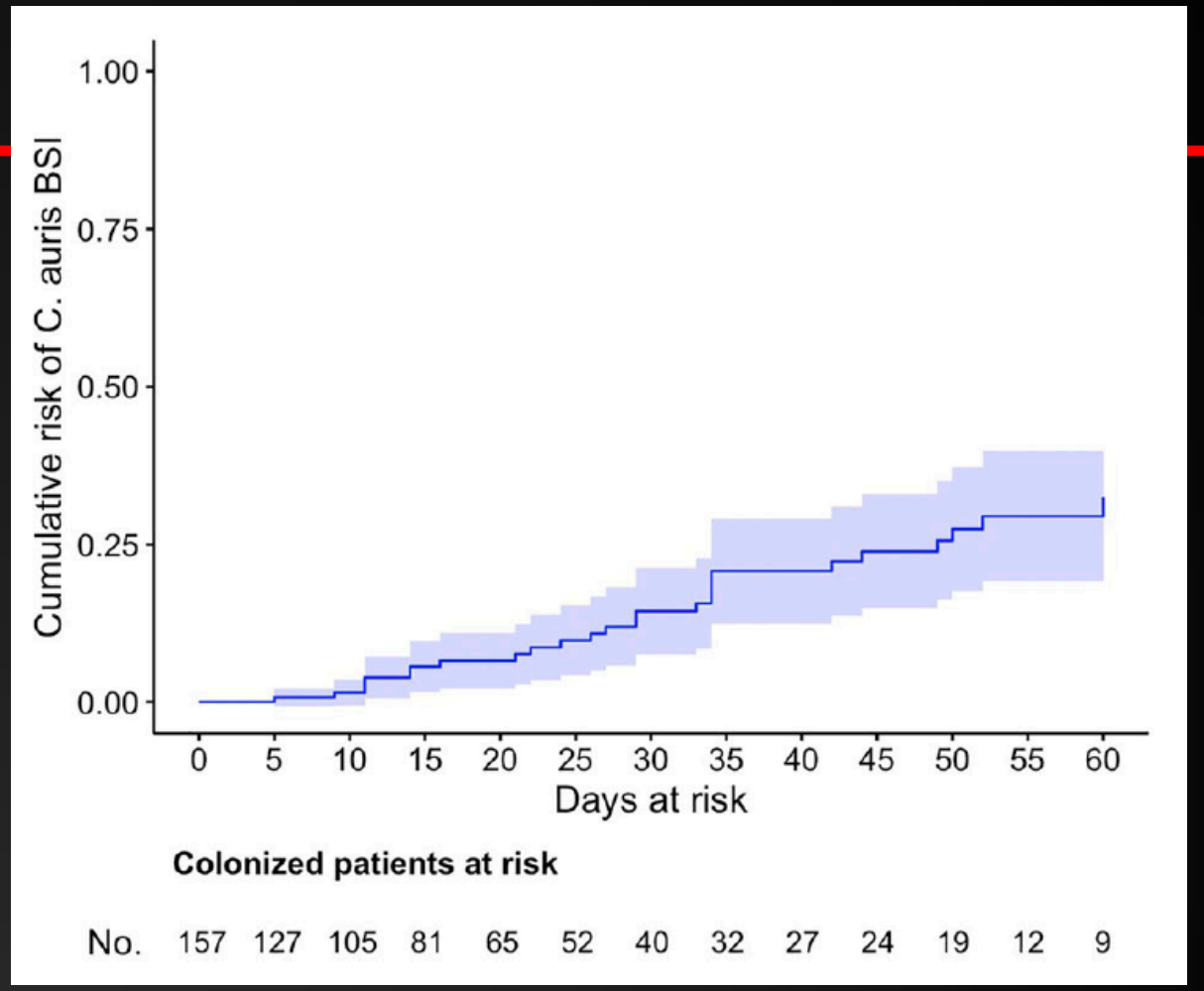
Infect Dis Ther (2022) 11:1149–1160
https://doi.org/10.1007/s40121-022-00625-9

ORIGINAL RESEARCH

Candida auris Candidemia in Critically Ill, Colonized Patients: Cumulative Incidence and Risk Factors

Federica Briano · Laura Magnasco · Chiara Sepulcri · Silvia Dettori · Chiara Dentone · Malgorzata Mikulska · Lorenzo Ball · Antonio Vena · Chiara Robba · Nicolò Patroniti · Iole Brunetti · Angelo Gratarola · Raffaele D'Angelo · Vincenzo Di Pilato · Erika Coppo · Anna Marchese · Paolo Pelosi · Daniele Roberto Giacobbe · Matteo Bassetti



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Il punto sulla situazione epidemiologica - Policlinico San Martino -

Dott.ssa L. Magnasco
Clinica Malattie Infettive
Policlinico San Martino

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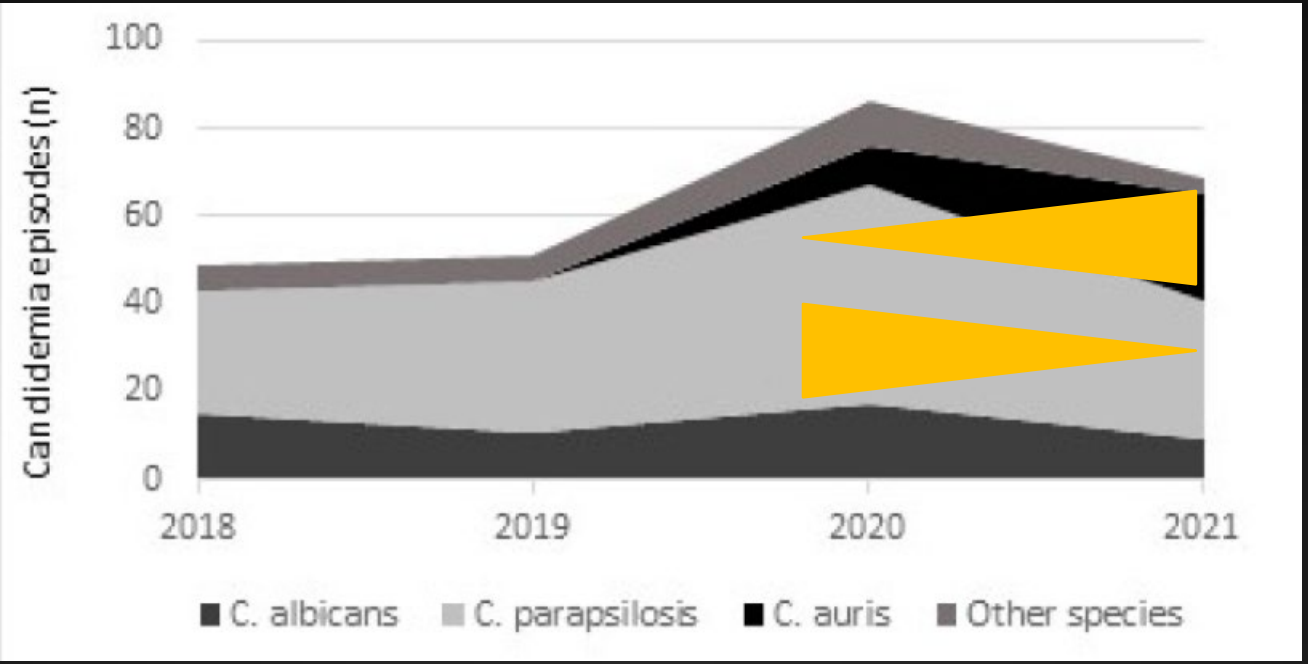
Pre- e post-COVID



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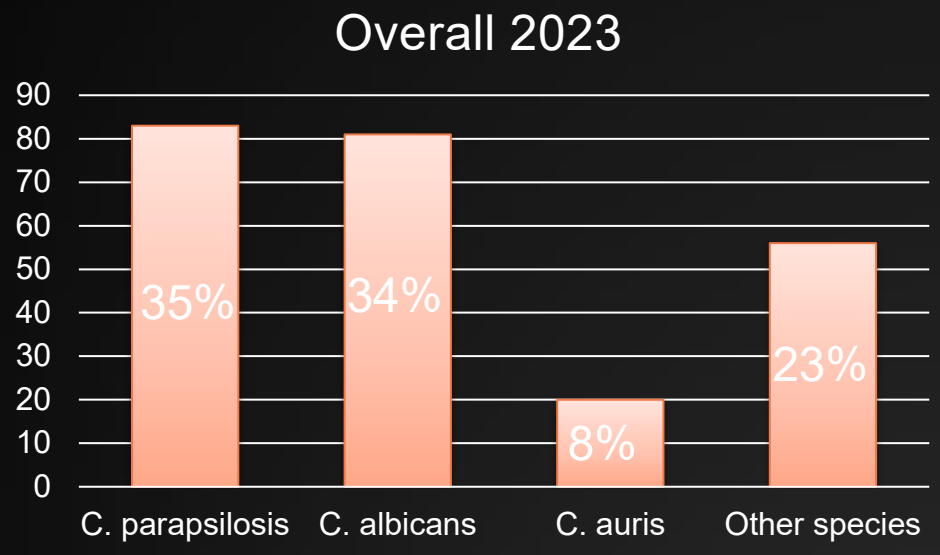
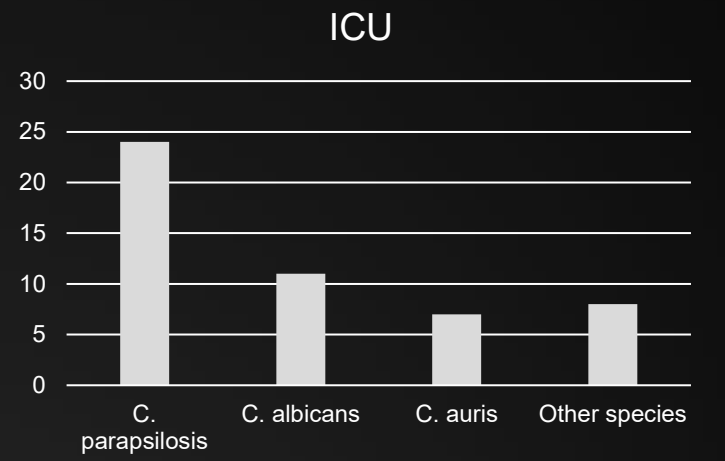
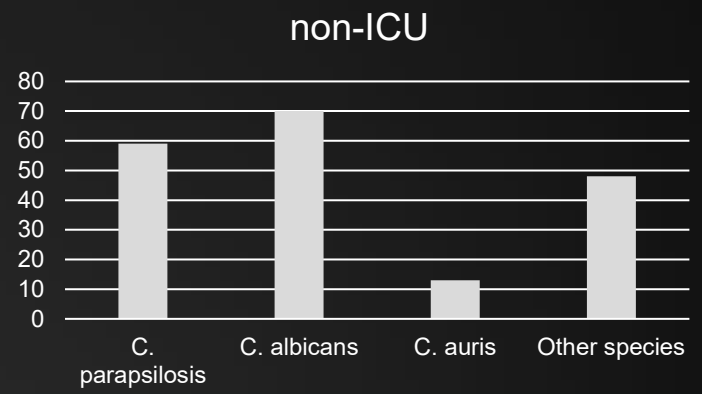
I dati del 2023



N= 240





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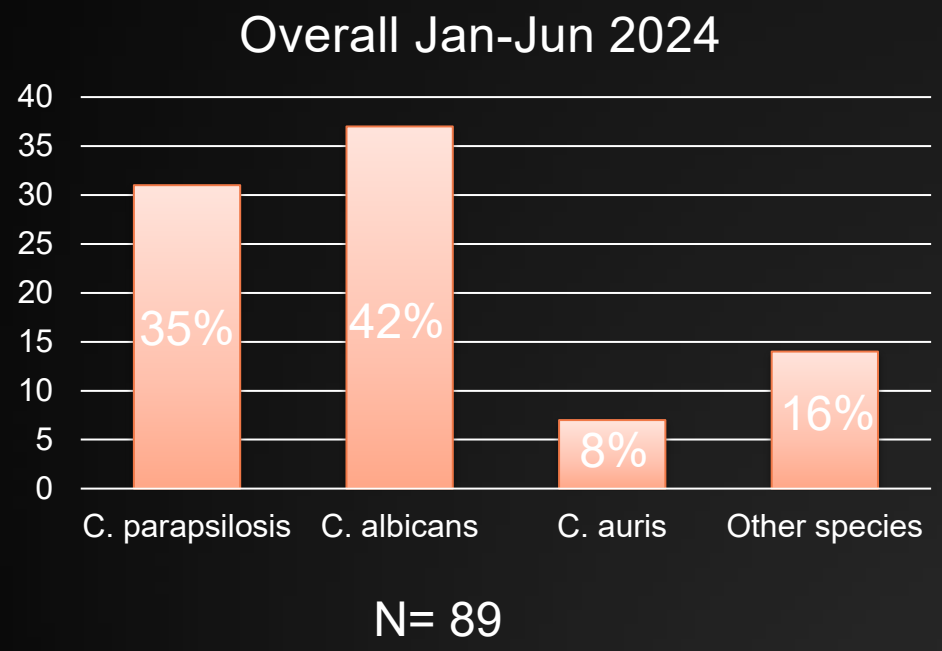
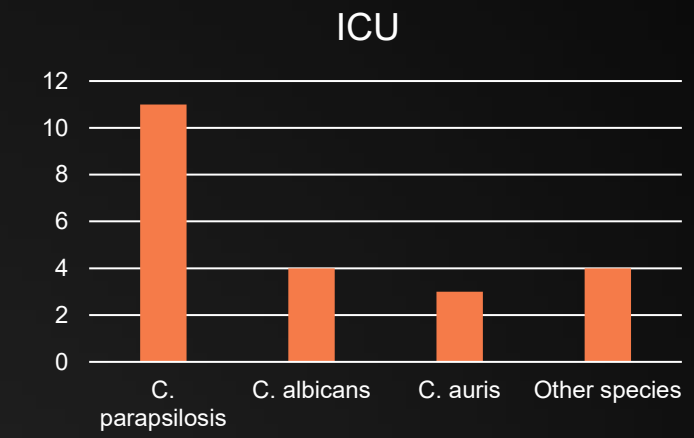
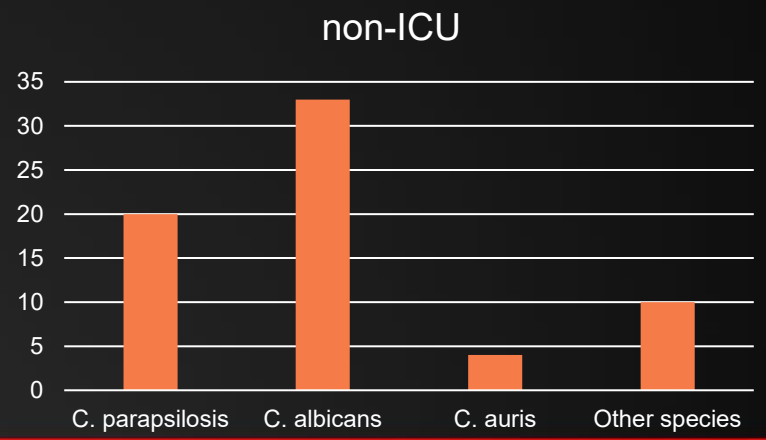
I primi 5 mesi del 2024



N= 89





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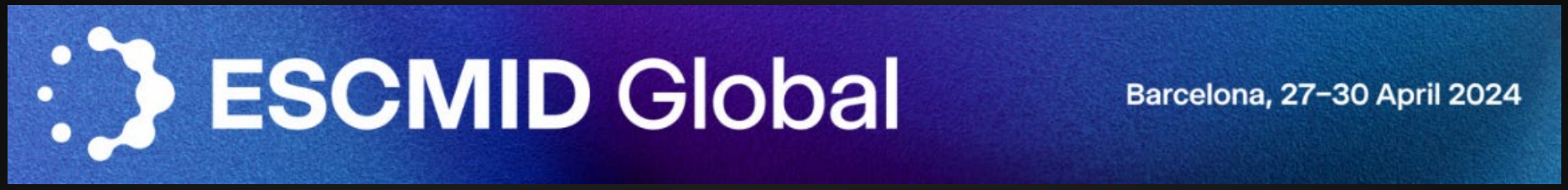
Come influisce l'epidemiologia locale sulla pratica clinica?



16:15 - 17:15

1-hour Symposium

SY135 - *CMI* session: implementation of diagnostics in real life

REPLAY

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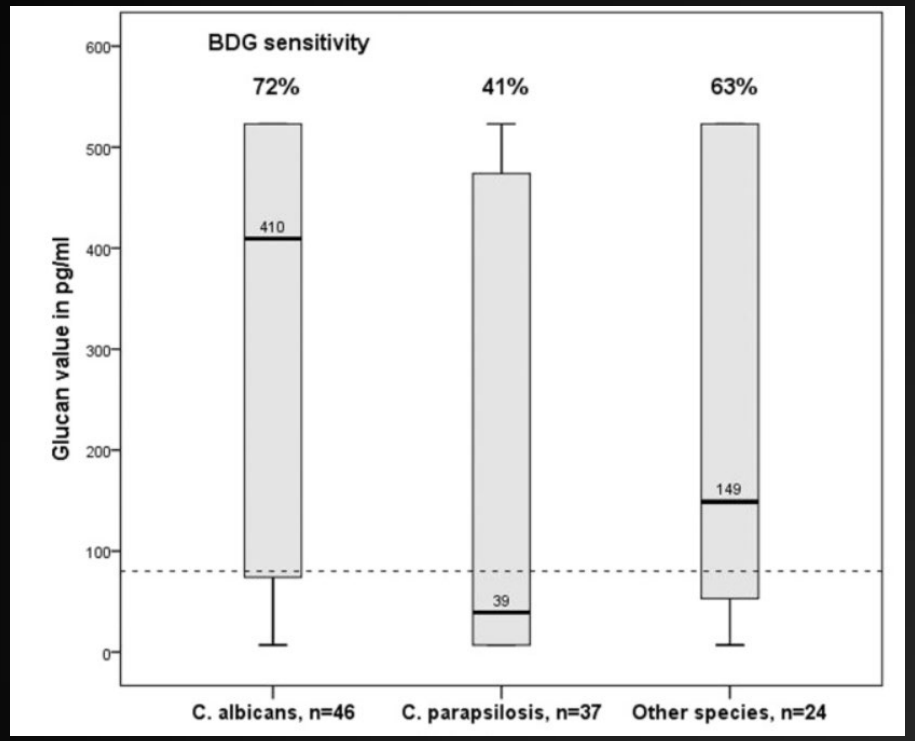
BDG e diverse specie di *Candida*



Mikulska M, CMI, 2016, 10.1016/j.cmi.2016.05.020

SOUTH AFRICA

BDG sensitivity:

C. albicans: 81%

C. parapsilosis: 72%

C. auris: 71%

Chibabai V, Mycoses 2019, 10.1111/myc.12982

PAKISTAN

Median serum BDG values:

C. auris: 62,43 pg/ml

non-*auris:* 236,88 pg/ml

Farooqi J, CMI 2021, 10.1016/j.cmi.2021.05.031

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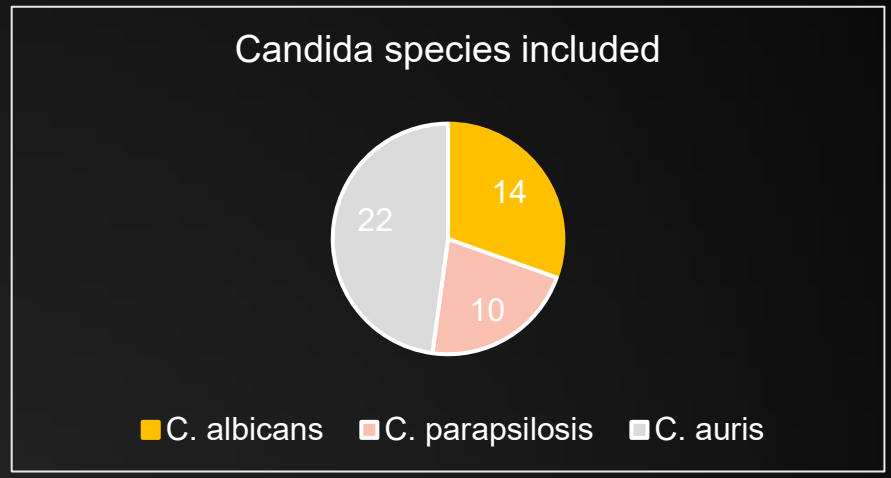
La nostra esperienza

- 46/200 strains causing candidemia included
  - 41% of patients admitted to ICU at the moment of candidemia onset
- Concomitant serum BDG available for 42/46 candidemia episodes
  - Median time from BDG determination to candidemia: 24h
- 36% of patients received empirical antifungals before diagnosis of candidemia
  - 64% of *C. auris* patients received mainly echinocandins for a median of 6.5 days befor onset of candidemia



Study period: Aug 1st, 2021 to Oct 7th, 2022*

*also 6 strains of *C. auris* from Jan-Jul 2021 included to increase sample size

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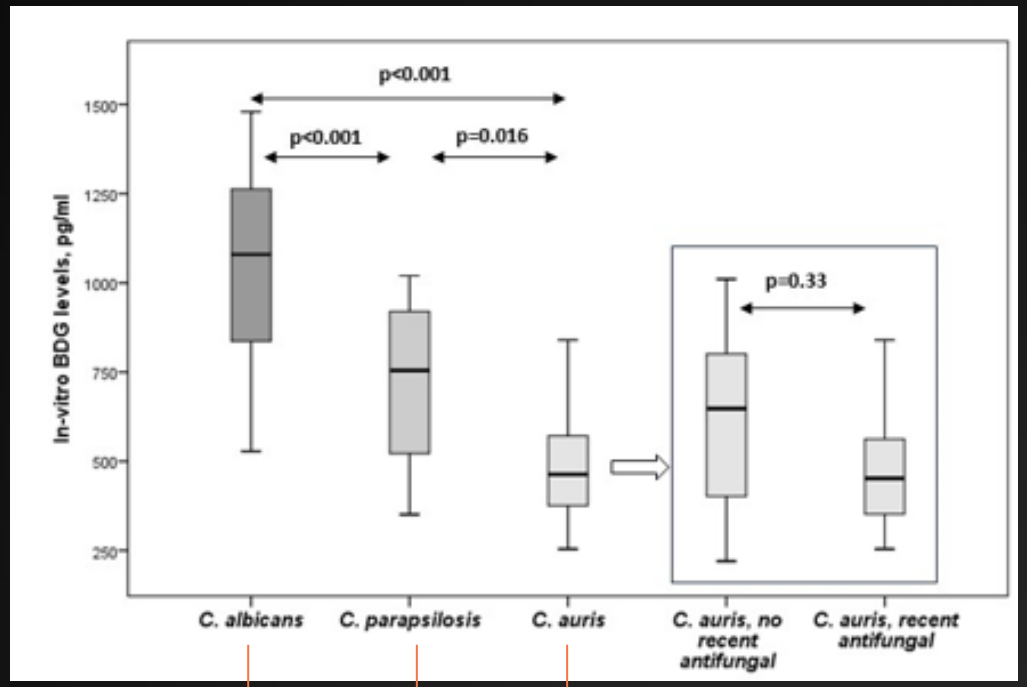
Risultati – *in vitro*



C. albicans
- *In vitro* BDG: **1080 pg/ml** (IQR 830-1276)

C. parapsilosis
- *In vitro* BDG: **755 pg/ml** (IQR 511-930)

C. auris
- *In vitro* BDG: **463 pg/ml** (IQR 679-648)

p<0.001

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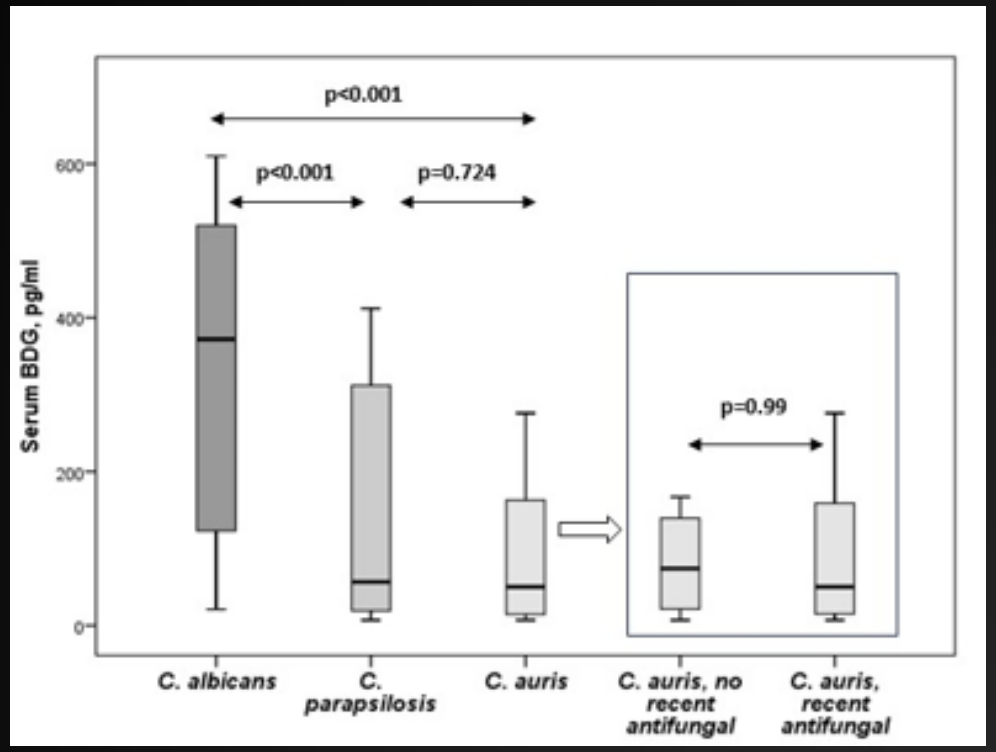
Risultati – *in vivo*



Serum BDG sensitivity in different *Candida* species

- *C. albicans*: • Serum BDG: **372 pg/ml** (IQR 102-520)
- *C. parapsilosis*: • Serum BDG: **57 pg/ml** (IQR 18-332)
- *C. auris*: • Serum BDG: **50 pg/ml** (IQR 15-161)

p=0.007

- *C. albicans*: Sensitivity 78%
- *C. parapsilosis*: Sensitivity 30%
- *C. auris*: Sensitivity 39%

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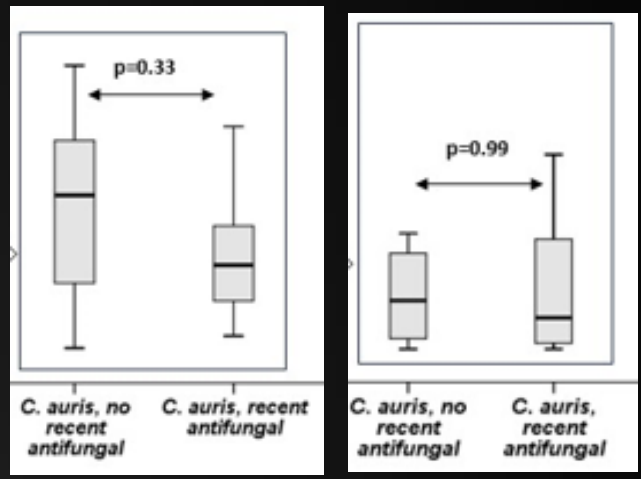
Altri fattori associati a bassi livelli di BDG

Candida species	p < 0,001 for in vitro p=0,004 for in vivo
Previous antifungal treatment	p=0,007 for in vitro **p=0,055 for in vivo**
Length of antifungal treatment	p= 0,006 for in vitro p=0,025 for in vivo
Previous echinocandin	p=0,004 for in vitro **p=0,064 for in vivo**
Candidemia onset in ICU	p= 0,011 for in vitro **NS for in vivo**

In vitro *In vivo*



A trend towards significance (p=0.08) observed for lower *in vitro* BDG levels among *C. auris* strains pre-treated with echinocandins (n=22)

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Quali implicazioni cliniche?

- Limitations: lower content of BDG observed in *C. parapsilosis* and *C. auris* strains – South Asian clade I, outbreak-related, highly homologous clones
- Know your local epidemiology and the performance of BDG testing in your clinical practice
- Caution needed in relying solely on BDG levels to discontinue antifungal treatment in high-risk patients in settings with high prevalence of certain non-*albicans* species

De Pascale G, Crit Care 2020, 10.1186/s13054-020-03265-y

Thank you

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