Fungal Infections In ICU

DM SEMINAR

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20/08/21 and 27/08/21

Outline

- Epidemiology
- Candida
- Aspergillosis
- Zygomycosis
- PGI Data

International Study of the Prevalence and Outcomes of Infection in Intensive Care Units

- EPIC II Study
- N=14414 adults, 1265 ICUs, 75 Countries
- Prospective, Point Prevalence Study

Vincent JL et al JAMA. 2009 Dec 2;302(21):2323-9.

- Seventy percent of infected patients had positive microbial isolates: 47% of the positive isolates were gram-positive, 62% gram-negative, and 19% fungal

	No. (%)[a]							
	All	Western Europe	Eastern Europe	Central/ South America	North America	Oceania	Africa	Asia
No. (%)	7087 (51.4)	3683 (49)	426 (56.4)	1290 (60.3)	607 (48.4)	285 (48.2)	89 (46.1)	707 (52.6)
Fungi								
Candida	843 (17)	495 (18.5)	66 (18.5)	92 (12.8)[b]	83 (18.2)	26 (12.7)	6 (11.1)	75 (15.7)
Aspergillus	70 (1.4)	44 (1.6)	1 (0.3)	5 (0.7)	12 (2.6)	3 (1.5)	0	5 (1)
Other	50 (1)	22 (0.8)	5 (1.4)	7 (1)	10 (2.2)	2 (1)	0	4 (0.8)

- Mortality of candidemia was higher than those of bloodstream infections caused by gram-positive and gram-negative bacteria (43 vs. 25 and 29%, respectively)

Vincent JL et al JAMA. 2009 Dec 2;302(21):2323-9.

Candida

- ‘Invasive candidiasis’ (IC) is an umbrella term for three clinical conditions: candidaemia; deep-seated candidiasis; and deep-seated candidiasis with associated candidaemia

Logan C et al. Intensive Care Med. 2020 Nov;46(11):2001-2014

Epidemiology

- C. albicans remains the dominant species in Europe
- Across India, C. tropicalis is the most common cause of ICU-acquired candidaemia
- C. albicans and C. parapsilosis predominate in Latin America
- USA sees a higher proportion of non-albicans cases (approximately, two-thirds), with increasing C. glabrata incidence

Logan C et al. Intensive Care Med. 2020 Nov;46(11):2001-2014

Epidemiologic and clinical characteristics of the 5 most common Candida species

Species	Geographic Concentration	Age Predilection	Relative Virulence	Characteristic Clinical Associations	Fluconazole Susceptibility
C albicans	Global	None	High	Endopthalmitis	+++
C glabrata	Europe, USA, Australia	Older	Intermediate	SOT	+
C tropicalis	SA, US, Asia	None	High	Immunosuppression	++
C parapsilosis	Europe, US, Australasia	Younger	Low	Medical devices	+++
C krusei	Europe, US	None	Intermediate	Hematolgical Malignancy	-

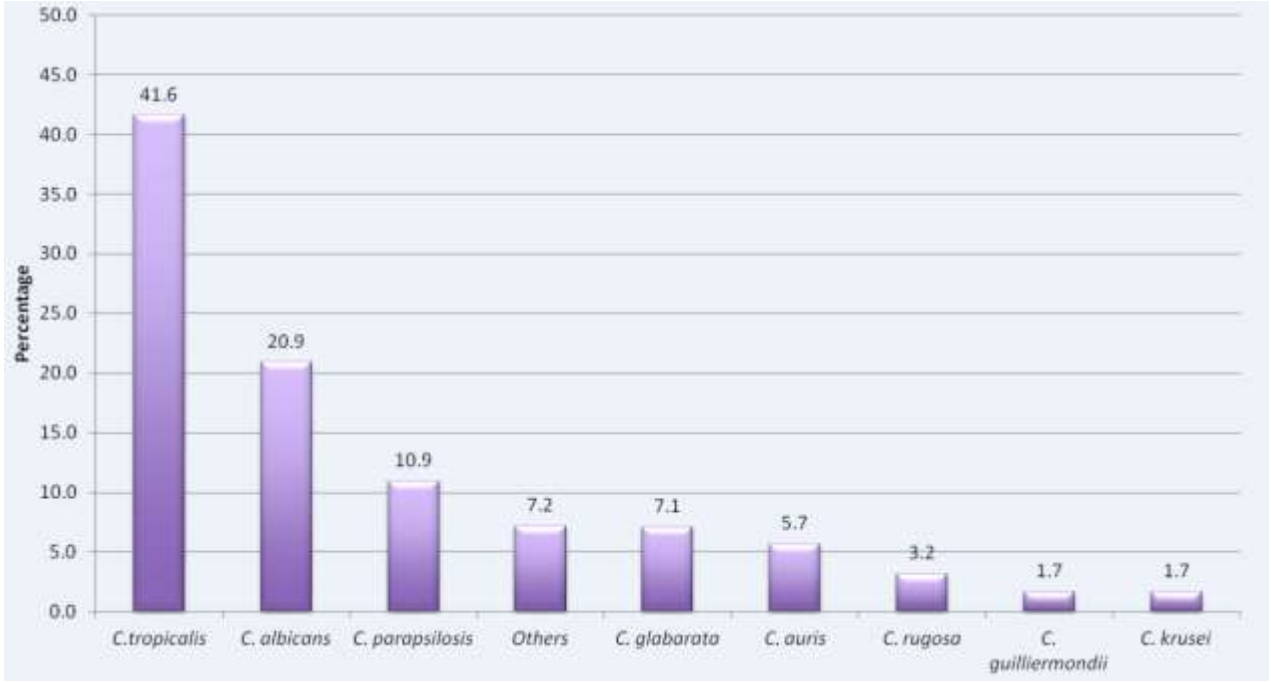
Epelbaum O et al. Clinics in chest medicine. 2017 Sep 1;38(3):493-509.

Incidence, characteristics and outcome of ICU-acquired candidemia in India

- Multicentric, observational study,
- 27 Indian ICUs
- Consecutive patients who acquired candidemia after ICU admission April 2011 through September 2012
- Total admitted: 215,112 patients
- Eleven were public sector institutions, while 16 were private/corporate hospitals
- Majority of adult patients were non-neutropenic (98.7 %) and were admitted to medical ICUs (n = 464; 50.8 %)

Chakrabarti A et al. Intensive Care Med. 2015 Feb;41(2):285-95.

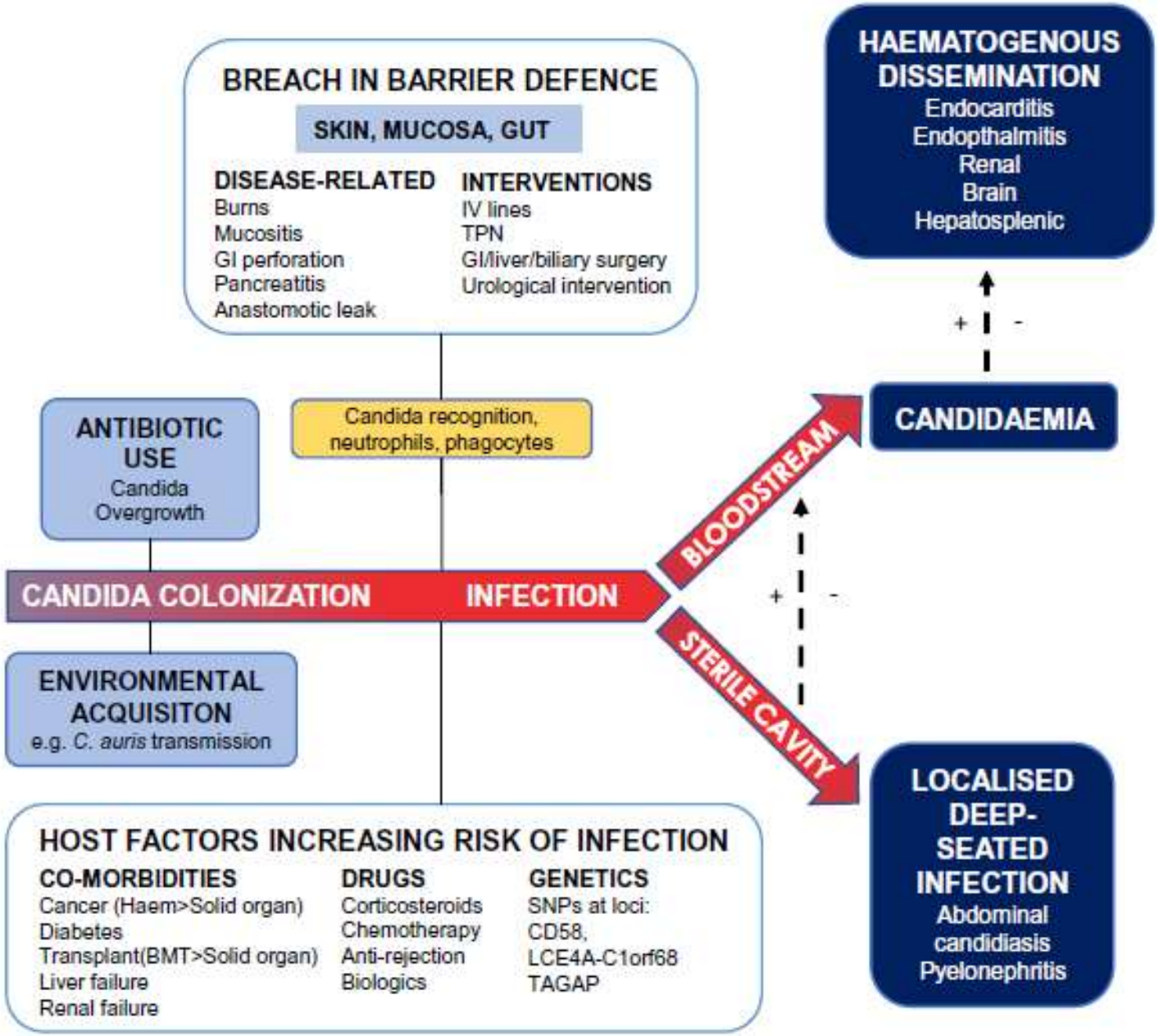
- Overall incidence of 6.51 cases/1,000 ICU admission; 65.2 % were adult
- Acquisition occurred early after admission to ICU (median 8 days; IQ: 4–15 days)
- High rate of isolation of Candida tropicalis (41.6 %)



Chakrabarti A et al. Intensive Care Med. 2015 Feb;41(2):285-95.

- Azole and multidrug resistance were seen in 11.8 and 1.9 % of isolates.
- Public sector hospitals reported a significantly higher presence of the relatively resistant C. auris (8.2 vs. 3.9 %; p = 0.008) and C. rugosa (5.6 vs. 1.5 %; p = 0.001).
- 30-day crude and attributable mortality rates of candidemia patients were 44.7 and 19.6 %, respectively
- Independent predictors of mortality included admission to public sector hospital, APACHE II score at admission, underlying renal failure, central venous catheterization and steroid therapy

Chakrabarti A et al. Intensive Care Med. 2015 Feb;41(2):285-95.



Key factors in the development of invasive candidiasis

Logan C et al. Intensive Care Med. 2020 Nov;46(11):2001-2014

Diagnosis

- There are no specific symptoms of candidemia, with fever unresponsive to antibacterial therapy being the most common clinical presentation

Bassetti M et al. Semin Respir Crit Care Med. 2019;40(4):524-539.

Risk prediction models

- Attempt to quantify the risk of a certain disease, can be used in two different ways:

(1) before the development of the disease,mainly with prevention purposes;

(2) at the onset of the disease, for triggering dedicated diagnostic algorithms and/or guiding early therapeutic choices

Bassetti M et al. Semin Respir Crit Care Med. 2019;40(4):524-539.

Risk prediction models

- Risk prediction models commonly give high negative predictive values and modest or low positive predictive ones
- They can therefore be used for ruling out the presence of IC in specific high-risk patients
- Their usefulness for targeting empirical antifungal treatment, i.e. for restricting it to those at greatest risk, is limited
- Nor have they been designed to monitor the response to antifungal treatment, with a view to reducing the duration of the therapy

Martin-Loeches I et al Intensive care medicine. 2019 Jun;45(6):789-805.

Candida Colonisation Index and Clinical Prediction Scores

Tool	Description	Performance	Reference
Candida Colonization Index	Ratio of the number of (non-blood) sites colonized with *Candida* spp /total number of sites cultured Threshold = 0.5	PPV = 66% NPV = 100%	*Pittet D et al, Ann Surg 1994*
Candida Score	Candida Score = TPN (1 pt), surgery (1pt), severe sepsis (2pt), multifocal Candida colonization (1pt) Threshold = 2.5	Sensitivity = 81% Specificity = 74% PPV = 16% NPV = 98%	*León C et al, Crit Care Med 2006*
Ostrosky-Zeichner Clinical Prediction Rule	Mechanical ventilation≥ 48hours AND Systemic antibiotic AND CVP (on any of day 1–3 of ICU adm) plus 1 of: any major surgery (days 7–0), pancreatitis (days 7–0), use of steroids/other immunosuppressive agents (days 7–0), use of TPN (days 1–3), or dialysis (days 1–3)	Sensitivity = 50% Specificity= 83% PPV = 10% NPV = 97%	*Ostrosky-Zeichner L et al, Mycoses 2011*

Logan C et al. Intensive Care Med. 2020 Nov;46(11):2001-2014

Blood Cultures

- In studies of autopsy-proven invasive candidiasis, the sensitivity of antemortem blood cultures has ranged from 21% to 71%
- Important caveats
  - Most notably, the studies largely comprised of patients with deep-seated infections that were likely to result from hematogenous seeding (Candidemia with deep seated infections)
  - Patients who had positive antemortem blood cultures but no evidence of organ infections on autopsy were not included
- By including such patients, the sensitivity of blood cultures in cases associated at some point with candidemia increases to 63%–83%

Clancy Cj et al. Clinical infectious diseases. 2013 May;56(9):1284-92.

Blood Cultures

- Mechanism of pathogenesis and Candida species also impact sensitivity
- Candidemia is believed to result most commonly from translocation across the gastrointestinal mucosa into the vasculature, or from direct inoculation via intravascular catheters
- Central venous catheter–related candidemia is associated with higher organism burdens than candidemia stemming from extravascular sources
- Candida cells translocating across the gastrointestinal mucosa are immediately transported to the liver, which is an efficient microbial filter
- *C. parapsilosis*, which often causes line associated candidemia in neonates, is associated with higher burdens than Candida albicans
- *C. glabrata* candidemia, which has been linked to gastrointestinal portals of entry, typically presents with lower burdens

Clancy Cj et al. Clinical infectious diseases. 2013 May;56(9):1284-92.

Blood Cultures

- *C. parapsilosis*, which often causes line associated candidemia in neonates, is associated with higher burdens than *C. albicans*
- *C. glabrata* candidemia, which has been linked to gastrointestinal portals of entry, typically presents with lower burdens

Clancy Cj et al. Clinical infectious diseases. 2013 May;56(9):1284-92.

Blood Cultures

- Median time to positivity is 2–3 days, and can take as long as 8 days
- *C. glabrata* and *C. parapsilosis* candidemia are often associated with longer and shorter times to positivity than *C. albicans*, respectively, in keeping with typical bloodstream concentrations

Clancy Cj et al. Clinical infectious diseases. 2013 May;56(9):1284-92.

Blood Cultures

- Standard automated blood culture systems are capable of detecting yeasts
- Specific blood culture bottles, such as the BACTEC Myco/F Lytic or Mycosis IC/F bottles (Becton– Dickinson Diagnostic Systems, Sparks, MD) or the BACT/ALERT FAN aerobic bottles (BioMérieux, Durham, NC) have been suggested to enhance the likelihood of recovering yeasts in blood cultures

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Blood Cultures

- Advent of mass spectrometry (MALDI-TOF) has significantly reduced the time required to identify Candida species in subcultures, without affecting the excellent diagnostic accuracy
- However, the yield of blood culture bottles for yeasts remains low, and this method has not been fully validated

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Blood Cultures

- Fluorescence in situ hybridization (PNA-FISH Yeast Traffic Light assay) differentiates between *C. albicans, C. parapsilosis* and *C. tropicalis* and the intrinsically azole resistant C. glabrata/C. krusei within 1 h of blood culture positivity

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Non-culture diagnostic tests

Potential Advantages	Potential Disadvantages
Rapid turn-around time	Do not recover organisms
Not dependent on viable organisms	May not speciate Candida or distinguish between fungi
May be positive prior to cultures, and stay positive during antifungal therapy	Narrow-spectrum (may detect only Candida among multiple pathogens)
May offer quantitative data with prognostic significance	May need to be run in batch by clinical microbiology laboratory due to limited number of samples
Multicopy targets and amplification may improve sensitivity	May have low threshold for contamination
May be coupled with detection of markers for drug resistance or other relevant phenotypes	Financial costs to patients and clinical microbiology laboratory

Clancy Cj et al. Clinical infectious diseases. 2013 May;56(9):1284-92.

Non-culture-based microbiological techniques available for the diagnosis of IC

- PCR-based tests DNA detection by PCR
- Miniaturized-magnetic resonance-based technology
- Antigen and Antibody Detection
- Candida species germ tube antibody (CAGTA)

PCR-based tests DNA detection by PCR

- In a meta-analysis, the pooled sensitivity and specificity of PCR for suspected invasive candidiasis were 95% and 92%, respectively
- In several studies, PCR results preceded positive blood cultures by 1 day to 4 weeks
- However, the lack of standardization remains a major limitation of this method
- Role of direct PCR testing of serum or blood samples in patients without candidemia also requires further investigation

Clancy Cj et al. Clinical infectious diseases. 2013 May;56(9):1284-92.

Miniaturized-magnetic resonance-based technology

- Fully automated technique that combines PCR technology with nanoparticle-based hybridization
- Pathogen DNA is amplified and then identified by agglomeration of super-magnetic particles
- Presence of pathogens can be established even in patients with a low fungal load (1–3 CFU per ml)
- Platform allows identification of the five predominant Candida species (*C. albicans, C. tropicalis, C. parapsilosis, C. krusei and C. glabrata*) within 3–5 h and without the need for prior incubation

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Miniaturized-magnetic resonance-based technology

- When compared with blood cultures, the sensitivity and specificity of this technique were each found to be nearly 100% for all tested species
- Ability of a miniaturized-magnetic resonance-based technology to detect Candida species in blood-culture negative IC (including deep seated IC) remains to be investigated

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Antigen and Antibody Detection

- Mannan antigen (Mn–Ag) and anti-mannan antibody (Mn–Ab)
- Antigen based assays are limited by rapid clearance from the bloodstream
- Concerns about the impact of immunosuppression on antibody detection
- In a meta-analysis of 14 studies, the sensitivity and specificity of mannan and anti-mannan IgG were 58% and 93% and 59% and 83%, respectively
- Values for the combined assay were 83% and 86%, with best performances for *C. albicans, C. glabrata*, and *C.tropicalis* infections

Clancy Cj et al. Clinical infectious diseases. 2013 May;56(9):1284-92.

βDG assay

- It is now increasingly being used to enable earlier diagnosis of IC
- βDG assay makes it easier to identify patients at risk of invasive infection due to Candida species and may inform the decision to start antifungal therapy in these patients
- Performance of βDG antigenemia is superior to that of risk prediction models and colonization indexes for predicting blood culture-negative IC

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- It probably performs best when used in high-risk patient populations; its sensitivity and specificity have been reported as 70–80% and 55–60% respectively
- Specificity can be further increased with moderate loss of sensitivity by using higher cut-off values (200 pg/ml or higher, instead of 80 pg/ml) or by requiring two consecutive positive tests for a definitive diagnosis
- βDG test shows an excellent NPV, and its utility is optimized when it is used in combination with risk prediction models or other fungal biomarkers (Mn–Ag, Mn–Ab or CAGTA), allowing either avoidance or early discontinuation of antifungal therapy in a significant proportion of patients
- βDG can also be positive in critically ill patients affected by IPA

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Causes of False-positive β-D-Glucan Results for Invasive Candidiasis

False-positive Results	Fungi That Yield Positive β-D-Glucan Results
Human blood products (albumin, immunoglobulin, coagulation factors, plasma protein fractions	Yeasts: *Candida spp, Trichosporon spp, Saccharomyces cerevisiae*
Hemodialysis	Molds: *Acremonium, Aspergillus spp, Fusarium spp*
Surgical gauze or other materials containing glucan	Dimorphic fungi: *Coccidioides immitis, Histoplasma capsulatum, Sporothrix schenckii*
Antibiotics such as piperacillin-tazobactam and ampicillin-clavulanate	Others: *Pneumocystis jiroveci*
Systemic bacterial infections	
Excess manipulation of sample	
Severe mucositis	

Clancy Cj et al. Clinical infectious diseases. 2013 May;56(9):1284-92.

Antifungal Prescribing Strategies

Prophylaxis	AFT prescribed to prevent fungal infection in at-risk hosts
Empirical	AFT prescribed in response to signs and symptoms of infection in an at-risk ICU host
Pre-emptive	AFT prescribed in response to diagnosis based on fungal markers
Targeted	AFT prescribed in response to microbiological confirmation of proven IC

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Antifungal Prophylaxis

Study	Population/Design	Intervention	Results
Playford et al, 2006	8 RCTs N =1606 SICU/Mixed	FCZ/KCZ prophylaxis vs placebo/no antifungal	Reduced IC by 1/2 and total mortality by ¼
Shorr et al, 2005	4 RCTs N = 626 SICU	FCZ vs placebo	Decreased the rate, but didn't improve survival
Vardakas et al, 2006	6 RCTs N= 941 SICU	FCZ/ITZ/KCZ vs placebo	Reduced rate but not in all-cause mortality
Cruciani et al, 2005	9 RCTs N= 1226 SICU	KCZ/FCZ vs placebo/treatment	Reduced rates of candidemia, mortality attributable to *Candida* infection and overall mortality

- Resistance to fluconazole and the emergence of non-albicans isolates are unwanted side effects that are often associated with the use of azoles for prophylaxis

- As impact on mortality remains controversial, ESICM/ESCMID task force recommends against the routine and universal administration of antifungal prophylaxis in critically ill patients

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Preemptive therapy

Study	Pre-emptive agent	Inclusion Criteria	Proportion of IC	Results
Piarroux et al, 2004	Fluconazole	Evidence of substantial colonization in the presence of multiple RF for candida infection Recent abdominal sx or recurrent gi perforations or anastomotic leakages Broad-spectrum antibiotics Other RF, such as CC, high APACHE II scores, and use of PN	Cases of proven candidiasis Retro cohort: 32/455 (7%) Prosp cohort: 18/478 (3.8%)	Incidence of SICU-acquired proven candidiasis significantly decreased from 2.2% to 0%
Tsuruta et al, 2007	Fluconazole	Patients with clinically documented candida infection (> 2 sites of colonization and positive βDG test (cut-off not given); Patients with possible IC (> 2 sites of colonization and positive β-D-glucan test)	Proven candida infection: 3/1000 admissions (6/1900 patients) Clinically documented candida infection: 13/1000 admissions (25 patients) Possible candida infection: 55/1000 admissions (104	Did not prevent possible CI from proceeding to clinically documented CI and did not lead to a better mortality rates

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Preemptive therapy

Study	Pre-emptive agent	Inclusion Criteria	Proportion of IC	Results
Hanson 2012 et al	Anidulafungin	SICU patients β-D-glucan testing at baseline and 2x weekly (cutoff 60 pg/mL) during ICU stay	Probable invasive candidiasis: 3/45 (6.6%) patients	No comment on mortality
Ostrosky-Zeichner, 2014 [MSG-01 trial]	Caspofungin	Ostrosky-Zeichner criteria	Placebo arm: 10/84 (12%) probable invasive candidiasis 4/84 (5%) proven invasive candidiasis Caspofungin arm: 9/102 (9%) probable invasive candidiasis 1/102 (1%) proven invasive candidiasis	Non-significant reduction in IC (9.8% vs 16.7%, p = 0.14) and no difference in all-cause mortality (16.7% vs 14.3%, p = 0.78)

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Preemptive therapy

Study	Pre-emptive agent	Inclusion Criteria	Proportion of IC	Results
Knitsch et al, 2015 [INTENSE trial]	Micafungin	Community-acquired (CAI) or nosocomially acquired (NAI) intra-abdominal infection requiring surgery and ICU stay and appearing within 48 h (NAI) or 72–120 h (CAI) of surgery expected minimum ICU stay of 48 h	Placebo arm: 11/124 (8.9%); micafungin arm: 13/117 (11.1%)	No reduction in IC incidence

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Preemptive therapy

- An observational study conducted in ICUs in Spain and Germany found that 32% of the patients with available microbiological results had invasive infections due to Candida species categorized as potentially resistant to intravenous fluconazole
- Similar results were described by Azoulay et al of 2047 patients across 169 ICUs in Belgium and France, 7.5% received systemic antifungal therapy, two-thirds of whom had no documented invasive fungal infections
- These observations consistently suggest excessive unnecessary use of pre-emptive antifungal therapy
- Overuse of antifungal therapy is a cause for concern from the cost perspective, but also from that of the emergence of antifungal resistance

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Empirical therapy

- Early empirical therapy is the standard of care and (source control if necessary) is a determinant of survival in critically ill patients with IC

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EMPIRICUS trial

Study	Design	Population	Intervention	Outcome
Timsit et al EMPIRICUS trial	Multi-centre (19 sites) double blind, placebo controlled RCT - France - 251 adult patients - Mixed ICUs	Mechanical ventilation 5 days, broad-spectrum antibiotics, venous/arterial line, *Candida* colonization at 1 site and ICUacquired sepsis	Randomized to: 1. 14 days of micafungin 2. Placebo At inclusion, serum BDG taken, colonization index and *Candida* score calculated	No improvement in 28-day fungal-free survival was demonstrated (68% vs 60.2%, p = 0.18), despite significant reduction in proven IC in the micafungin arm (3% vs 12%, p = 0.008) Subgroup analysis suggested a trend towards better survival in those with SOFA score > 8 (HR, 1.69 [95% CI 0.96–2.94], p = 0.07)

Timsit JF et al. JAMA. 2016 Oct 18;316(15):1555-1564

Empirical therapy

- Identifying the subset of ICU patients who could benefit from early AFT remains a key challenge

- Use of additional criteria such as biomarkers might help in more accurate selection of the target population; but then, treatment based with such selection can no longer be defined empirical

Logan C et al. Intensive Care Med. 2020 Nov;46(11):2001-2014

Empirical therapy

- Empirical antifungal therapy might be considered only in patients with septic shock and multi-organ failure (MOF) who have more than 1 extra-digestive site (i.e. urine, mouth, throat, upper and lower respiratory tracts, skin folds, drains, operative site) with proven Candida species colonization

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Empirical therapy

- Echinocandins are currently considered the first line of therapy in critically ill patients

- Arguments in favor of echinocandins include
  - their wider spectrum of activity (that also includes C. krusei and C. glabrata), given the increasing incidence of invasive infection due to non-albicans Candida species,
  - and their favourable safety and drug-interaction profile

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S.N	Study	Drugs	Treatment Duration
1	Rex et al, 1994	Fluconazole vs amphoB	≥14 d after last positive blood culture
2	Mora-Duarte et al, 2002	Caspofungin vs amphoB	10 d intravenous and all therapy >14 d after last positive culture
3	Rex et al 2003	Fluconazole vs amphoB	≥14 d after last positive blood culture, amphotericin B component 5–8 d
4	Kullberg et al 2005	Voriconazole vs amphoB followed by fluconazole	≥14 d after last positive blood culture

SN	Study	Drugs	Treatment Duration
5	Reboli et al 2007	Anidulafungin vs fluconazole	≥14 d after last positive blood culture
6	Kuse et al 2007	Micafungin vs lipo amphoB	≥14 d
7	Pappas et al 2007	Micafungin then possible switch to fluconazole vs caspofungin then possible switch to fluconazole	≥14 d after last positive blood culture

Andes D et al. Clin Infect Dis. 2012 Apr;54(8):1110-22.

Population	Outcome	Results
1915 patients, 7 studies Randomised, double blind	Primary outcome: 30-day all-cause mortality. Secondary outcome: clinical and microbiologic success, defined as symptom resolution and negative cultures at the end of therapy (typically 14 days)	Patients randomized to receive an echinocandin had significantly better survival rates than those who received either a polyene or a triazole (mortality, 27% for echinocandins vs 36% for other regimens [P< .0001], 36% for triazoles vs 30% for other drugs [P =.006], and 35% for polyenes vs 30% for other drugs [P =.04])

Andes D et al. Clin Infect Dis. 2012 Apr;54(8):1110-22.

Design/Setting	Intervention	Outcome
Prospective, Monocentric Cohort study N=130	Groups according to the initial antifungal strategy: fluconazole, echinocandin, or lipo amphotericin B	15-day and 30-day mortality

Murri R et al. Eur J Clin Microbiol Infect Dis. 2016 Feb;35(2):187-93

Table 3 Data distribution among the three antifungal starting therapies

Variables	All patients (n=130)	Starting with fluconazole (n=50)	Starting with echinocandin (n=73)	Starting with AmfB (n=5)	p-Value	p-value (fluconazole vs. echinocandin group)
Males	70	25 (50.0)	41 (56.2)	4 (80)	0.24	0.26
Age, years, mean (SD)	65.6 (19.2)	63.9 (21.6)	66.8 (17.1)	63.6 (24.5)	0.75	0.56
At least two comorbidities	25	6 (12.0)	16 (21.9)	3 (60.0)	0.04	0.19
Risk factors						
Antibiotics (30 days)	51	18 (36.0)	28 (38.3)	5 (100)	0.03	0.53
CVC	92	35 (70)	55 (75.3)	2 (40.0)	0.28	0.56
Malignancy	26	13 (26.0)	10 (13.7)	3 (60.0)	0.03	0.13
Dialysis	4	0 (0)	4 (5.5)	0 (0)	0.36	0.23
Surgery (30 days)	6	2 (4.0)	3 (4.1)	1 (20.0)	0.41	0.96
Hospitalization (90 days)	60	24 (48.0)	33 (45.2)	3 (60.0)	0.53	0.41
Steroids	2	0 (0)	2 (2.7)	0 (0)	0.66	0.48
Clinical characteristics						
APACHE II score, mean (SD)	15.1 (6.2)	14.8 (6.3)	14.9 (6.9)	20.8 (9.9)	0.07	0.16
APACHE II score above 15 (%)		23 (46)	34 (46.6)	3 (60.0)	0.83	0.95
Sepsis severity						
- SIRS	79	33 (66.0)	45 (61.6)	1 (20)		
- Severe sepsis	32	12 (24.0)	17 (23.3)	3 (60)	0.33	0.81
- Septic shock	16	5 (10.0)	10 (13.7)	1 (20)		
Admitted to ICU	16	8 (16.0)	7 (9.6)	1 (20.0)	0.64	0.49
Time to removal of CVC, mean (SD), n=92	4.4 (5.4)	3.9 (4.6)	4.3 (4.6)	–	0.67	0.67
Microbiological characteristics						
Non-*C. albicans*	56 (43.1)	40 (80.0)	31 (42.5)	5 (100)	0.04	0.48
C. parapsilosis	30 (23.1)	14 (28.0)	14 (19.2)	2 (40)	0.005	0.39
Polymicrobial	39 (30.0)	15 (30.0)	23 (31.5)	1 (20)	0.76	0.63
15-days surviving patients (%)	104 (80)	46 (92)	55 (75.3)	3 (60)	0.03	0.018
30-days surviving patients (%)	90 (69.2)	42 (84)	45 (61.6)	3 (60)	0.02	0.009

- No differences in epidemiological and clinical parameters (APACHE II score, clinical severity, rate of admission to ICU) were found between patients starting with fluconazole and those starting with echinocandin
- No differences in 15-day and 30-day mortality were observed between patients with and without C. albicans candidemia
- In patients with candidemia admitted to medical or surgical wards, clinical severity but not the initial antifungal strategy were significantly correlated with mortality

Murri R et al. Eur J Clin Microbiol Infect Dis. 2016 Feb;35(2):187-93

- Fluconazole should be considered the first treatment option for critically ill patients with low severity of disease (i.e. without septic shock and/or MOF) in settings with low fluconazole resistance

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Study/Objectives	Population	Settings
Systematic literature review from August to September 2017 To determine whether treatment with echinocandins or other available drugs, confers a therapeutic or survival benefit over amphotericin B in critically ill adults with invasive candidiasis	Inclusion criteria were: (1) studies describing critically ill adults with invasive candidiasis, (2) studies describing therapeutic benefit or survival as an outcome, and (3) studies comparing amphotericin B, deoxycholate or lipid preparations, with any newer antifungal agent Fluconazole as a first-line agent was excluded from the review, as resistance patterns in non-albicans Candida species means it may not be considered an acceptable empiric drug choice.	Eight studies, N= 2352 5 RCTs and 3 Observational studies

Keane S et al. Expert Rev Anti Infect Ther. 2018 Nov;16(11):839-847

Study	Study Drug	Therapeutic Efficacy at end of Antifungal Therapy	Therapeutic Efficacy at Follow-Up (6–12 Weeks)	All-Cause Mortality at end of Antifungal Therapy	All-Cause Mortality at Follow-Up (6– 12 Weeks)
Mora-Duarte et al., 2002 (MIIT Population)	Caspofungin vs Amphotericin B Deoxycholate	71.4% vs 61.7%, p = 0.09	56.6% vs 47.5%, p value not calculated (not significant)	Similar between groups; Data not provided	34.2% vs 30.4%, p = 0.53
DiNubile et al., 2007; ICU Cohort	Caspofungin vs Amphotericin B Deoxycholate	67.5% vs 56.1%, p value not calculated (not significant)	-	-	45% vs 40%, p value not calculated (not significant)
Kuse et al., 2007 (ITT Population	Micafungin vs Liposomal Amphotericin B	71.6% vs 68.2%, difference after stratification 3.9% (95%CI [−3.9 to 11.6])	-	18% vs 17%, p value not calculated (not significant)	40% vs 40%, p value not calculated (not significant)
DuPont et al., 2009; ICU Cohort	Micafungin vs Liposomal Amphotericin B	62.5% vs 66.4%, p = 0.58	-	20.8% vs 16.4%, p = 0.40 (Day 8)	38.3% vs 34.5%, p = 0.59 (Day 30)
Kullberg et al., 2005 (MITT Population)	Voriconazole vs Amphotericin B Deoxycholate/ Fluconazole	70% vs 74%, p = 0.42	41% vs 41%, p = 0.96	-	36% vs 42%, p = 0.23

Keane S et al. Expert Rev Anti Infect Ther. 2018 Nov;16(11):839-847

- No evidence that choosing between echinocandins, voriconazole or amphotericin B formulations as first-line therapy for critically ill adults with invasive infection due to Candida species is associated with a therapeutic or survival benefit

Keane S et al. Expert Rev Anti Infect Ther. 2018 Nov;16(11):839-847

Complications of Candidemia in ICU

- In a recent study, Candida species infective endocarditis was reported in 4.2% of patients with candidemia
- Ocular candidiasis may be found in 16% of patients with candidemia
- Ocular candidiasis is manifested mainly as chorioretinitis
- All patients with candidemia must undergo an evaluation to detect organ involvement
- Work-up should include transthoracic (TTE) or transoesophageal echocardiography (TEE) and fundoscopy

Martin-Loeches I et al Intensive care medicine. 2019 Jun;45(6):789-805.

De-escalation

- Studies (Bailly et al and Vazquez et al, albeit not RCTs) have demonstrated the safety of this approach at day 5 in proven IC
- In candidaemia, de-escalation from echinocandins to fluconazole for azole-susceptible isolates, when repeat BCs are negative and the patient is clinically stable is recommended within 5–7 days in IDSA, and at 10 days in ESCMID guidelines

Logan C et al. Intensive Care Med. 2020 Nov;46(11):2001-2014

Duration of treatment

- Candidemia should be treated for at least 14 days after the first negative blood culture
- It is also suggested that IC without positive blood cultures should be treated for 10–14 days
- Adequate source control (catheter removal, appropriate drainage, surgical control) should be performed early, if clinically feasible, in every critically ill patient with IC
- In cases where an intravascular catheter or any other foreign material cannot be removed, echinocandins should not be de-escalated to an azole because of their enhanced activity against biofilm (best practice statement)

Martin-Loeches I et al Intensive care medicine. 2019 Jun;45(6):789-805.

Emergence of C. auris in ICU

- *C. auris* isolates can be polyresistant resistant to azoles, polyenes or echinocandins
- In study from India, 5.3% cases from 19 of 27 ICUs were due to C. auris
- RF associated with C. auris infection were admission in public sector hospitals, longer duration of ICU stay and central venous catheter, and prior antifungal exposure
- 30 day crude mortality of C. auris infection was 42%, and attributable mortality was 27%

Aspergillus: Epidemiology

- *Aspergillus* spp. are isolated from lower respiratory tract samples in 0.7%–7% of critically ill patients, with findings suggesting invasive pulmonary aspergillosis in around half of these patients based on criteria including EORTC/MSG criteria and autopsy studies

Jenks JD et al Mycoses. 2021 Sep;64(9):1002-1014

Epidemiology of invasive aspergillosis in critically ill patients: clinical presentation, underlying conditions, and outcomes

- Observational study
- 30 ICUs, 8 countries
- N= 563
- Culture and/or direct examination and/or histopathologic sample positive for Aspergillus spp at any site between January 2000 and January 2011; post-mortem diagnosis of IA
- Diagnosis based on

(1) the EORTC/Mycosis Study Group (MSG) criteria (proven, probable, possible IA or not classifiable) and

(2) “AspICU” criteria

Taccone FS et al . Crit Care. 2015 Jan 12;19(1):7.

Epidemiology of invasive aspergillosis in critically ill patients: clinical presentation, underlying conditions, and outcomes

- 266 were colonized (47%), 203 had putative IA (36%) and 94 had proven IA (17%).
- Lung was the most frequent site of infection (94%), and Aspergillus fumigatus the most commonly isolated species (92%)
- Most common reasons for ICU admission were respiratory disease (n = 222, 39%) and cardiovascular disease (n = 147, 26%)
- Most common comorbid conditions were chronic obstructive pulmonary disease (COPD) (n = 174, 31%) and diabetes (n = 92, 16%)
- Patients with IA had higher incidences of cancer and organ transplantation than those with colonization
- Mortality was 38% among colonized patients, 67% in those with putative IA and 79% in those with proven IA ($P < 0.001$)

Taccone FS et al . Crit Care. 2015 Jan 12;19(1):7.

Table 5 Risk factors for mortality among patients with proven or putative invasive aspergillosis

Variable	Univariable analysis		Multivariable analysis	
	P-value	OR (95% CI)	*P*-value	OR (95% CI)
Age, yr	0.008	1.023 (1.006 to 1.040)	0.001	1.034 (1.014 to 1.055)
Male	0.264	0.751 (0.455 to 1.241)		
BMI	0.024	1.069 (1.009 to 1.133)		
Septic shock	0.689	1.158 (0.565 to 2.374)		
Pneumonia	0.880	0.948 (0.476 to 1.888)		
Primary brain injury	0.216	0.218 (0.020 to 2.437)		
Acute cardiac failure	0.225	3.655 (0.450 to 29.660)		
Sepsis on admission	0.110	1.503 (0.912 to 2.478)		
APACHE[a] II score at admission	0.003	1.049 (1.017 to 1.083)		
Diabetes	0.576	1.211 (0.619 to 2.371)		
Chronic heart disease	0.030	3.890 (1.140 to 13.266)		
COPD	0.605	0.872 (0.520 to 1.463)		
Liver failure	0.070	2.749 (0.922 to 8.192)		
HIV	0.564	0.441 (0.027 to 7.132)		
Smoking	0.937	1.029 (0.509 to 2.078)		
Alcohol abuse	0.298	0.639 (0.276 to 1.483)		
Chronic dialysis	0.148	4.615 (0.582 to 36.603)		
Bone marrow transplant	0.013	3.875 (1.326 to 11.327)	0.039	3.352 (1.060 to 10.598)
Solid tumor	0.085	2.241 (0.894 to 5.617)		
Cancer	0.769	1.101 (0.579 to 2.094)		
Neutropenia	0.646	0.827 (0.368 to 1.858)		
Chemotherapy/radiotherapy	0.525	0.802 (0.405 to 1.586)		
Solid organ transplant	0.877	1.055 (0.534 to 2.084)		

Taccone FS et al . Crit Care. 2015 Jan 12;19(1):7.

Corticosteroids	0.248	1.376 (0.801 to 2.366)			
Immune deficit	0.117	0.342 (0.090 to 1.306)			
Aspergillus species	0.040	2.183 (1.038 to 4.592)			
Lung involvement	0.998	1.001 (0.300 to 3.340)			
SOFA score at diagnosis	<0.001	1.180 (1.107 to 1.256)	<0.001	1.140 (1.062 to 1.224)	
Vasopressor therapy at diagnosis	<0.001	4.309 (2.299 to 8.078)			
Mechanical ventilation at diagnosis	<0.001	6.498 (2.590 to 16.303)	0.009	3.916 (1.408 to 10.891)	
Renal replacement therapy at diagnosis	<0.001	3.293 (1.895 to 5.722)	0.011	2.339 (1.212 to 4.516)	

[a]APACHE, Acute Physiology and Chronic Health Evaluation; BMI, Body mass index; CI, Confidence interval; COPD, Chronic obstructive pulmonary disease; IA, Invasive aspergillosis; OR, Odds ratio; RRT, Renal replacement therapy; SOFA, Sequential Organ Failure Assessment.

Taccone FS et al . Crit Care. 2015 Jan 12;19(1):7.

Risk factors for IPA in ICU patients

1. High risk

- Neutropenia (500/mm3)
- Hematological malignancy
- Allogeneic HSCT

2. Intermediate risk

- Prolonged treatment with corticosteroids before admission to the ICU
- Autologous HSCT
- COPD
- Liver cirrhosis
- Solid organ cancer
- HIV infection
- Lung transplantation
- Systemic immunosuppressive therapy

Bassetti M et al. Intensive Care Med. 2017 Sep;43(9):1225-1238

Risk factors for IPA in ICU patients

3. Low risk

- Severe burns
- Solid organ transplant
- Steroid treatment for >7 days
- Prolonged stay in the ICU (>21 days)
- Malnutrition
- Post cardiac surgery
- Near drowning

Bassetti M et al. Intensive Care Med. 2017 Sep;43(9):1225-1238

Revised EORTC/MSG criteria (2019)

- Newly revised EORTC/MSG criteria are only applicable to the subset of ICU patients with underlying haematological malignancies, solid organ transplant recipients or severe immunosuppression, but not to the ICU population as a whole
- Furthermore, even those non-neutropenic ICU patients who fulfil EORTC/MSG criteria based on host factors and develop IA may present with an atypical clinical presentation or radiological findings, and equivocal diagnostic test results, particularly due to the low sensitivity of galactomannan (GM) and other tests performed in blood
- EORTC/MSG criteria have only very limited applicability in the ICU setting

Jenks JD et al Mycoses. 2021 Sep;64(9):1002-1014

AspICU Algorithm

Proven invasive pulmonary aspergillosis

(Identical to EORTC/MSG criteria (2008))

Microscopic analysis on sterile material: histopathologic, cytopathologic, or direct microscopic examination of a specimen obtained by needle aspiration or sterile biopsy in which hyphae are seen accompanied by evidence of associated tissue damage. Culture on sterile material: recovery of Aspergillus by culture of a specimen obtained by lung biopsy

Blot SI et al, Am J Respir Crit Care Med. 2012 Jul 1;186(1):56-64.

AspICU Algorithm

<u>Putative invasive pulmonary aspergillosis (all four criteria must be met)</u>

1. Aspergillus-positive lower respiratory tract specimen culture (= entry criterion)
2. Compatible signs and symptoms (one of the following)
   - Fever refractory to at least 3 d of appropriate antibiotic therapy
   - Recrudescent fever after a period of defervescence of at least 48 h while still on antibiotics and without other apparent cause
   - Pleuritic chest pain
   - Pleuritic rub
   - Dyspnea
   - Hemoptysis
   - Worsening respiratory insufficiency in spite of appropriate antibiotic therapy and ventilatory support

Blot SI et al, Am J Respir Crit Care Med. 2012 Jul 1;186(1):56-64.

AspICU Algorithm

3. Abnormal medical imaging by portable chest X-ray or CT scan of the lungs

4. Either 4a or 4b

4a. Host risk factors (one of the following conditions)

- Neutropenia (absolute neutrophil count ,500/mm3) preceding or at the time of ICU admission
- Underlying hematological or oncological malignancy treated with cytotoxic agents
- Glucocorticoid treatment (prednisone equivalent, .20 mg/d)
- Congenital or acquired immunodeficiency

Blot SI et al, Am J Respir Crit Care Med. 2012 Jul 1;186(1):56-64.

AspICU Algorithm

- 4b. Semiquantitative Aspergillus-positive culture of BAL fluid (+ or ++), without bacterial growth together with a positive cytological smear showing branching hyphae

Blot SI et al, Am J Respir Crit Care Med. 2012 Jul 1;186(1):56-64.

AspICU Algorithm

Aspergillus respiratory tract colonization

- When >1 criterion necessary for a diagnosis of putative IPA is not met, the case is classified as Aspergillus colonization

Blot SI et al, Am J Respir Crit Care Med. 2012 Jul 1;186(1):56-64.

Modified AspICU Algorithm

CLINICAL+ RADIOLOGICAL + MYCOLOGICAL

Invasive pulmonary aspergillosis

1. ~~Aspergillus-positive lower respiratory tract specimen culture (= entry criterion)~~
2. Compatible signs and symptoms (one of the following)

CLINICAL

- Fever refractory to at least 3 d of appropriate antibiotic therapy
- Recrudescent fever after a period of defervescence of at least 48 h while still on antibiotics and without other apparent cause
- ~~Pleuritic~~ chest pain or Pleuritic rub
- Dyspnea
- Hemoptysis
- Worsening respiratory insufficiency in spite of appropriate antibiotic therapy and ventilatory support

Schauwvlieghe AFAD et al Lancet Respir Med. 2018 Oct;6(10):782-792.

Modified AspICU Algorithm

RADIOLOGICAL

3. Abnormal medical imaging by portable chest X-ray or CT scan of the lungs

4. ~~Either 4a or 4b~~

~~4a. Host risk factors (one of the following conditions)~~

~~4b. Semiquantitative Aspergillus-positive culture of BAL fluid (+ or ++), without bacterial growth together with a positive cytological smear showing branching hyphae~~

MYCOLOGICAL

One or more of the following :

- Histopathology or direct microscopic evidence of dichotomous septate hyphae with positive culture for Aspergillus from tissue
- A positive Aspergillus culture from a bronchoalveolar lavage (BAL).
- A galactomannan optical index on BAL of ≥1
- A galactomannan optical index on serum of ≥0·5

Schauwvlieghe AFAD et al Lancet Respir Med. 2018 Oct;6(10):782-792.

IPA in COPD: Bulpa criteria

Proven IPA

- Histopathological or cytopathological examination, from needle aspiration or biopsy specimen obtained from any pulmonary lesion present for <3 months, showing hyphae consistent with Aspergillus and evidence of associated tissue damage, if accompanied by any one of the following:

1) Positive culture of Aspergillus spp. from any LRT sample

2) Positive serum antibody/antigen test for A. fumigatus (including precipitins)

3) Confirmation that the hyphae observed are those of Aspergillus by a direct molecular, immunological method and/or culture

Bulpa P et al, Eur Respir J. 2007 Oct;30(4):782-800.

Probable IPA

- As for proven IPA but without confirmation that Aspergillus is responsible (points 1, 2 and 3 are not present or tested).

OR

- COPD patient, usually treated with steroids and severe according to GOLD (stage III or IV), with recent exacerbation of dyspnoea[a], suggestive chest imaging[b] (radiograph or CT scan; <3 months[c]) and one of the following:

1) Positive culture[d] and/or microscopy for Aspergillus from LRT
2) Positive serum antibody test for A. fumigatus (including precipitins)
3) Two consecutive positive serum galactomannan tests

Bulpa P et al, Eur Respir J. 2007 Oct;30(4):782-800.

Possible IPA

COPD patient, usually treated by steroids and severe according to GOLD (stage III or IV), with recent exacerbation of dyspnoea[a], suggestive chest imaging[b] (radiograph or CT scan; <3 months[c]), but without positive Aspergillus culture or microscopy from LRT or serology.

Bulpa P et al, Eur Respir J. 2007 Oct;30(4):782-800.

Colonisation

COPD patient with positive Aspergillus culture from LRT without exacerbation of dyspnoea, bronchospasm or new pulmonary infiltrate

Bulpa P et al, Eur Respir J. 2007 Oct;30(4):782-800.

a: Exacerbation of dyspnoea and/or bronchospasm resistant to appropriate treatment including antibiotics;

b: pulmonary lesion(s) unresponsive to appropriate antibiotics (refers to dose, route, spectrum and activity against cultured bacteria);

c: pulmonary lesions, especially cavitary, present for >3 months are better classified as chronic pulmonary aspergillosis, unless direct tissue invasion is demonstrated;

d: standard or sabouraud culture, or molecular detection test when licensed

Bulpa P et al, Eur Respir J. 2007 Oct;30(4):782-800.

Diagnostic Tests

- Histology and Culture
- Galactomannan
- βDG assay
- PCR
- Lateral flow assay and lateral flow device

Histology and culture

- Identification of hyphae forms in tissue biopsied from a normally sterile site
- On direct microscopic examination, *Aspergillus* is narrow (3–12 µm wide) with septated, hyaline, acute angle branching hyphae with 45-degree branching
- Although rare, the presence of conidial heads is pathognomonic for the diagnosis of aspergillosis
- On microscopy, *Aspergillus* can be confused with several other filamentous fungi including *Scedosporium* spp. And *Fusarium* spp. so definitive identification of the pathogen by culture is desirable

Jenks JD et al Mycoses. 2021 Sep;64(9):1002-1014

Histology and culture

- When recovered *Aspergillus* begins to develop within 24–48 h on fungal media and sheep blood agar, with colonies appearing as velutinous, grey-blue-green colonies
- Yield can be lower in ICU patients who may lack traditional clinical signs and symptoms of infection and have atypical radiological findings of IA
- Microscopy and culture alone cannot distinguish between colonisation and infection
- Cultures are slow and sensitivity ranges between 20% and 50%
- Lung biopsies are often difficult to perform in critically ill patients who may have other comorbid conditions, may be hemodynamically unstable or have respiratory distress, or coagulation disorders making biopsy challenging

Jenks JD et al Mycoses. 2021 Sep;64(9):1002-1014

Galactomannan

- Antigen-based testing
- Now considered the ‘gold-standard’ test
- GM is a polysaccharide found in the cell wall of *Aspergillus* spp. and is released by growing hyphae and germinating spores or conidia.
- In immunocompromised patients with angio-invasive growth, GM can be detectable in serum, although GM is often not present in the serum of non-neutropenic patients, in which airway-invasive growth is more typical. Thus, GM testing from BALF is preferred in this setting
- For conventional GM testing, a positive result is based on an optical density (OD) cut-off GM index of ≥0.5 from serum and >1.0 from BALF

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- False positive have been reported in those on amoxicillin–clavulanate, piperacillin–tazobactam, and cefepime (S.GM and BALF); patients receiving carbapenems and ceftriaxone (BALF)
- False negative results in patients on mold-active prophylaxis

Jenks JD et al Mycoses. 2021 Sep;64(9):1002-1014

Sensitivity and specificity in non-neutropenic hosts

- One meta-analysis (incl 27 studies) published in 2006 reported an overall sensitivity of serum galactomannan assay of 71% and specificity of 89%. When onco-hematological patients were excluded from the analysis, the sensitivity and specificity of the test dropped to 22% and 84%, respectively
- Although in hematological patients the GM test may enable the early diagnosis of IA monitoring the treatment response, further studies are mandatory in non-neutropenic patients since these aspects remain to be determined in this population

Bassetti Met al. Infect Dis Ther. 2018 Mar;7(1):17-27

Diagnostic performance of GM for the diagnosis IPA in critically ill patients with histology (biopsy/autopsy) as reference

Study Test (cutoff)	Design	IPA Prevalence N/Total (%)	Sensitivity	Specificity	PPV	NPV	Population
Meersseman et al., 2008	Obs, Prosp	26/72 (36)					ICU patients with various predisposing factors, and infiltrates and/or signs/symptoms that could suggest IA
Serum GM (0.5 OD)			42 (23–63)	93 (82–99)	79 (49–95)	74 (61–85)	
BALF GM (0.5 OD)			88 (70–98)	87 (74–95)	79 (60–92)	93 (81–99)	
BALF culture and/or direct examination			58 (37–77)	70 (54–82)	51 (33–71)	74 (59–86)	

Bassetti M et a; J Infect. 2020 Jul;81(1):131-146.

Diagnostic performance of S. GM for the diagnosis IPA in critically ill patients with existing definitions as reference

Study Test (cutoff)	Design	IPA Prevalence N/Total (%)	Sensitivity	Specificity	PPV	NPV	Population
Zhang et al., 2015	Obs, retro EORTC/MSG 2008						Mixed hematologic (classical host factors present in 40.5% of patients) and non-hematologic popul who underwent serum and BALF GM testing in the suspicion of IPA
0.5 OD		Proven/probable 28/121 (23)	68 (48–84)	94 (86–98)	76 (55–91)	91 (83–96)	

Bassetti M et a; J Infect. 2020 Jul;81(1):131-146.

Diagnostic performance of S. GM for the diagnosis IPA in critically ill patients with existing definitions as reference

Study Test (cutoff)	Design	IPA Prevalence N/Total (%)	Sensitivity	Specificity	PPV	NPV	Population
Fortun et al., 2016	Obs, retro EORTC/MSG 2008 with pulmonary infiltrates or consolidation non-respons to broad-spectrum antibacterial						Non-hematological immunosuppressed or COPD patients who underwent BALF GM testing in the suspicion of IPA.
0.5 OD		Proven/probable 9/35 (26)	11 (0–32)	96 (89–100)	50 (0–100)	76 (61–90)	COPD patients
0.5 OD		Proven/probable 22/153	36 (16–57)	94 (90–98)	50 (26–75)	90 (85–95)	Other patients

Bassetti M et a; J Infect. 2020 Jul;81(1):131-146.

Diagnostic performance of S. GM for the diagnosis IPA in critically ill patients with existing definitions as reference

Study Test (cutoff)	Design	IPA Prevalence N/Total (%)	Sensitivity	Specificity	PPV	NPV	Population
Imbert et al., 2016	Obs, retro EORTC/MSG 2008 with alcoholic cirrhosis, a long stay in ICU and severe ARDS as added host factors						Non-neutropenic patients deemed at risk of IPA
0.5 OD		Proven/probable 32/496	66 (47–81)	91 (88–94)	34 (22–47)	97 (96–99)	

Bassetti M et a; J Infect. 2020 Jul;81(1):131-146.

Diagnostic performance of BAL GM for the diagnosis IPA in critically ill patients with existing definitions as reference

Study Test (cutoff)	Design	IPA Prevalence N/Total (%)	Sensitivity	Specificity	PPV	NPV	Population
Bellanger et al., 2018	Obs, retro EORTC/MSG 2008 for hematologic pts and positive culture, PCR, or GM for ICU patients						Mixed population (hematology [38.5%] plus ICU [61.5%]).
0.5 OD		Proven/probable 27/597 (5)	65 (46–80)	93 (90–94)	25 (16–36)	99 (97–99)	
0.8 OD			50 (32–68)	95 (94–67)	29 (18–43)	98 (97–99)	
1.5 OD			42 (26–61)	97 (96–98)	36 (21–53)	98 (96–99)	

Bassetti M et a; J Infect. 2020 Jul;81(1):131-146.

Diagnostic performance of BAL GM for the diagnosis IPA in critically ill patients with existing definitions as reference

Study Test (cutoff)	Design	IPA Prevalence N/Total (%)	Sensitivity	Specificity	PPV	NPV	Population
Fortun et al 2016	Obs, retro EORTC/MSG 2008 with pulmonary infiltrates or consolidation non-respons to broad-spectrum antibacterial						Non-hematologic immunosuppressed or COPD pt who underwent BALF GM testing in the suspicion of IPA
0.5 OD		Proven/probable 9/35 (26)	89 (68–100)	88 (76–100)	73 (46–99)	96 (88–100)	COPD
1.0 OD			67 (36–98)	96 (89–100)	86 (60–100)	89 (78–100)	
1.5 OD			67 (36–98)	96 (88–100)	86 (60–100)	89 (77–100)	

Bassetti M et al. J Infect. 2020 Jul;81(1):131-146.

Diagnostic performance of BAL GM for the diagnosis IPA in critically ill patients with existing definitions as reference

Study Test (cutoff)	Design	IPA Prevalence N/Total (%)	Sensitivity	Specificity	PPV	NPV	Population
Fortun et al., 2016	Obs, retro EORTC/MSG 2008 with pulmonary infiltrates or consolidation non-respons to broad-spectrum antibacterial						
0.5 OD		Proven/probable 22/153 (14)	86 (72–100)	84 (79–91)	49 (33–64)	97 (94–100)	Other patients
1.0 OD			82 (66–98)	94 (90–98)	69 (52–87)	97 (94–100)	
1.5 OD			73 (54–91)	94 (90–98)	67 (48–86)	95 (92–99)	

Bassetti M et a; J Infect. 2020 Jul;81(1):131-146.

βDG assay

- Role of BDG for diagnosis IA remains unclear, as elevated levels may simply represent fungal translocation of *Candida* components form the gut and not necessarily pulmonary *Aspergillus* infection with airway invasion
- Sensitivity has ranged from 55 to 95 percent and the specificity has ranged from 77 to 96 percent
- Its NPV was as high as 80–90%, thus making 1-3-b-D-glucan potentially useful to rule out the diagnosis of IA rather than to confirm it

Jenks JD et al Mycoses. 2021 Sep;64(9):1002-1014

PCR and LFA and LFD

- Pooled sensitivity and specificity of PCR from blood are 79% and 80% for a single positive test result and 60% and 95% for two consecutive positive test results
- Lastly and perhaps most importantly, PCR from serum has a sensitivity as low as 11% in ICU patients, although the sensitivity improved to 56% in BALF specimens
- LFA and LFD: POC diagnostic tests for the diagnosis of IA; Simple to use, do not require advanced laboratory equipment, with results available in under an hour
- Optimum standardisation and performance is yet to investigated

Jenks JD et al Mycoses. 2021 Sep;64(9):1002-1014

Clinical Presentations

- In non-neutropenic patients with more airway-invasive IA, fever is present in around 70% of patients compared to over 95% of neutropenic patients
- Cough and chest pain are also less frequent among non-neutropenic patients (28% and 11%, respectively, versus 67% and 33% in neutropenic patients)
- Despite angio-invasion occurring more frequently in neutropenic patients, hemoptysis may not occur more frequently in neutropenic compared to non-neutropenic patients

Jenks JD et al Mycoses. 2021 Sep;64(9):1002-1014

Spectrum in critically ill

- IA can manifest in ICU population in different histopathological forms depending on the strength of the immune response and the load of the infecting fungus
- Patients with hematologic cancers and neutropenia have scant inflammation and extensive hyphal angioinvasion, leading to vascular thrombosis, tissue infarction, and extrapulmonary dissemination
- HSCT recipients with graft versus host disease (GVHD) tend to suffer from severe lung inflammation with a low Aspergillus burden, resulting in fungal pneumonia with coagulative necrosis and cavitation
- Both groups usually exhibit a high incidence of extrapulmonary dissemination

Dutkiewicz R et al. Proc Am Thorac Soc. 2010 May;7(3):204-9

Spectrum in critically ill

- In the severely immunocompromised host, IPA usually presents with fever that persists despite broad-spectrum antibiotics during periods of deep and prolonged neutropenia. Chest pain and hemoptysis are also prominent symptoms

Dutkiewicz R et al. Proc Am Thorac Soc. 2010 May;7(3):204-9

Spectrum in critically ill

- Clinical findings of IA (ie fever, shortness of breath, cough) strongly overlap with those observed in severe influenza and COVID-19
- IA of the paranasal sinuses that may progress rapidly to cause CNS IA is seen rarely in non-neutropenic patients, except those with profound immunosuppression or uncontrolled diabetes

Jenks JD et al Mycoses. 2021 Sep;64(9):1002-1014

Spectrum in critically ill

- Aspergillus tracheobronchitis (ATB) is increasingly recognized in ICU patients with IA
- Described in neutropenic as well as nonneutropenics patients with COPD, AIDS, and lung transplantation
- Classified into ulcerative, pseudomembranous, and obstructive categories
- Ulcerative ATB occurs predominantly in lung transplant patients at the site of bronchial anastomosis, and is histologically characterized by hyphal invasion of the bronchial mucosa and/ or cartilage
- It carries the best prognosis, as lung transplant recipients usually undergo frequent surveillance bronchoscopies allowing for early detection and initiation of appropriate antifungal therapy

Dutkiewicz R et al. Proc Am Thorac Soc. 2010 May;7(3):204-9

Spectrum in critically ill

- Pseudomembranous and obstructive ATB carry a near 100% mortality and are often seen in patients who are mechanically ventilated
- Pseudomembranous ATB involves extensive inflammation of the tracheobronchial tree, with Aspergillus-containing pseudomembranes overlying the mucosa
- Obstructive ATB is characterized by thick mucus plugs filled with Aspergillus without evidence of bronchial inflammation
- Both pseudomembranous and obstructive ATB are often missed because of low clinical suspicion and nonspecific diagnostic findings
- Lobar atelectasis and unilateral wheeze from obstructive lesions are clues to the diagnosis
- Incidence of macroscopic lesions compatible with ulcerative or pseudomembranous aspergillosis is higher in patients who were neutropenic patients

Imaging

- Computed tomography (CT) of the chest is the imaging modality of choice to diagnose IA
- Most typical imaging findings including the halo sign and the air crescent sign have shown high sensitivity (80%) and specificity (60–98%) in neutropenic patients
- Nevertheless, both signs are uncommon, have a lower sensitivity (5–24%) and can be found even in non-infectious lesion processes in non-neutropenic patients
- Radiographic findings of consolidation, ground-glass infiltrates, and pleural effusions may be seen more commonly
- In addition, many ICU patients have radiologic abnormalities masked by underlying acute processes (pleural effusion, atelectasis or ARDS)

Bassetti M et al. Infect Dis Ther. 2018 Mar;7(1):17-27

Prophylaxis in IPA

- Posaconazole, voriconazole, and/or micafungin during prolonged neutropenia for those who are at high risk for IA

Patterson TF et al. Clin Infect Dis. 2016 Aug 15;63(4)

Prophylaxis in IPA

- No current recommendations for IPA prophylaxis in non-neutropenic ICU patients, except in ICU patients after SOT
- Antifungal prophylaxis with either a systemic triazole such as voriconazole or itraconazole or an inhaled AmB product for 3 to 4 months after lung transplant
- Antifungal prophylaxis for lung transplant recipients is also reinitiated in patients receiving immunosuppression augmentation with either thymoglobulin, alemtuzumab, or high-dose corticosteroids

Patterson TF et al. Clin Infect Dis. 2016 Aug 15;63(4)

Empirical therapy

- Empirical AFT involves treatment of febrile patients during periods of neutropenia
- In high risk patients with prolonged neutropenia and/or severe immunosuppression (GVHD, biologic agents, high dose GC) with pulmonary nodules, IMI is suspected and treated while diagnosis is pursued
- Empiric antifungal therapy is not recommended for patients who are anticipated to have short durations of neutropenia (duration of neutropenia <10 days), unless other findings indicate a suspected IFI

Uptodate

Patterson TF et al. Clin Infect Dis. 2016 Aug 15;63(4)

Pre-emptive therapy

- Studies limited to population with allogenic HCT recepients and/or hematologic malignancies
- Results may have suggested benefit in limiting antifungal use, none provides definitive clinical or survival benefits

Uptodate

Treatment in IPA

- Primary treatment with voriconazole
- Alternative therapies include
  - Liposomal AmB,
  - Isavuconazole

Patterson TF et al. Clin Infect Dis. 2016 Aug 15;63(4)

Voriconazole in IPA

Study	Design/Setting	Population	Intervention	Outcome	Results
Herbrecht et al, 2002	RCT	Definite or probable IA, Hematopoietic-cell transplant, hematologic cancer, aplastic anemia, or MDS; or other immunocompromising conditions, incl (AIDS), steroid therapy, and SOT	Voriconazole vs amphotericin for primary therapy of IA	Complete or Partial response	At week 12, successful outcomes seen among non neutropenic patients 54% vs 31.5% (Voriconazole vs AmphoB group)

Herbrecht R. N Engl J Med. 2002 Aug 8;347(6):408-15.

Voriconazole in IPA

Study	Design/Setting	Population	Outcome	Results
Garcia-Vidal et al, 2015	Retrospective	Proven and probable IA according to EORTC/MSG 2008	Mortality was assessed at 90 days from day of diagnosis (overall mortality)	92/152 (60.5%) patients with IA died; IA-related in 62 cases; Most common cause of IA-related death was respiratory failure (50/62). Voriconazole treatment was associated with reduced risk of death (HR 0.43; 95% CI, 0.20-0.93

Garcia-Vidal C et al PLoS One. 2015 Mar 24;10(3):e0120370

Voriconazole in IPA

- Voriconazole is recommended for IPA due to A. fumigatus if the isolate is voriconazole susceptible (susceptible if MIC <1mg/L), whilst in the case of resistance (MIC >2 mg/L) liposomal amphotericin B therapy is preferred
- Where the voriconazole MIC equals 2 mg/L (intermediate) the response to voriconazole monotherapy is unknown
- Importantly, especially in ICU patients, therapeutic drug monitoring (TDM) of voriconazole is used to avoid treatment failure, resistance development and toxicity

Cuenca-Estrella M et al. J Antimicrob Chemother. 2019 Mar 1;74(Suppl 2):ii9-ii15

Voriconazole in IPA

- TDM is recommended as voriconazole pharmacokinetics are non-linear and drug levels can fluctuate throughout the treatment based on drug–drug interactions and changes in hepatic clearance and in patients with liver insufficiency, as is frequently observed in ICU patients
- Several ICU-relevant side effects should be considered when using voriconazole: corrected QT interval prolongation, liver dysfunction and encephalopathy are the most common in the ICU setting

Cuenca-Estrella M et al. J Antimicrob Chemother. 2019 Mar 1;74(Suppl 2):ii9-ii15

Isavuconzole

Design	Population	Intervention	Outcome	Results
Phase 3, double-blind	Hematological malignancy, Allogenic BMT/HSCT, Neutropenia, Steroid use EORTC/MSG 2008	ICZ I.V for 2 days then I.V/Orally vs VCZ IV for 2 days then IV/Orally	All-cause mortality from first dose of study drug to day 42 in patients who received at least one dose of the study drug	All-cause mortality from fi rst dose of study drug to day 42 for was 19% with ICZ (48 patients) and 20% with VCZ (52 patients) Most patients (247 [96%] receiving ICZ and 255 [98%] receiving VCZ) had treatment emergent adverse events (p=0·122);

Isavuconazole was non-inferior to voriconazole for the primary treatment of suspected invasive mould disease

Maertens JA et al. Lancet. 2016 Feb 20;387(10020):760-9.

Posaconzole

Design	Population	Intervention	Outcome	Results
Phase 3, double-blind 26 countries 91 study sites	Allogenic HSCT, neutropenia, prolonged steroids EORTC/MSG Criteria 2008	Oral/IV PCZ vs Oral/IV VCZ for 12 weeks or less	Primary: All-cause mortality up until day 42 in the ITT population (defined as randomly assigned participants who received ≥1 dose of study drug)	Mortality up until day 42 was 15% (44 of 288) in the posaconazole group and 21% (59 of 287) in the voriconazole group (treatment difference –5·3% [95% CI –11·6 to 1·0]; p<0·0001) Overall incidence of treatment-related adverse event rates in the ITT population was 30% for posaconazole and 40% for voriconazole (treatment difference −10·2% [95% CI –17·9 to –2·4])

Posaconazole was non-inferior to voriconazole for all-cause mortality up until day 42 in participants with IA

Maertens JA et al. Lancet. 2021 Feb 6;397(10273):499-509.

Liposomal Amphotericin B

Design	Population	Intervention	Outcome	Results
AmBiLoad trial Phase 3, double-blind	Hematologic malignancy, stem cell transplant, neutropenia EORTC/MSG Criteria 2008	LAmpB 3mg/kg vs 10mg/kg for 14 days, f/b 3mg/kg per day	Primary: favorable (i.e., complete or partial) response at the end of study drug treatment. Survival and safety outcomes	• Favorable response was achieved in 50% and 46% of patients in the 3- and 10-mg/kg groups, respectively (P>0.05) • Respective survival rates at 12 weeks were 72% and 59% (P>0.05) • Significantly higher rates of nephrotoxicity and hypokalemia were seen in the high-dose group

Cornely OA et al. Clin Infect Dis. 2007 May 15;44(10):1289-97

Combination Chemotherapy

- The use of combination antifungal therapy for IPA is debated, although theoretically this can achieve:
  - (i) potential synergistic effects;
  - (ii) a broader antifungal spectrum;
  - and (iii) potentially a reduction of acquired resistance

  In vitro and animal studies demonstrated synergistic or additive effects of a mould-active triazole (itraconazole, voriconazole or posaconazole) or amphotericin B with an echinocandin, but few human studies support this practice

Bassetti M et al Intensive Care Med. 2017 Sep;43(9):1225-1238

Combination Chemotherapy

- The use of combination therapy may be considered a therapeutic solution:

  (i) in cases of resistance (e.g. Cyp51a mutations)

  (ii) in central nervous system aspergillosis due to azole-resistant Aspergillus

  (iii) as broad initial coverage pending pathogen identification

  (iv) for salvage therapy in refractory disease

  (v) until adequate plasma concentrations of voriconazole can be documented

Bassetti M et al Intensive Care Med. 2017 Sep;43(9):1225-1238

Epidemiology and clinical outcomes of invasive mould infections in Indian intensive care units (FISF study)

- Consecutive patients with proven or probable/putative IMIs
- Categorised into classical (neutropenia, malignancy, transplant recipients on immunosuppression) and non-classical (chronic obstructive pulmonary disease, diabetes, liver disease and glucocorticoids) risk groups
- ICUs of 11 tertiary care centers
- 398 patients with IMIs (96 proven, 302 probable) were identified; prevalence of 9.5 cases/ 1000 ICU admissions
- IMIs were diagnosed at a median of 4 days after ICU admission

Chakrabarti A et al J Crit Care. 2019 Jun;51:64-70

Epidemiology and clinical outcomes of invasive mould infections in Indian intensive care units (FISF study)

- 145 and 253 subjects with classical and non-classical risk groups, respectively
- Majority (n = 321, 80.7%) of the subjects had pulmonary disease; Next major sites were rhino-orbito-cerebral (7.5%), and sinuses only (5.8%)
- Aspergillus spp. were the commonest (82.1%) isolates; Mucorales were detected in 14.4% subjects.
- A high APACHE II score and IMI due to mucormycosis were significant predictors of mortality

Chakrabarti A et al J Crit Care. 2019 Jun;51:64-70

Summary of the results of direct microscopy and fungal isolation of 234 cases (single isolate in 173 subjects, multiple isolates in 17 subjects; and only direct microscopy positive in 44 subjects).

Fungal species isolated (total no. of subjects = 190)		Number of subjects
Aspergillus spp.		142
	A. flavus	67
	A. fumigatus	56
	A. terreus	8
	A. niger	6
	Unidentified *Aspergillus* species	5
Mucorales		25
Rhizopus spp.		19
	R. arrhizus	11
	R. microsporus	1
	Unidentified *Rhizopus* species	7
Mucor spp.		4
Apophysomyces variabilis		2
Fusarium spp.		4
Curvularia lunata		1
Pythium insidiosum		1
Multiple isolates		17
	A. flavus, A. niger	2
	Multiple *Aspergillus* species (not identified)	3
	A. flavus, A. fumigatus	5
	A. flavus, A. terreus	1
	A. flavus, A. terreus, and aseptate hyphae on smear	1
	Aspergillus spp., *Rhizopus* spp.	1
	A. fumigatus, R. arrhizus	1
	A. flavus and aseptate hyphae on smear	1
	A. fumigatus, Mucor spp.	1
	Fusarium solani, A. flavus	1
Only direct microscopy positive (no. of subjects = 44)	Aseptate hyphae	25
	Septate hyphae	15
	Septate + aseptate	4

Chakrabarti A et al J Crit Care. 2019 Jun;51:64-70

- Nosocomial mucormycosis was reported in 3 previously well individuals while receiving intensive care for acute hemorrhagic pancreatitis, for cardiogenic shock, and for a ruptured intra-abdominal aortic aneurysm
- In two cases, the condition was first seen as progressive cavitary pneumonia refractory to antibacterial therapy
- Mucoraceae was identified only at autopsy
- Each patient had received large doses of corticosteroids and broad-spectrum antibiotics, and all had suffered from respiratory failure, acute renal failure with acidosis, and severe hyperglycemia in association with total parenteral nutrition

Agger WA et al. Mucormycosis. Arch Intern Med. 1978 Jun;138(6):925-7.

- Retrospective, 16 French ICUs, 2008-2017
- 74 patients
- 60 patients (81%) were immunocompromised: 41 had hematological malignancies, 9 were solid organ transplant recipients, 31 received long-term steroids, 11 had diabetes, 24 had malnutrition
- Only 21 patients survived to ICU stay (28.4%) with a median survival of 22 days (Q1–Q3 = 9–106) and a survival rate at day 28 and day 90, respectively, of 35.1% and 26.4%
- Survivors were significantly younger (p = 0.001), with less frequently hematological malignancies (p = 0.02), and less malnutrition (p = 0.05). Median survival in patients with hematological malignancies (n = 41) was 15 days (Q1–Q3 = 5–23.5 days)

Claustre J et al. Ann Intensive Care. 2020 Jun 8;10(1):74

Mucormycosis: Risk factors

- Immunocompromised patients
- Hematological malignancies
- Hematopoietic stem cell transplant recipients
- Solid organ transplant recipients
- Diabetes mellitus
- Major surgery patients
- IDUs
- Severe trauma and burn patients
- Deferoxamine therapy

Paiva Ja et al. Curr Opin Infect Dis. 2018 Apr;31(2):187-193

Clinical Presentation

- Presentation of mucormycosis is rather like Aspergillus infection
- Clues favoring the mucor over IA are:
  - institution with high incidence of mucormycosis
  - iron overload, hyperglycemia
  - and prior voriconazole or echinocandin use
  - oral necrotic lesions in hard palate or nasal turbinates
  - chest wall cellulitis adjacent to a lung infarct
  - acute vascular event

Paiva Ja et al. Curr Opin Infect Dis. 2018 Apr;31(2):187-193

- Clues favoring the mucor over IA are:
  - multiple lung nodules and pleural effusion
  - or reverse halo sign (ground glass attenuation surrounded by ring consolidation) on lung CT
  - negative glucan and galactomannan
  - or no response to voriconazole and suspicion of fungal pneumonia

Paiva Ja et al. Curr Opin Infect Dis. 2018 Apr;31(2):187-193

Manifestations

- Manifestations of pulmonary mucormycosis are frequently fever and unresolving pulmonary infiltrates, despite the use of broad spectrum antibiotics
- Respiratory mucormycosis may involve the lung parenchyma and the pulmonary vascular system but also the bronchial tree and trachea

Bassetti M et al J Antimicrob Chemother. 2017 Mar 1;72(suppl_1):i39-i47

- Rhino-cerebral mucormycosis remains an important clinical presentation of mucormycosis, particularly in Asia and in patients with diabetes mellitus
- Necrosis evolves rapidly, although cases of chronic slowly evolving lesions in immunocompetent hosts are occasionally reported
- Mucormycosis complicating wound infections or other skin lesions, including intravenous needle punctures, is well known and should be suspected in the presence of progressive necrosis of any extent
- These may occur in traumatic wounds in completely immunocompetent hosts, such as patients in the ICU

Bassetti M et al J Antimicrob Chemother. 2017 Mar 1;72(suppl_1):i39-i47

- Detection of both GM and 1–3-b-D-glucan is futile in mucormycosis because Mucorales do not produce these biomarkers
- Confirmation of the diagnosis requires a positive culture from tissues that are ordinarily sterile, based on samples that have been obtained under sterile conditions
- Combination of a clinically compatible setting with positive clinical samples obtained from non-sterile samples, such as respiratory secretions, makes the diagnosis only probable

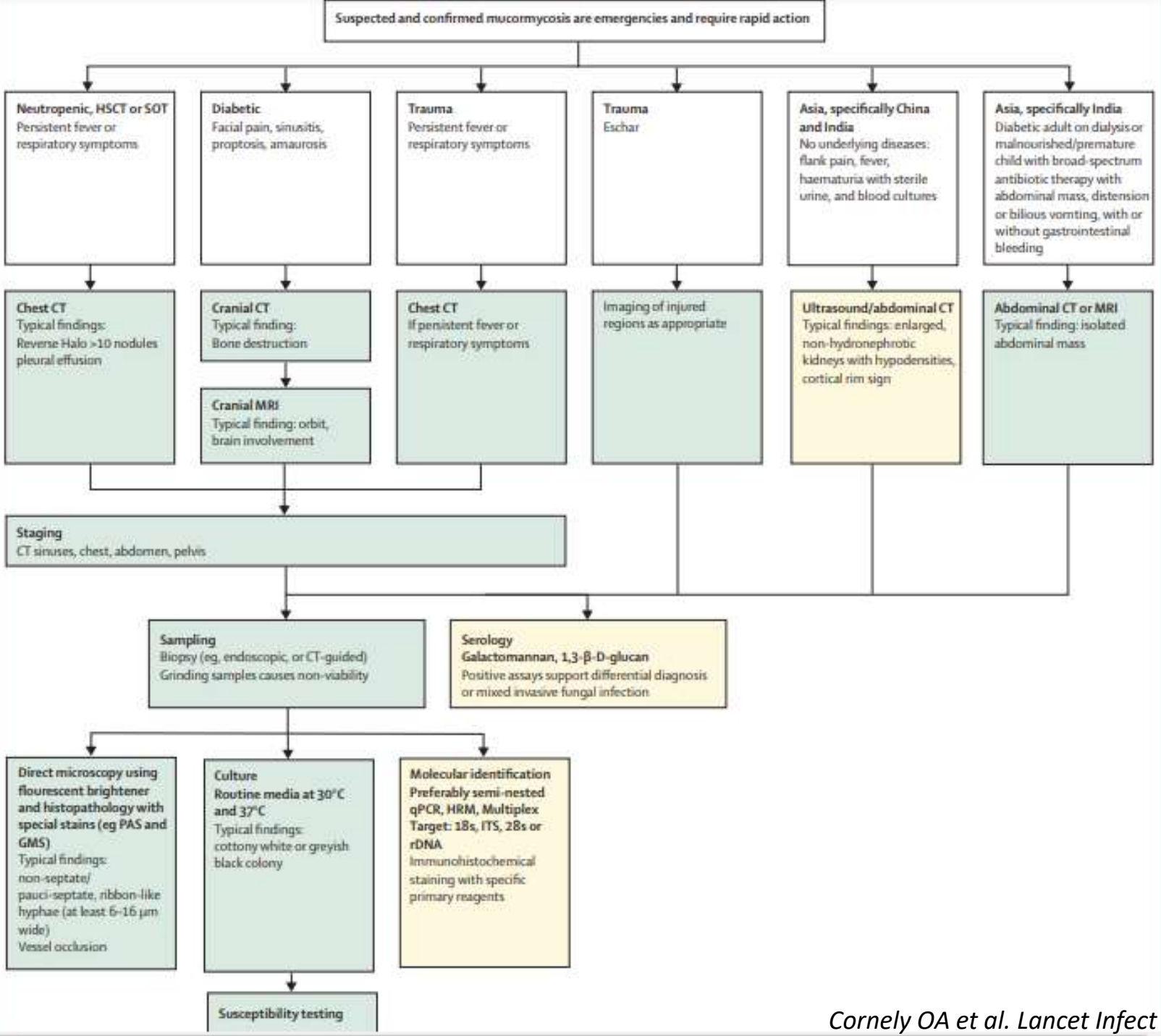
Bassetti M et al J Antimicrob Chemother. 2017 Mar 1;72(suppl_1):i39-i47

- Tissue biopsy is essential, and the presence of broad, non-septate hyphae invading the tissues and vessels, with right angles and a ribbon-like appearance, is adequate to confirm the diagnosis
- In the case of pulmonary infections, samples may be obtained by open pulmonary resection but also by transthoracic CT-guided procedures and, in the case of rhino-cerebral forms, by samples obtained through nasal endoscopy

Bassetti M et al J Antimicrob Chemother. 2017 Mar 1;72(suppl_1):i39-i47

- Samples must be approached carefully in the clinical microbiology laboratory and should not be triturated in preparation for culture

Bassetti M et al J Antimicrob Chemother. 2017 Mar 1;72(suppl_1):i39-i47



Cornely OA et al. Lancet Infect Dis. 2019 Dec;19(12):e405-e421.

Therapeutic approach

Bassetti M et al J Antimicrob Chemother. 2017 Mar 1;72(suppl_1):i39-i47

First line monotherapy

Cornely OA et al. Lancet Infect Dis. 2019 Dec;19(12):e405-e421.

	Intention	Intervention	SOR	QOE	Reference
Any	To cure and to increase survival rates	Amphotericin B, any formulation, escalation to full dose over days	D	IIu	Chamilos[1] (N–70, give full daily dose from day 1)
Any	To cure and to increase survival rates	Amphotericin B, liposomal, 5–10 mg/kg per day	A	IIu	Gleissner[144] (N–16, haematology); Pagano[109] (N–5); Cornely[106] (N–4); Pagano[105] (N–44); Rüping[67] (N–21); Shoham[59] (N–28); Skiada[17] (N–130); Lanternier[104] (N–34, 18 haematology, six diabetic); Kyvernitakis[108] (N–41); Stanzani[107] (N–97, increased renal toxicity with cyclosporine)
CNS involvement	To cure	Amphotericin B, liposomal, 10 mg/kg per day, initial 28 days	A	III	Ibrahim[112] (Animal); Lanternier[104] (N–9)
SOT adults	To cure	Amphotericin B, lipid formulation; dose not given	A	IIh	Singh[145] (N–25); Sun[146] (N–14); Lanternier[147] (N–3)
SOT adults	To cure	Amphotericin B, lipid complex; 10 mg/kg per day	A	III	Forrest[124] (N–6, 3 of 6 died)
Any, without CNS involvement	To cure	Amphotericin B, lipid complex; 5 mg/kg per day	B	IIu	Larkin[113] (N–10); Ibrahim[112] (animal); Skiada[17] (N–7)
Haematological malignancy	To cure	Amphotericin B, liposomal; 1–<5 mg/kg per day ± surgery	C	III	Nosari[130] (N–13, 8 of 13 treated, 5/8 died); Li[148] (N–7, 2 of 7 died)
Any	To cure	Isavuconazole PO or IV; 3 x 200 mg day 1–2, 1 x 200 mg/d from day 3	B	IIh	Marty[93] (N–21, 11 haematology, 4 diabetes, overall mortality comparable to amphotericin B formulations)
Any	To cure	Posaconazole DR tablet or intravenously 2 x 300 mg day 1, 1 x 300 mg from day 2	B	IItu	Duarte;[122] Maertens;[124] Cornely;[123] Cornely[125] (higher trough levels than oral suspension, intravenous bridging when oral dosing not feasible)
Any	To cure	Posaconazole oral suspension; 4 x 200 mg/day or 2 x 400 mg/day	C	IIu	Rüping[67] (N–8); Skiada[17] (N–17); Dannaoui[149] (animal, emphasises preference of amphotericin B, liposomal)
Any	To cure	Amphotericin B, deoxycholate, any dose (if alternative therapy available)	D	IIt	Walsh[116] (renal toxicity); Pagano[109] (N–9); Roden[11] (N–532); Ullmann[115] (renal toxicity); Chakrabarti[66] (N–10); Skiada1[17] (N–21)
Orbital mucormycosis	To cure	Retrobulbar injection of amphotericin B deoxycholate in addition to systemic therapy	D	III	Hirabayashi[150] (N–1, post-injection inflammatory response, risk for acute compartment syndrome)

IV=intravenous. PO=per os (taken orally). SOR=strength of recommendation. QOE=quality of evidence. N=number of individuals. SOT=solid organ transplantation. DR=delayed release.

Table 2: **Recommendations on first-line antifungal monotherapy for mucormycosis by population type**

First line combination therapy

Reference	Population	Intervention	Comment
Kyvernitakis CMI 2016	N=27, Any	Liposomal amphotericin B + caspofungin	No benefit for combination
Klimko Mycoses 2014	N=36, Haematologic malignancy	Liposomal amphotericin B + caspofungin	Combination treatment (52%) was associated with favourable prognosis
Kyvernitakis CMI 2016	N=16, Haematologic malignancy	Liposomal amphotericin B + posaconazole oral suspension	No benefit for combination
Jenks IJAA 2018	N=10, Any	Liposomal amphotericin B + (posaconazole DR tablet or iv)	Overall survival 4/6 in those with combination versus 0/4 in those with single agent therapy
Kyvernitakis CMI 2016	N=106,Haematologic malignancy	Liposomal amphotericin B + caspofungin + posaconazole	No benefit for combination

Cornely OA et al. Lancet Infect Dis. 2019 Dec;19(12):e405-e421.

Antifungal salvage treatment

- In general, there are two drug-related reasons for treatment failures, refractory mucormycosis or toxicity of first-line regimens—ie, intolerance to a drug
- For amphotericin B formulations, particularly renal toxicity can be a limiting factor, while for the azole class hepatic toxicity has the highest prevalence
- Toxicity can be caused by previous antifungals, or expected due to pre-existing organ damage
- Only two drug classes have proven efficacy in mucormycosis, thus salvage treatment mostly means switching to the other class

Cornely OA et al. Lancet Infect Dis. 2019 Dec;19(12):e405-e421.

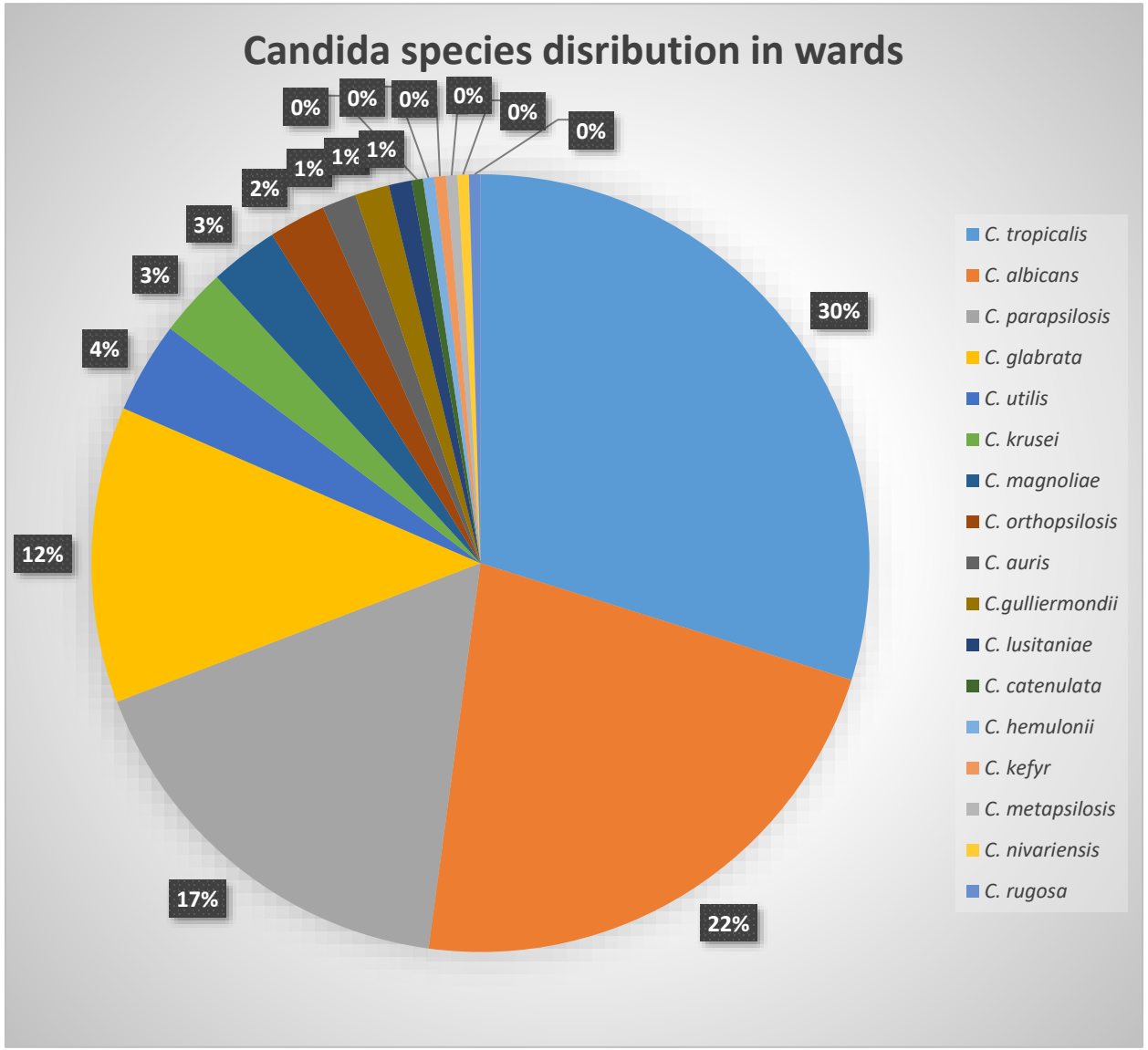
Antifungal salvage treatment

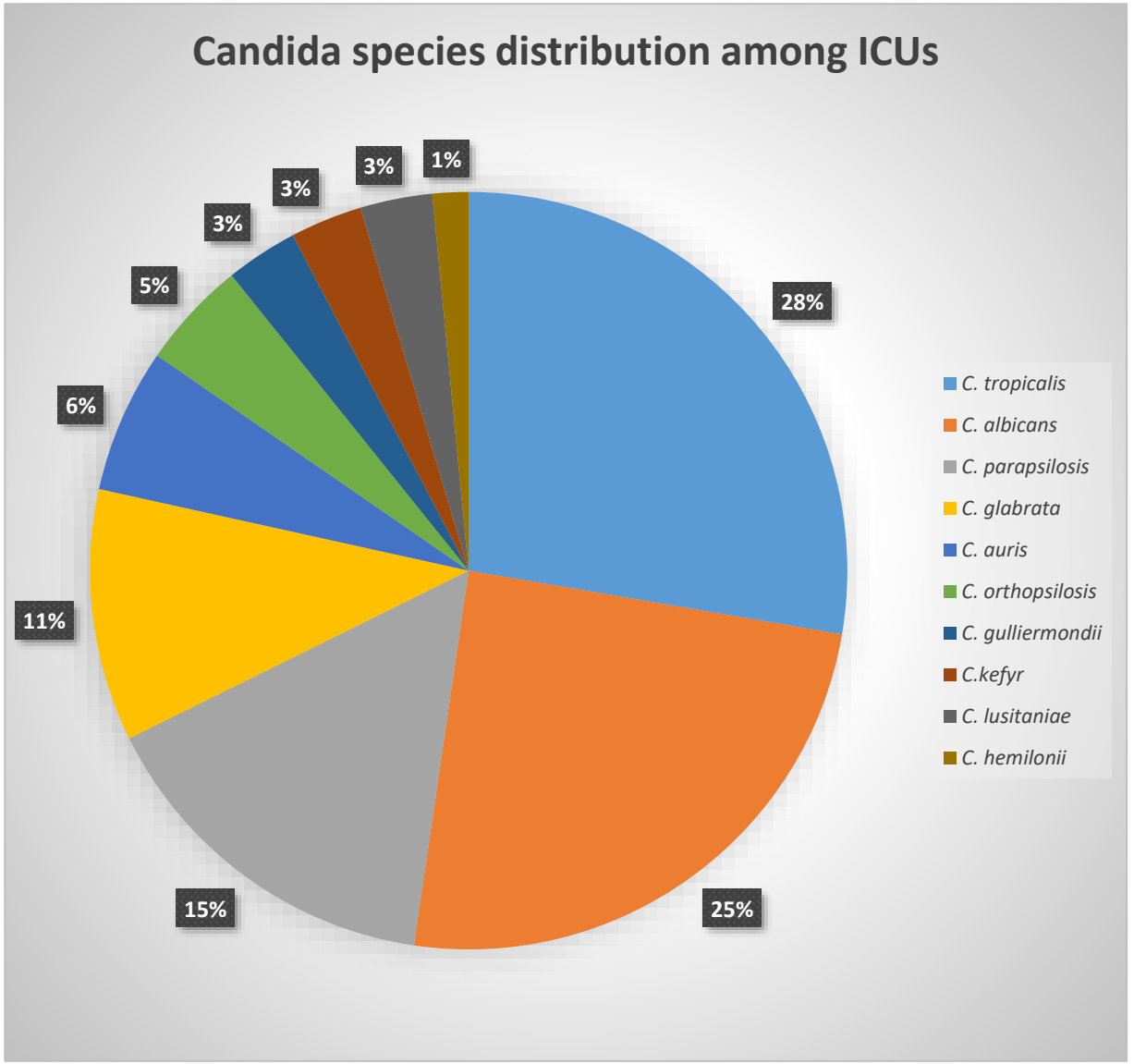
- Isavuconazole is strongly supported as salvage treatment
- Posaconazole delayed release tablets or infusions are strongly supported for salvage treatment, and when available should be preferred over posaconazole oral suspension, which in turn is marginally supported for salvage treatment
- In cases of primary treatment failure with isavuconazole or posaconazole, recommendations for all three lipid based amphotericin B formulations

Cornely OA et al. Lancet Infect Dis. 2019 Dec;19(12):e405-e421.

Reference	Population	Intervention	Comment
Marty Lancet ID 2016	Refractoriness	Isavuconazole iv or po	N=11
Cornely JAC 2017	Refractoriness	Posaconazole DR tablet or iv	N=237
Lanternier JAC 2015	Refractoriness	Amphotericin B, liposomal 10 mg/kg	N=44
Skiada CMI 2011	Refractoriness	Posaconazole oral suspension	N=61
DiPippo Mycoses 2018	Toxicity	Isavuconazole iv or po	N=23
Cornely JAC 2017	Toxicity	Posaconazole DR tablet or iv	N=237
Pagano Haematol 2004	Toxicity, renal	Amphotericin B, liposomal 5 mg/kg	N=8, prior amphotericin B deoxycholate
Vehreschild CRM 201	Toxicity	Posaconazole oral suspension	N=15

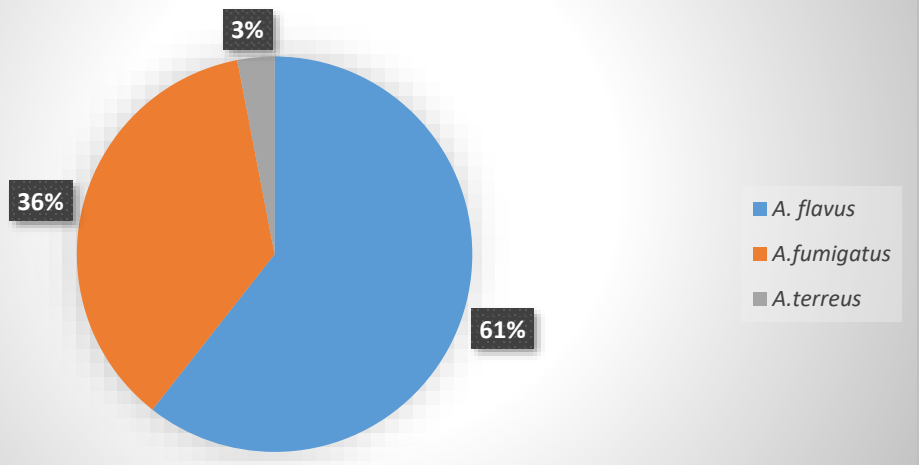
Cornely OA et al. Lancet Infect Dis. 2019 Dec;19(12):e405-e421.



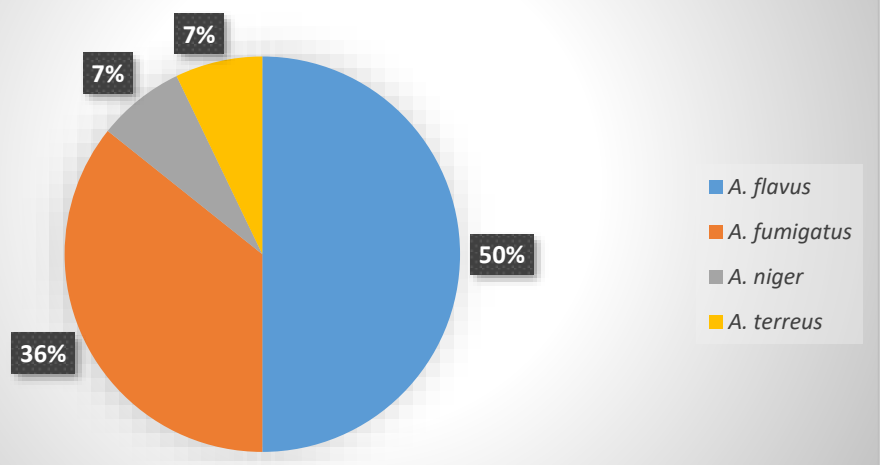


Courtesy: Prof Shivaprakash

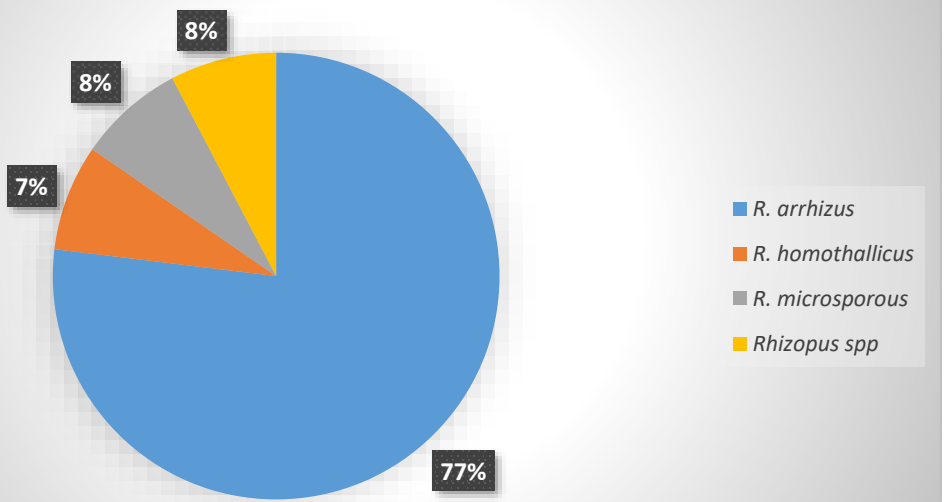
Aspergillus species distribution across various wards



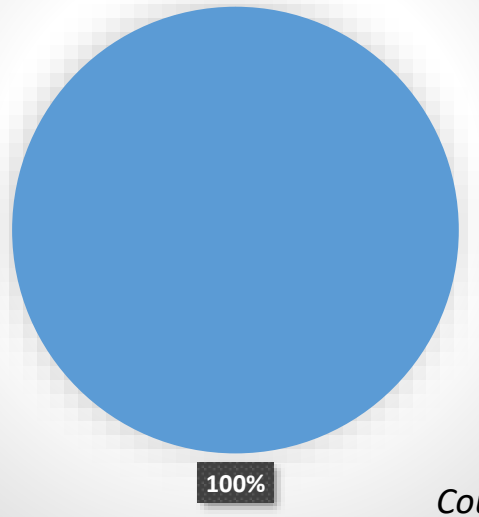
Aspergillus species distribution across ICUs



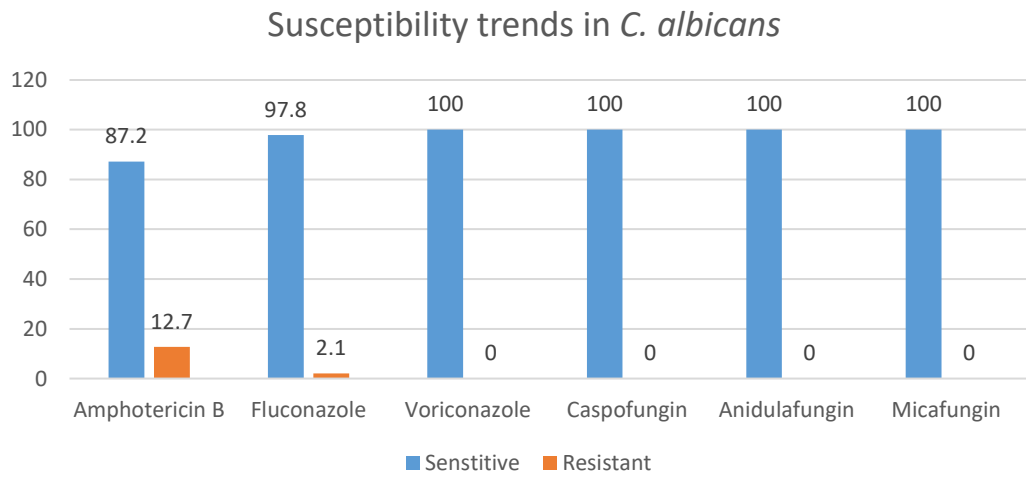
Mucorales across wards

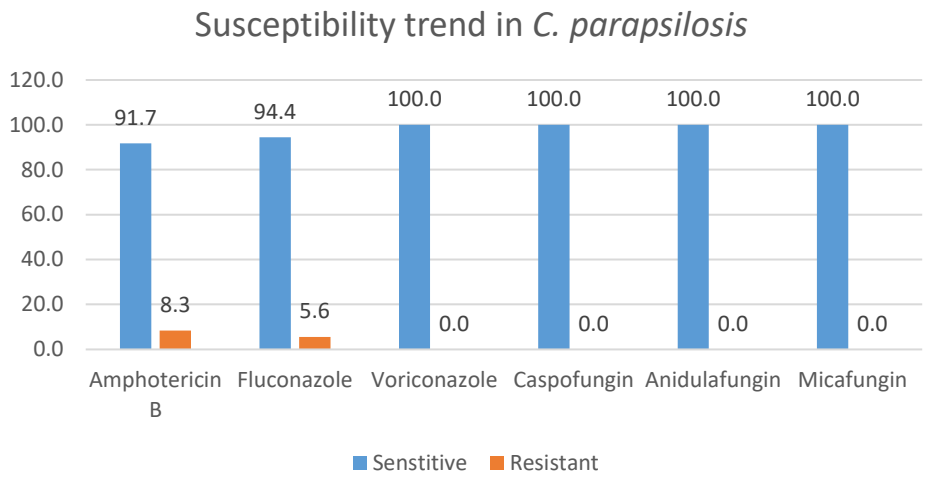


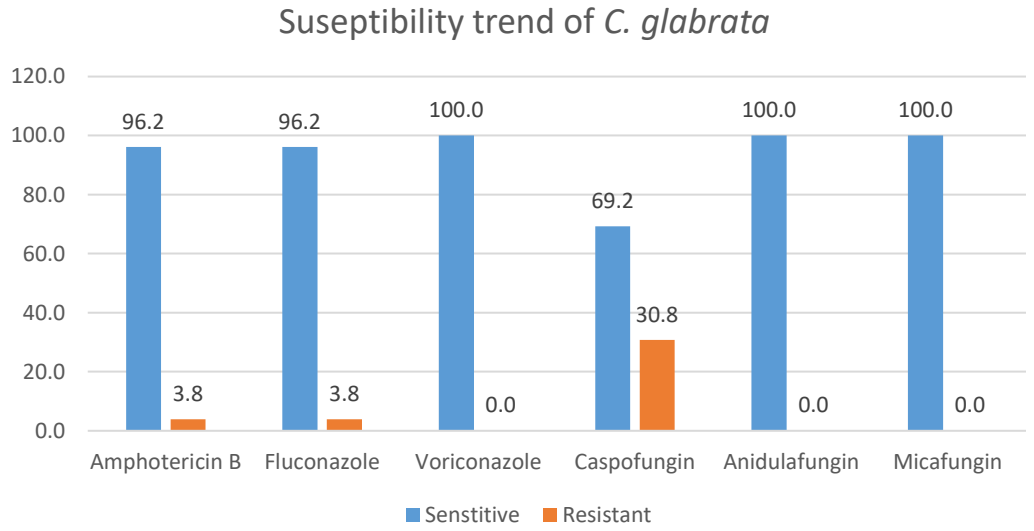
Mucorales across ICUs

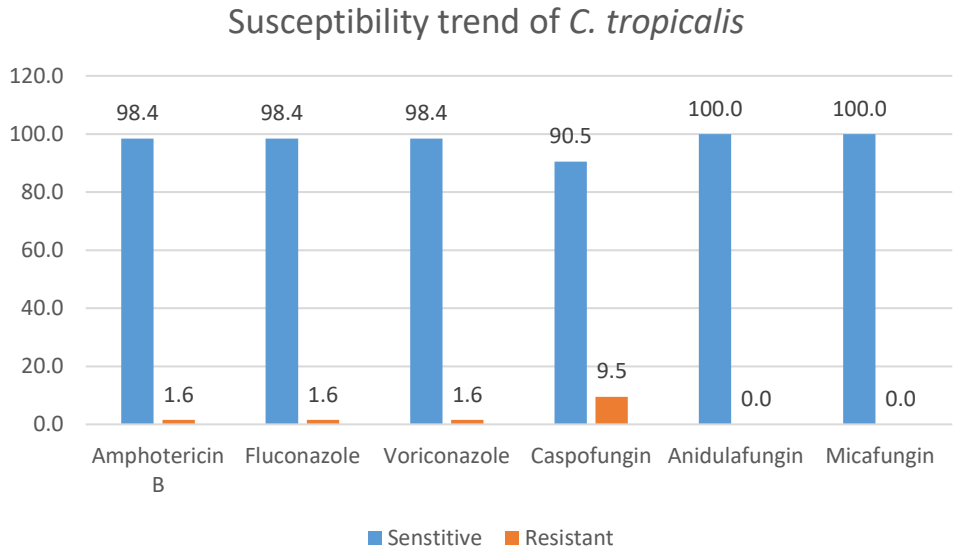


Courtesy: Prof Shivaprakash









Courtesy: Prof Shivaprakash