Aplicarea principiilor de ”Antifungal stewardship” în România. Perspectiva clinicianului

Dr Mihaela ZAHARIA

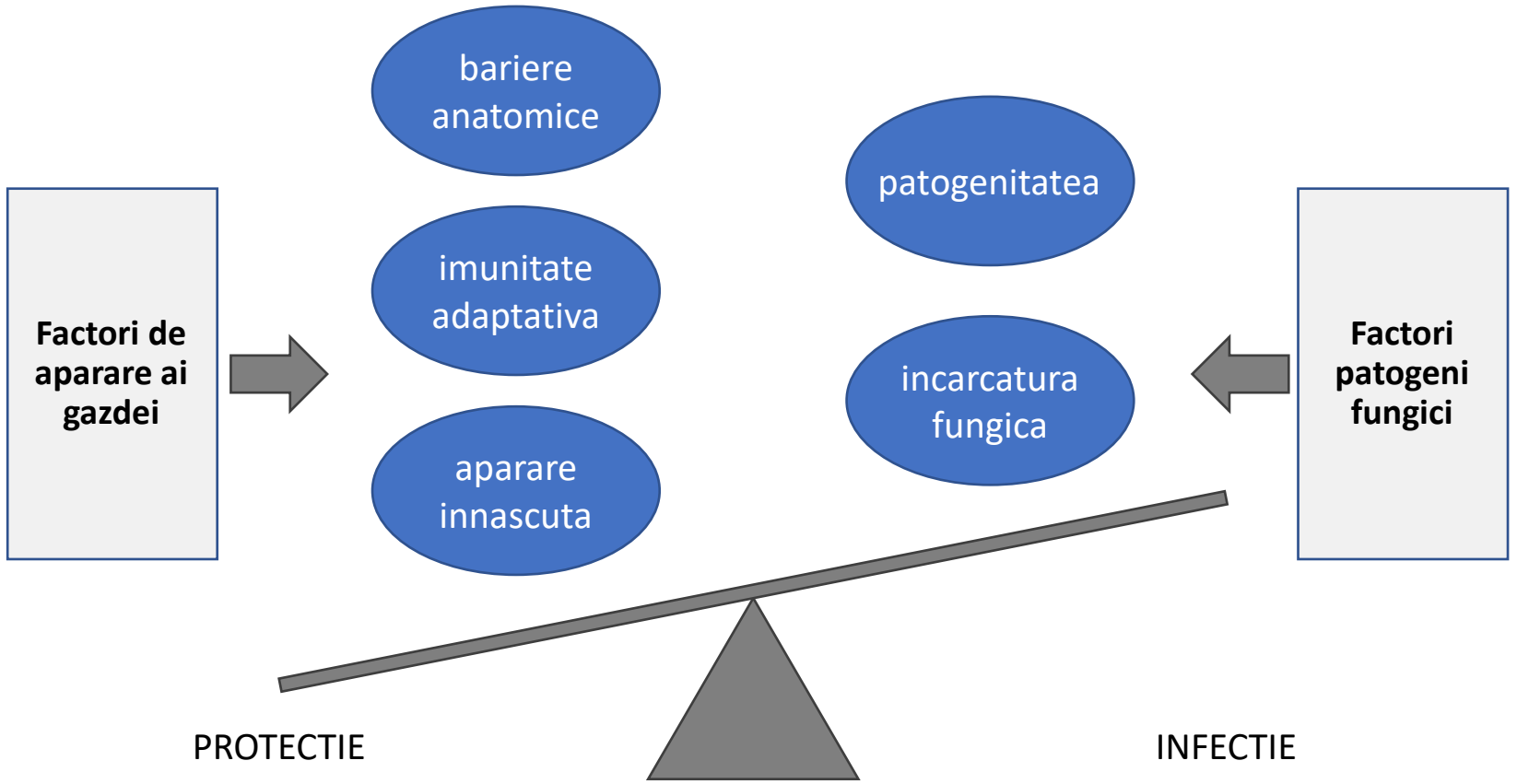
Plan prezentare

- Generalitati
- Stewardship antibiotic
- Tratamentul antifungic
- Patologie fungica
  - Aspergiloza pulmonara
  - Mucormicoza
  - Candidiaza invaziva
    - *C Auris*
- Concluzii

De ce infectiile fungice sunt mai rare?

Infectiile fungice apar ca urmare a dezechilibrului intre apararea gazdei si agresivitatea patogenului

Balanta gazda/patogen:
Conditii bazale



Infectii fungice cu risc vital – la nivel global

http://www.gaffi.org/why/fungal-disease-frequency/

Infectii fungice	Mortalitate	Nr decese - estimate
Meningita Cryptococcica	15–20% (USA) >50% (tari in curs de dezvoltare)	180,000
Pneumocystoza	≈15% in AIDS ≈50% non-AIDS	>200,000 AIDS >80,000 non-AIDS
Aspergilloza invaziva	≈50% mortalitate – tari in curs de dezvoltare –daca tratament ~30% mortalitate in leucemia ~45-70% in BPOC ~30% mortalite (dc tratament) in AIDS ~50% non-AIDS	>500,000 (multe cazuri nediagnosticate la niv global)
Candida bloodstream infections	≈40% mortalitate dc tratament	>350,000
Aspergilloza pulmonara cronica	≈15% mortalitate (tari in curs de dezvoltare)	>450,000
Keratita fungica	Pierderea vederii >60%	≈>600,000 cazuri de pierdere a vederii
TOTAL	Probabil subestimata semnificativ	>1,600,000

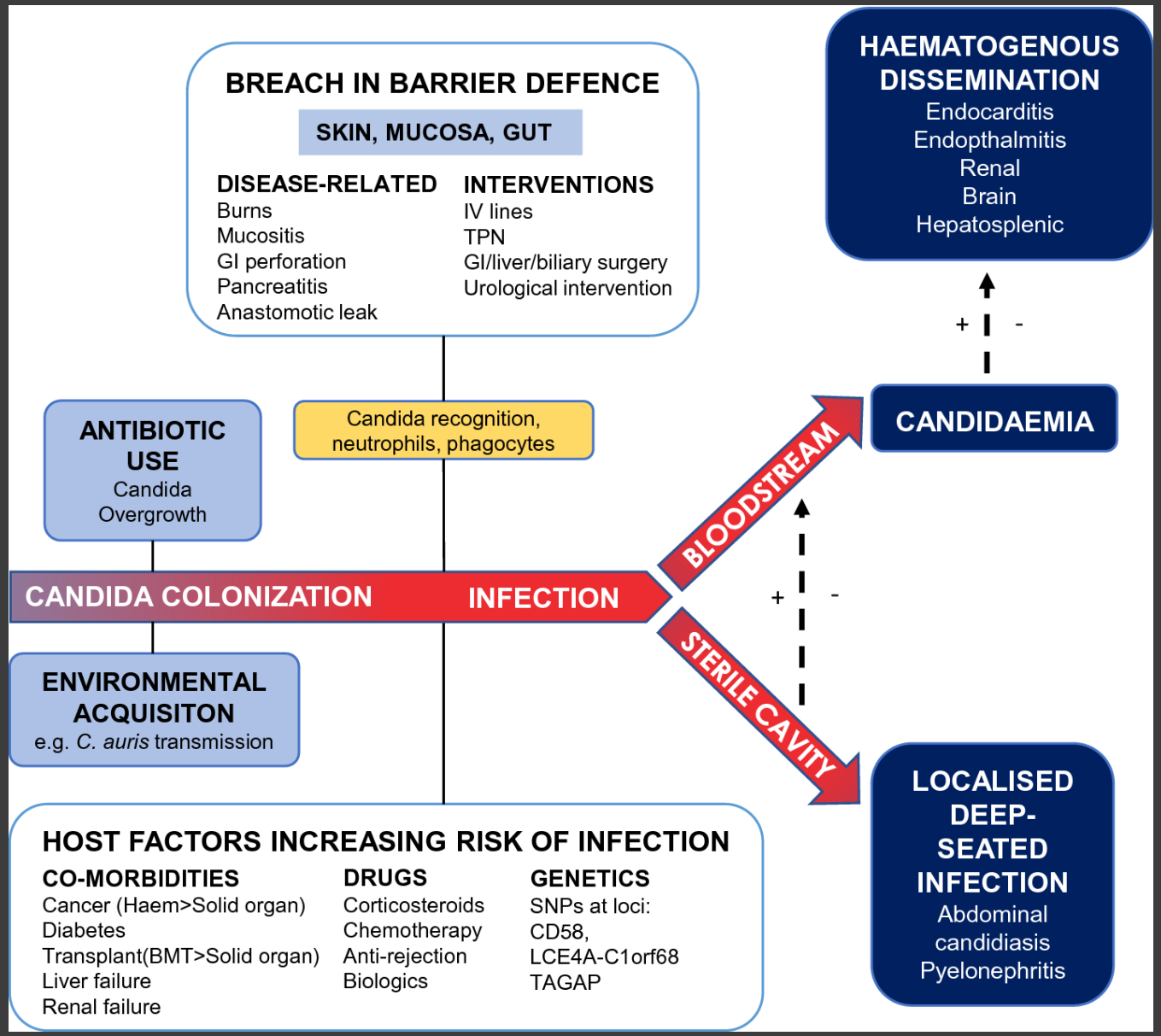
Pacienti la risc pentru infectii fungice invazive – fungi filamentosi

- Hemopatii
  - Leucemie acuta mieloida - AML (chemoterapie de inductie sau consolidare)[1,2]
  - Sdr mielodisplazic - MDS[2]
  - Leucemie acuta limfocitara - ALL[2]
  - Anemie aplastica severa[2]
  - Transplant hematopoietic celule stem HSCT[2,3]
  - Boala grefa versus gazda - GvHD, tratament imunosupresor[2]
  - Noi tratamente (ex., ibrutinib)[4]

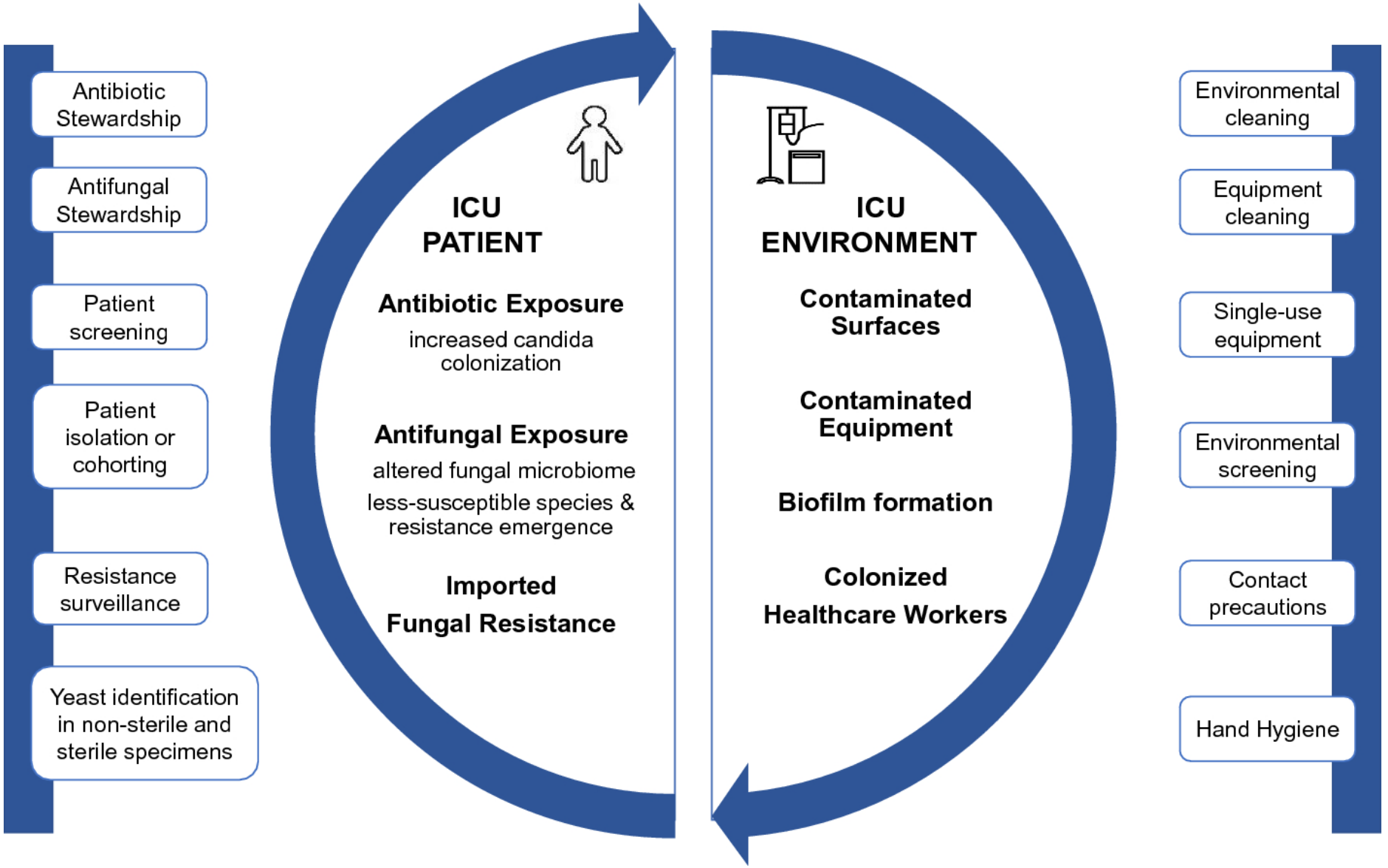
- Transplant de organ solid - SOT[5]
- ICU
  - Gripa[5], SARS-CoV-2[6]
  - BPOC[7]
- Tratament imunosupresor[6]
- Diabet zaharat[8]

ALL, acute lymphocytic leukaemia; AML, acute myeloid leukaemia; COPD, chronic obstructive pulmonary disease; GvHD, graft-versus-host disease; HSCT, haematopoietic stem-cell transplantation; ICU, intensive care unit; MDS, myelodysplastic syndrome; SARS-CoV-2; severe acute respiratory syndrome coronavirus 2.

1. Pagano L, *et al. Haematologica*. 2010;95(4):644–50; 2. Pagano L, *et al. Blood Rev*. 2017;31(2):17–29; 3. Marty FM, *et al. Lancet Infect Dis*. 2016;16(7):828–37; 4. Serota DP, *et al. Clin Infect Dis.* 2018;66(9):1482–3;
5. Schauwvlieghe AFAD, *et al. Lancet Respir Med*. 2018;6(10):782–92; 6. Shafiekhani M, *et al. Virol J.* 2022;19(1):35; 7. Shahi M, *et al. Curr Med Mycol.* 2015;1(3):45–51; 8. Poradzka A, *et al. Acta Pol Pharm*. 2013;70(4):587–96.



Factori de risc pentru infectii fungice invazive – Candida spp



Logan C., *Intensiv Care Medicine 29 sept 2020*

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10 reguli de baza in dezvoltarea programului de stewarship antifungic

1. Evitarea profilaxiei antifungice pe cat posibil – indicatie conform ghidurilor
2. Diferentierea intre infectie si colonizare
3. Folosirea metodelor de diagnostic rapid pentru un diagnostic precoce al IF
4. Limitarea terapiei empirice luandu-se in calcul factorii de risc
5. Promovarea tratamentului fungic precoce pre-emptive luand in calcul factorii de risc si biomarkerii fungici disponibili
6. Tratament de prima intentie adecvat
7. Controlul sursei de infectie in primele 48h (schimbare catetere, drenaj focar infectie, interventie chirurgicala la nevoie)
8. Folosirea dozelor adecvate de antifungice: doze subopotimale → asociate cu rezistenta
9. Dezescaladare oricand este posibil (in maxim 5 zile)
10. Reevaluarea terapiei cu oprirea precoce daca nu se confirma infectia si cu verificarea duratei de tratament corespunzatoare IF diagnosticate.

IC, invasive candidiasis.
Bassetti M et al. Intensive Care Med 2017: DOI: 10.1007/s00134-017-4922-x.

Cel mai recent guideline – stewardship antifungic

INTERNAL MEDICINE JOURNAL | RACP Specialists. Together

Supplement Article | Free Access

Consensus guidelines for antifungal stewardship, surveillance and infection prevention, 2021

Anna Khanina, Shio Yen Tio, Michelle R. Ananda-Rajah, Sarah E. Kidd, Eloise Williams, Lynette Chee, Karen Urbancic, Karin A. Thursky, Australasian Antifungal Guidelines Steering Committee

First published: 22 December 2021 | https://doi.org/10.1111/imj.15586 | Citations: 3

Argumente

- Prescrierea antifungicelor in profilaxie/tratament implica:
  - Povara economica pt sistemul medical
  - Reactii adverse ale medicatiei
  - Reactii adverse secundare interactiunii medicamentoase
  - Aparitia rezistentei la antifungice

- Cresterea populatia la risc pt IFD (prin cresterea numarului bolilor neoplazice, cresterea numarului cazurilor de transplant, evolutia medicatie imunomodulatoarea etc)

  - → este necesar standardizarea strategiilor antifungice intraspitalicesti sub coordonarea Stewardshipul antifungic

Probleme identificate – arii care au fost optimizate

- Durata lunga a tratamentului profilactic/empiric antifungic
- Alegerea neadecvata a agentului antifungic
- Doza inadecvata de incarcare /intretinere
- Management suboptimal al interactiunilor medicamentoase
- Lipsa efectuarii monitorizarii concentratiei serice terapeurice (TDM) pentru antifungicele cu anumite caracteristici farmacologice

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Suplimentar s-a obtinut

- Imbunatatirea strategiilor de diagnostic si diferentierea mai clara infectie /colonizare
    - CT toracic
    - Folosirea biomarkerilor fungici,, metodelor de identificare rapide din ser (T2Candida, PCR Candida) si PCR din alte produse patologice etc
    - Identificarea precisa a patogenului izolat in culturi
- Rata mare de acceptarea a propunerilor comisiei de stewardship antifungic

INTERNAL MEDICINE JOURNAL | RACP Specialists. Together

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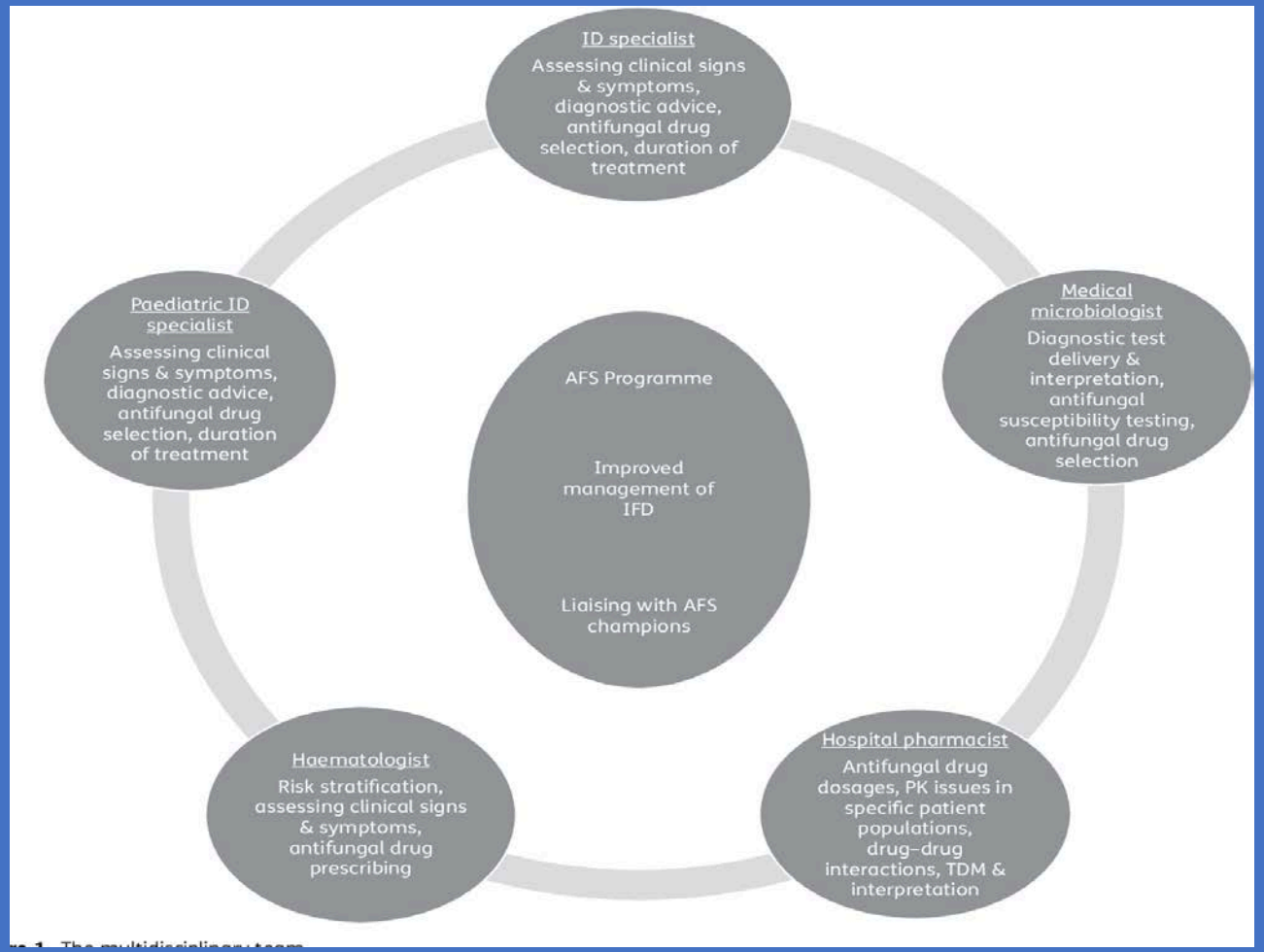
Stewardship antifungic – echipa multi-disciplinara



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Antifungicele sistemice

Nystatin
1949

Ketoconazole
Amphotericine B
1960’

Flucytosine
1970’

Formes lipidiques AmB
Fluconazole
Itraconazole
1990’

Caspofungine
2001

Voriconazole
2002

Posaconazole
2005

Micafungine
Anidulafungine
2007

Isavuconazole
2016

Polyenes
Azoles
Echinocandines
5FC

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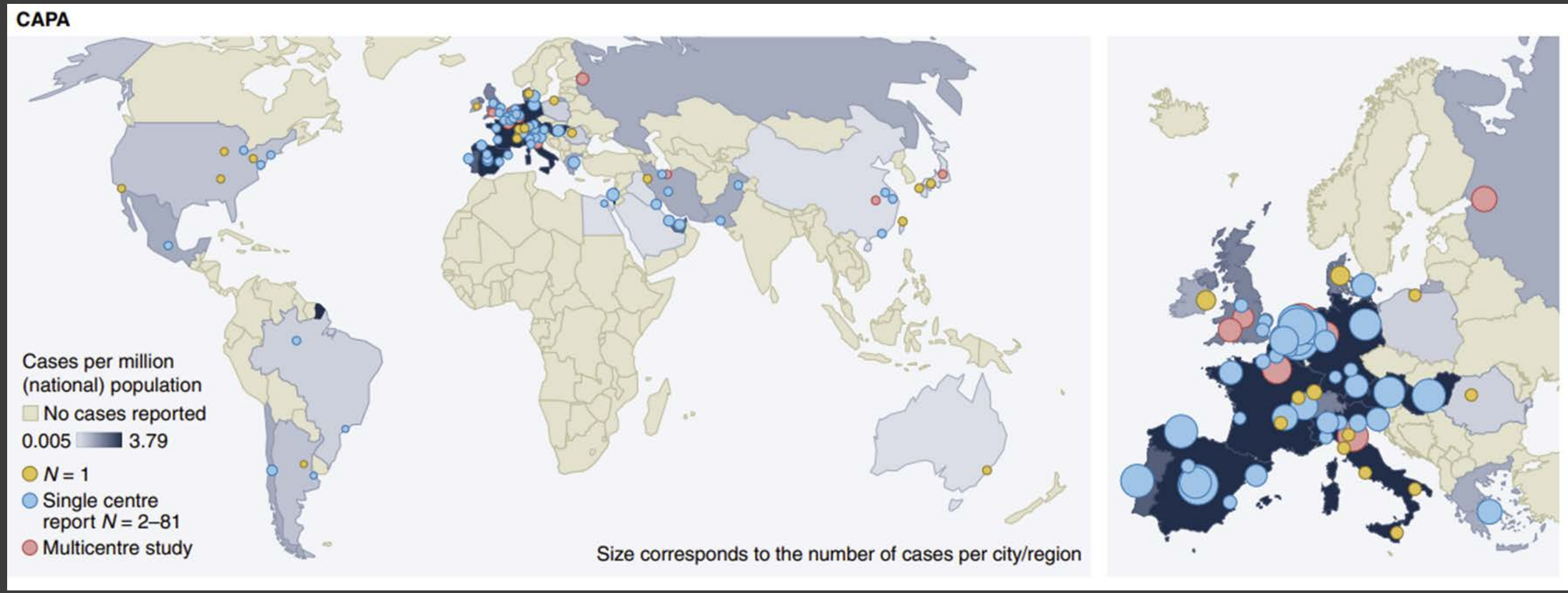


Global distribution of COVID-19-associated pulmonary aspergillosis

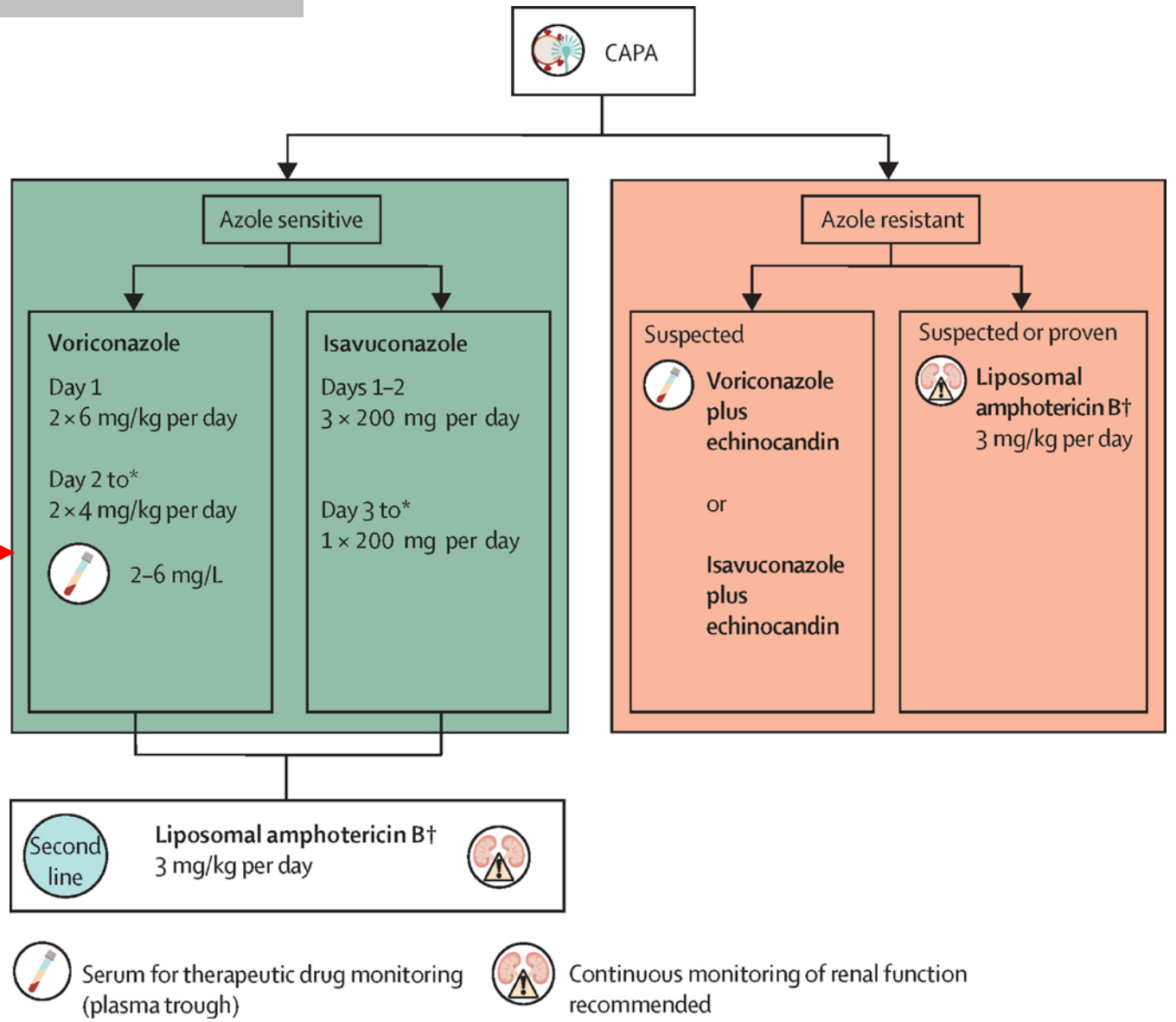
- CAPA, COVID-19-associated pulmonary aspergillosis.
- Hoenigl M, *et al. Nat Microbiol*. 2022;7(8):1127–40.

CAPA – Aspergiloza pulmonara asociata infectiei SARS-CoV2 (COVID-19 Associated Pulmonary Aspergillosis)

- Inclusi 3148 pacienti cu COVID-19 din 28 studii
- Incidenta generala : 10.2%
- CAPA a fost asociata cu o mortalitate de 55%

(Mitaka et al, *Mycoses 2021 Apr 25*)

ECMM/ISHAM consensus criteria 2020: Tratament CAPA



TDM

Durata optima neclara, dar comisia expertilor sugereaza 6-12 sapt

La pacient imunocompromis cel mai probabil un tratament indelungat este necesar – fara a se mentiona perioada

Koehler P, et al. Lancet Infect Dis 2021; 21: e149–62 Published Online December 14, 2020 https://doi.org/10.1016/ S1473-3099(20)30847-1

ECIL-6 therapy: Recomandari pt IA 2017[a]

ECIL-6 recomandari prima linie tratament in Aspergiloza invaziva [1]		
	Grade	**Comentarii**
Voriconazole[2]	A I	Doza zilnica: 2 × 6 mg/kg Ziua 1 apoi 2 × 4 mg/kg (initiere cu terapie orala: C III)
Isavuconazole[3]	A I	Doza zilnica 1-3 zile 3 x 200mg /zi apoi 200 mg/zi[3]
Liposomal amphotericin B[4]	B I	Doza zilnica: 3 mg/kg
Caspofungin[5]	C II	N/A

[a]These guidelines may differ from your local guidelines.

IA, invasive aspergillosis; ECIL, European Conference on Infections in Leukemia.

1. Tissot F, *et al. Haematologica*. 2017;102(3):433–44; 2. VFEND® Summary of Product Characteristics. Updated 6 May 2022. Available at: https://www.ema.europa.eu/en/documents/product-information/vfend-epar-product-information_en.pdf. Last accessed 20 September 2022; 3. Cresemba® Summary of Product Characteristics. Updated 29 Jul 2022. Available at: https://www.ema.europa.eu/en/documents/product-information/cresemba-epar-product-information_en.pdf. Last accessed 20 September 2022; 4. AmBisome® Summary of Product Characteristics. Updated 14 Nov 2019. Available at: https://www.medicines.org.uk/emc/product/1022/smpc. Last accessed 20 September 2022; 5. Caspofungin Summary of Product Characteristics. Updated 16 Apr 2021. Available at: https://www.medicines.org.uk/emc/product/8956/smpc. Last accessed 20 September 2022.

Aspergiloza pulmonara invaziva: Recomandari de tratament la pacientul cu hemopatie maligna [a]

GHID[1]	ISAVUCONAZOLE[2]	VORICONAZOLE[3]	L-AMB[4]	POSACONAZOLE[5]
ECIL-6	A I	A I	B I	-
ESCMID/ECMM 2018	A I – A II	A I – A II	B II	-
IDSA 2016	A II	A I	A II	-

Noi dovezi in ceea ce priveste posaconazole (neincluse inca in ghidurile oficiale pentru tratamentul IA):

Maertens 2021[6] (Factori de risc: neutropenia, allo-HSCT, T-cell suppressants, corticosteroid , immunosuppression congennitala, altii)	**Posaconazole a fost non-inferior voriconazolului[b] si participantii au avut numeric mai putin EA legate de tratament decat in grupul tratat cu voriconazole**

[a]These guidelines may differ from your local guidelines.

[b]All-cause mortality up until Day 42 was 15% versus 21% in the posaconazole group versus the voriconazole group, respectively (treatment difference: –5.3% [p<0.0001]; 10% non-inferiority margin). Shown in a patient population with proven, probable or possible IA (ITT population = 575; aged 13 years or older; across 91 study sites in 26 countries) randomly assigned to either posaconazole or voriconazole for up to 12 weeks.

allo-HSCT, allogeneic haematopoietic stem-cell transplantation; ECIL, European Conference on Infections in Leukaemia; ECMM, European Confederation of Medical Mycology; ERS, European Respiratory Society; ESCMID, European Society of Clinical Microbiology and Infectious Diseases; IA, invasive aspergillosis; IDSA, Infectious Diseases Society of America; ITT, intention to treat; L-AmB, liposomal amphotericin B; TRAE, treatment-related adverse event.

1. Jenks JD, *et al. Drug Des Devel Ther.* 2018;12:1033–44; 2. Cresemba® Summary of Product Characteristics. Updated 29 Jul 2022. Available at: https://www.ema.europa.eu/en/documents/product-information/cresemba-epar-product-information_en.pdf. Last accessed 20 September 2022; 3. VFEND® Summary of Product Characteristics. Updated 6 May 2022. Available at: https://www.ema.europa.eu/en/documents/product-information/vfend-epar-product-information_en.pdf. Last accessed 20 September 2022. 4. AmBisome® Summary of Product Characteristics. Updated 14 Nov 2019. Available at: https://www.medicines.org.uk/emc/product/1022/smpc. Last accessed 20 September 2022. 5. Noxafil® Summary of Product Characteristics. Updated 22 Feb 2022. Available at: https://www.ema.europa.eu/en/documents/product-information/noxafil-epar-product-information_en.pdf. Last accessed 20 September 2022; 6. Maertens J, *et al. Lancet.* 2021;397(10273):499–509.

Farmacologie azoli

	Voriconazole	Posaconazole	Isavuconazole
Bioavailability	>90% (but lower in children)	OS: Variable, saturable oral absorption; food intake, especially with high fat content, increases oral bioavailability; gastric acid inhibitors decrease drug absorption	>95% (no significant food effect has been found with oral administration). Isavuconazonium sulphate, a water-soluble prodrug that is rapidly and almost completely (99%) converted to isavuconazole via plasma esterases[2]
Protein binding	58%	>98%	>98%
Volume of distribution	4.6 L/kg	5–25 L/kg	4.4–7.7 L/kg
Time to reach steady state	2 days	7–10 days	14 days
Tissue penetration			
- Lung tissue	Good	Good	Good
- Cerebrospinal fluid	Good	Poor	Poor in CSF, good in brain
- Vitreous humour	Good	Limited	Good
- Urine	<2%	<0.1%	ND
Metabolism	Hepatic via CYP2C19, 2C9 and CYP3A4	Hepatic by UGT1A4	Hepatic via CYP3A4
Half-life	6 hours (but non-linear PK)	25–35 hours	56–104 hours
Primary route of elimination	Renal (all metabolites)	Faeces	Faeces

- 1. Seyedmousavi S, *et al. Expert Rev Anti Infect Ther.* 2015;13(1):9–27;
2. Cresemba® Summary of Product Characteristics, 2018.

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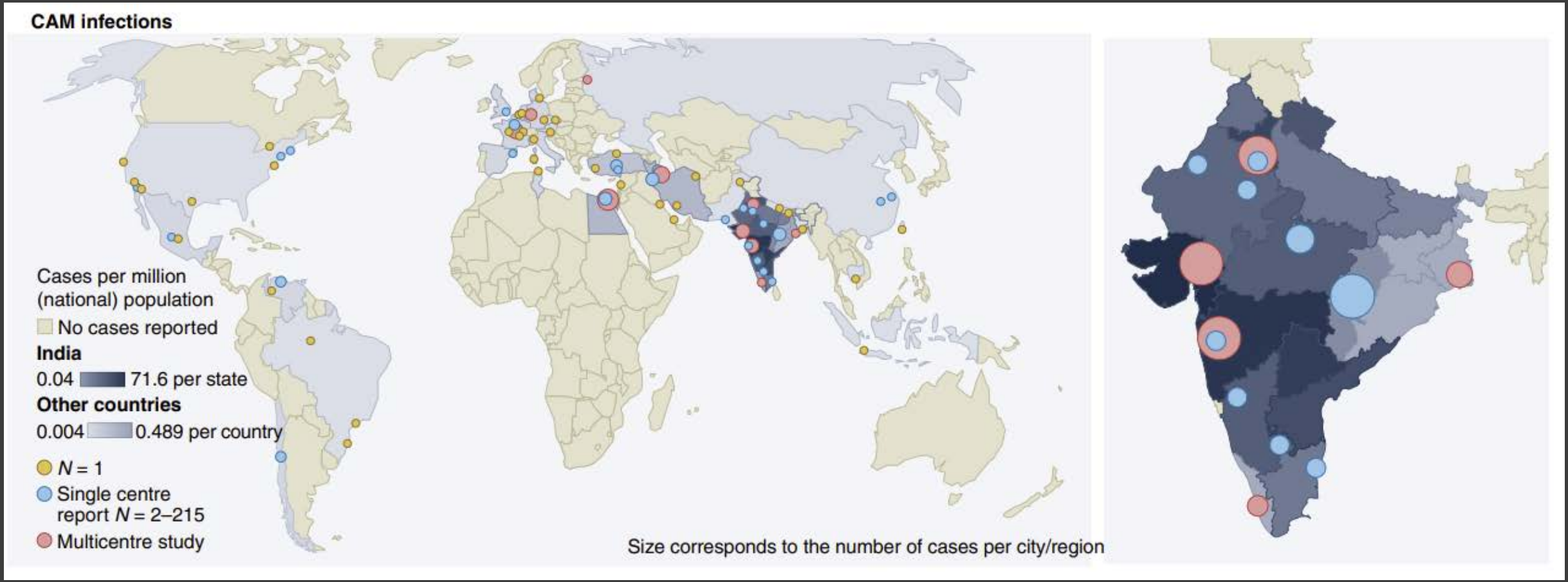
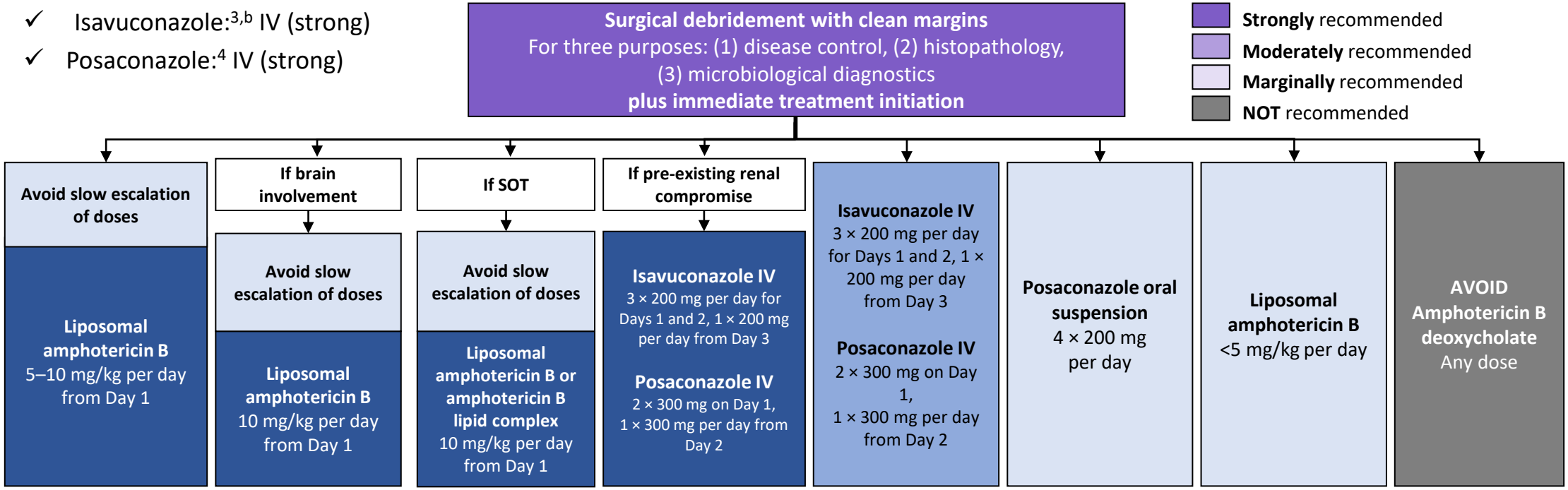


Global distribution of COVID-19-associated mucormycosis

- CAM, COVID-19-associated mucormycosis.
- Hoenigl M, *et al. Nat Microbiol*. 2022;7(8):1127–40.

Mucormycosis: ECMM/MSG ERC recomandari initiere tratament[a]

- Prima linie[1] (luand in calcul localizare, disfunctie renala)
  - Amphotericin B liposomala[2] IV 5–10 mg/kg (strong recommendation)
  - Afectare renala:
    - ✓ Isavuconazole:[3,b] IV (strong)
    - ✓ Posaconazole:[4] IV (strong)



[a]These guidelines may differ from your local guidelines; [b]Isavuconazole is indicated for the treatment of mucormycosis in patients for whom amphotericin B is inappropriate.[3]

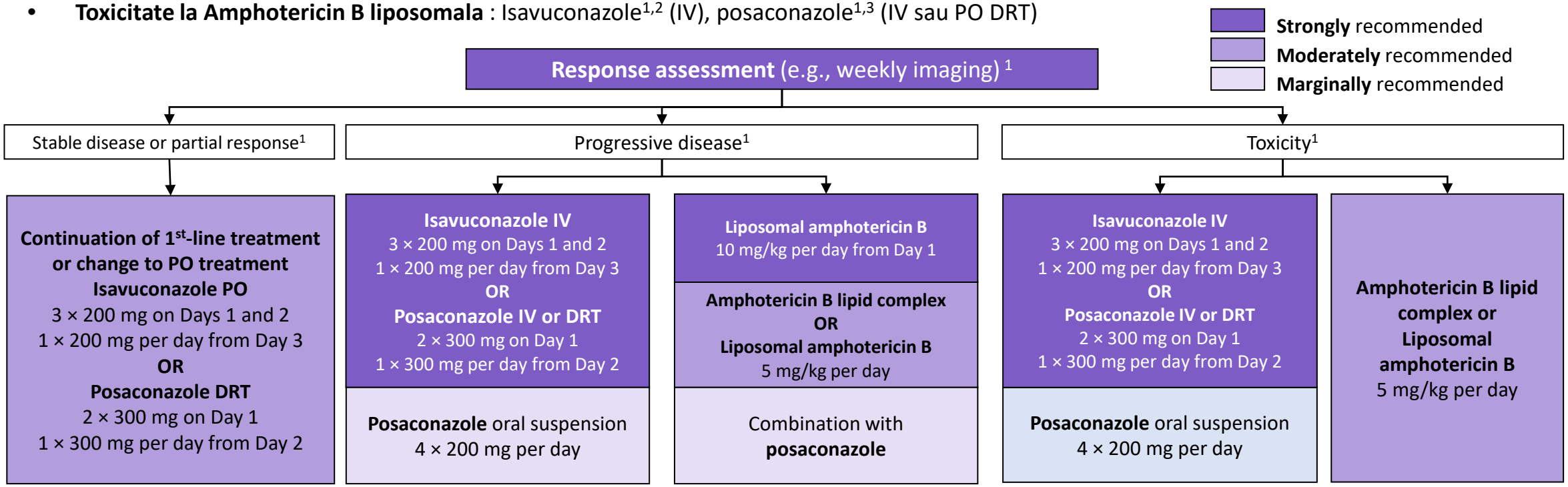
ECMM, European Confederation of Medical Mycology; IV, intravenous; MSG ERC, Mycoses Study Group Education and Research Consortium; SOT, solid organ transplantation.

1. Cornely OA, *et al. Lancet Infect Dis.* 2019;19(12):e405–21; 2. AmBisome® Summary of Product Characteristics. Updated 14 Nov 2019. Available at: https://www.medicines.org.uk/emc/product/1022/smpc. Last accessed 20 September 2022; 3. Cresemba® Summary of Product Characteristics. Updated 29 Jul 2022. Available at: https://www.ema.europa.eu/en/documents/product-information/cresemba-epar-product-information_en.pdf. Last accessed 20 September 2022; 4. Noxafil® Summary of Product Characteristics. Updated 22 Feb 2022. Available at: https://www.ema.europa.eu/en/documents/product-information/noxafil-epar-product-information_en.pdf. Last accessed 20 September 2022.

Mucormycosis: ECMM/MSG ERC recomandari de tratament - faza de continuare [a]

Bazat pe evolutia bolii si pe aparitia toxicitatii (efecte secundare):[1]

- **Infwctiw stabilizata sau raspuns partial**: Isavuconazole[1,2] (PO) sau posaconazole[1,3] (PO DRT)
- **Progresia bolii**: Isavuconazole[1,2] (IV), posaconazole[1,3] (IV) sau liposomal amphotericin B[1,4]
- **Toxicitate la Amphotericin B liposomala** : Isavuconazole[1,2] (IV), posaconazole[1,3] (IV sau PO DRT)



[a]These guidelines may differ from your local guidelines. DRT, delayed-release tablet; ECMM, European Confederation of Medical Mycology; IV, intravenous; MSG ERC, Mycoses Study Group Education and Research Consortium; PO, oral.

1. Cornely OA, *et al. Lancet Infect Dis.* 2019;19(12):e405–21; 2. Cresemba® Summary of Product Characteristics. Updated 29 Jul 2022. Available at: https://www.ema.europa.eu/en/documents/product-information/cresemba-epar-product-information_en.pdf. Last accessed 20 September 2022; 3. Noxafil® Summary of Product Characteristics. Updated 22 Feb 2022. Available at: https://www.ema.europa.eu/en/documents/product-information/noxafil-epar-product-information_en.pdf. Last accessed 20 September 2022; 4. AmBisome® Summary of Product Characteristics. Updated 14 Nov 2019. Available at: https://www.medicines.org.uk/emc/product/1022/smpc. Last accessed 20 September 2022.

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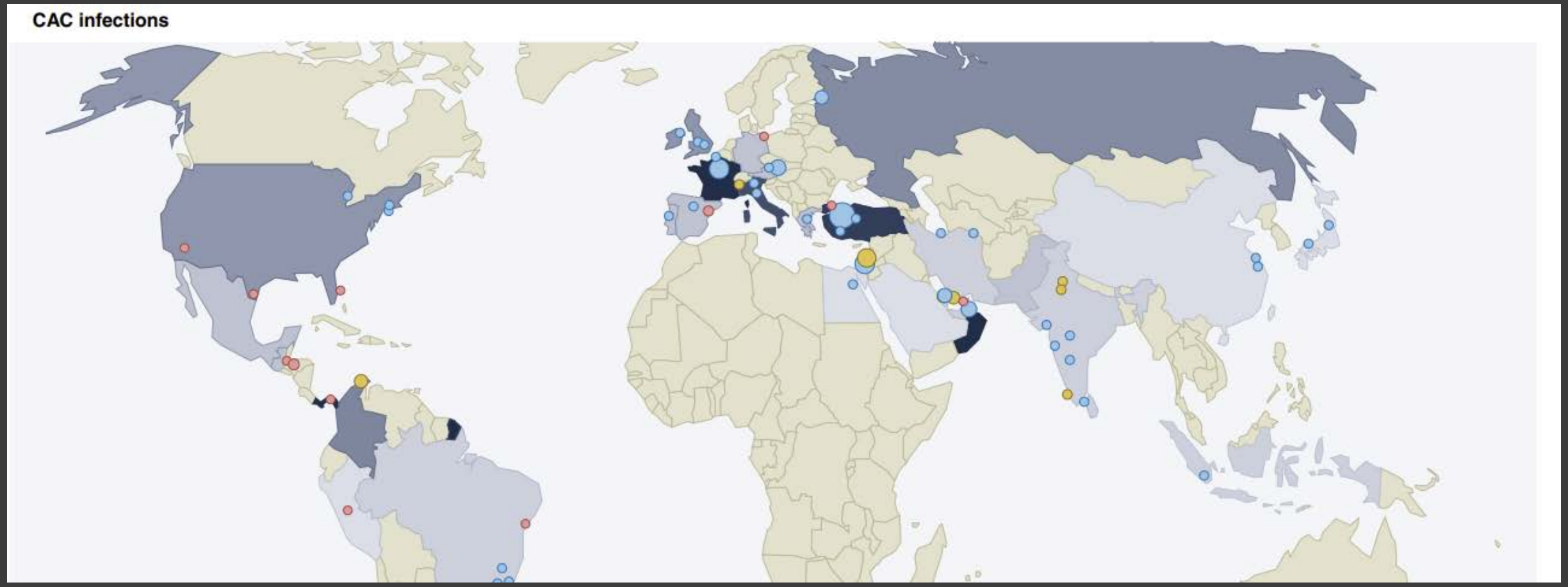

Global distribution of COVID-19-associated candidiasis

- CAC, COVID-19-associated candidiasis.
- Hoenigl M, *et al. Nat Microbiol*. 2022;7(8):1127–40.

Consensus guidelines for the diagnosis and management of invasive candidiasis in haematology, oncology and intensive care settings, 2021

Caitlin Keighley, Louise Cooley, Arthur J. Morris, David Ritchie, Julia E. Clark, Peter Boan, Leon J. Worth,

" CITE

https://doi.org/10.1111/imj.15589

Published in Internal Medicine Journal

- Immunocompromised state
  - Haematological malignancy
  - Neutropenia
  - Inherent or primary immune deficiency
  - Solid organ or haemopoietic stem cell transplantation
  - Chemotherapeutic agents, particularly those associated with mucositis
  - Receipt of corticosteroid therapy
- Gastrointestinal tract disease
  - Gastrointestinal malignancy
  - Liver disease
  - Recent surgery, particularly abdominal or hepatobiliary
- Intensive care unit admission
- Intravenous agents
  - Receipt of total parenteral nutrition
  - Transfusion
  - Intravenous drug use
- Presence of indwelling medical devices
  - Central venous catheter (CVC)
  - Indwelling urinary catheter
  - Tenckhoff catheter
- Extremes of age
  - Elderly
  - Neonates
  - Very low birthweight infants
- Receipt of broad-spectrum antibiotic agent/s
- Trauma and burns patients

Species-specific risk factors include association of *C. parapsilosis* complex infection with the presence of a CVC, association of *C. tropicalis* with haematology populations, and association of *C. auris* with admission to a healthcare facility with known *C. auris* outbreak, presence of indwelling medical devices and the use of antifungal agents.

Factori de risc pt candidiaza invasiva

Consensus guidelines for the diagnosis and management of invasive candidiasis in haematology, oncology and intensive care settings, 2021

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https://doi.org/10.1111/imj.15589

Published in Internal Medicine Journal

Table 4 Performance of non-culture-based tests to screen for *Candida* infection in adults in low-prevalence settings (adapted from Johnson *et al.*[60])

	Serum 1-3-β-D-Glucan	Serum mannan/anti-mannan	Blood T2Candida	Blood PCR *Candida* spp.
Sensitivity	80%	58%	91%	73%
Specificity	80%	93%	98%	95%
PPV†	9%	13%	0.5%	17%
NPV†	>99%	99%	>99%	99%

†2% prevalence. NPV, negative predictive value; PCR, polymerase chain reaction; PPV, positive predictive value.

Alegerea celui mai potrivit antifungic empiric pt pacient din terapie intensiva - Factori de luat in considerare

Factori	Rationament
Stabilitatea clinica a pacientului	Actiune fungicida (ex. echinocandin) – preferat daca pacient instabil
Expunere anterioara la antifungice	Utilizarea anterioara si prelungita a azolilor sau echinocandine se asocieaza cu cresterea riscului de rezistenta
Colonizari fungice	Evaluarea riscului de infectie cu tulpini de *Candida* cu potential de rezistenta
Epidemiologia locala	Evaluarea riscului de infectie cu tulpini de *Candida* cu potential de rezistenta *(ex C. auris)*
Locul de infectie si eventuala diseminare	Echinocandine: concentratii mici in LCR, lichid sinovial, umoarea apoasa, creier si urina Amphotericin B: renal penetration of AmBd greater than L-AMB
Medicatie asociata	Triazoles: inhibia mai multe izoenzime ale cytochrome P450 - multiple interactiuni medicamentoase. Atentie asociere cu medicatie hepato-toxic si cardio-toxic. Amphotericina: Atentie la asociere cu nefrotoxice / medic ce afecteaza balanta electrolitica
Insuficiente de organ	Evaluarea antifungicului si a dozei in prezenta insuficientei renale sau hepatice.
Prezenta de CRRT/ECMO	Evaluarea antifungicului si a dozei in prezenta daca CRRT/ECMO
Monitoriz. concentratiei serice terap (TDM)	Esential pt voriconazol si flucytosine (eficienta si efecte secundare)

1.AmBd amphotericin deoxycholate, *ECMO* extracorporeal membrane oxygenation, *L-AMB* liposomal amphotericin, *RRT* renal replacement therapy

Logan C, et al. Intensive Care Med (2020) 46:2001–2014 https://doi.org/10.1007/s00134-020-06240-x

Consensus guidelines for the diagnosis and management of invasive candidiasis in haematology, oncology and intensive care settings, 2021

Caitlin Keighley, Louise Cooley, Arthur J. Morris, David Ritchie, Julia E. Clark, Peter Boan, Leon J. Worth,

CITE

https://doi.org/10.1111/imj.15589

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Table 5 Recommended first-line antifungal therapy for adult patients with candidaemia prior to susceptibility testing

Clinical state	Antifungal agent (SoR/QoE)											
	Azole				Echinocandin						Amphotericin B formulation			
	Fluconazole		Voriconazole		Anidulafungin		Caspofungin		Micafungin		L-AMB†		D-AMB	
Critically ill or neutropenic	B	II	NR		A	I	A	I	A	I	B	I	C	II
Clinically stable with no neutropenia or risk factors for azole resistance	B	II	C	II	A	I	A	I	A	I	B	II	C	II

†Liposomal amphotericin B has equivalent efficacy to echinocandins (though a higher rate of toxicity) and is an alternative agent in high-risk patients where echinocandins cannot be used or resistance suspected.[25,84,85] D-AMB, amphotericin B deoxycholate; L-AMB, liposomal amphotericin B; NR, not recommended; QoE, quality of evidence; SoR, strength of recommendation.

Table 10 Non-pharmacological management of candidaemia

Management	Recommendation	SoR	QoE
Vascular catheter removal	Early removal of vascular catheters where possible	A	I
	When catheter removal is not possible, an echinocandin or lipid formulation of amphotericin B is preferred for biofilm penetration	C	III
Infectious diseases consultation	All patients with candidaemia should receive an infectious diseases consultation	A	I
Echocardiography	TOE is preferred to TTE in patients with prosthetic heart valves and candidaemia	A	II
	Echocardiogram should be performed in in all patients with candidaemia and risk factors for endocarditis (e.g. prosthetic heart valves, implantable cardiac device, valvular heart disease, persistent positive blood cultures, new heart murmur, heart failure, embolic phenomena, prolonged presence of CVC)	B	III
	Echocardiogram should be considered for all patients with candidaemia	B	III
Ophthalmological review	Ophthalmological examination should be considered in all patients with candidaemia	B	III
	Ophthalmological examination is recommended for all neonates with candidaemia or candiduria	A	III
Bundles	Multimodal strategies for management of candidaemia should be implemented in healthcare settings	A	II
Antifungal stewardship	Healthcare facilities managing patients with invasive candidiasis and candidaemia should implement an antifungal stewardship programme inclusive of antifungal post-prescription review	A	II

CVC, central venous catheter; QoE, quality of evidence; SoR, strength of recommendation.

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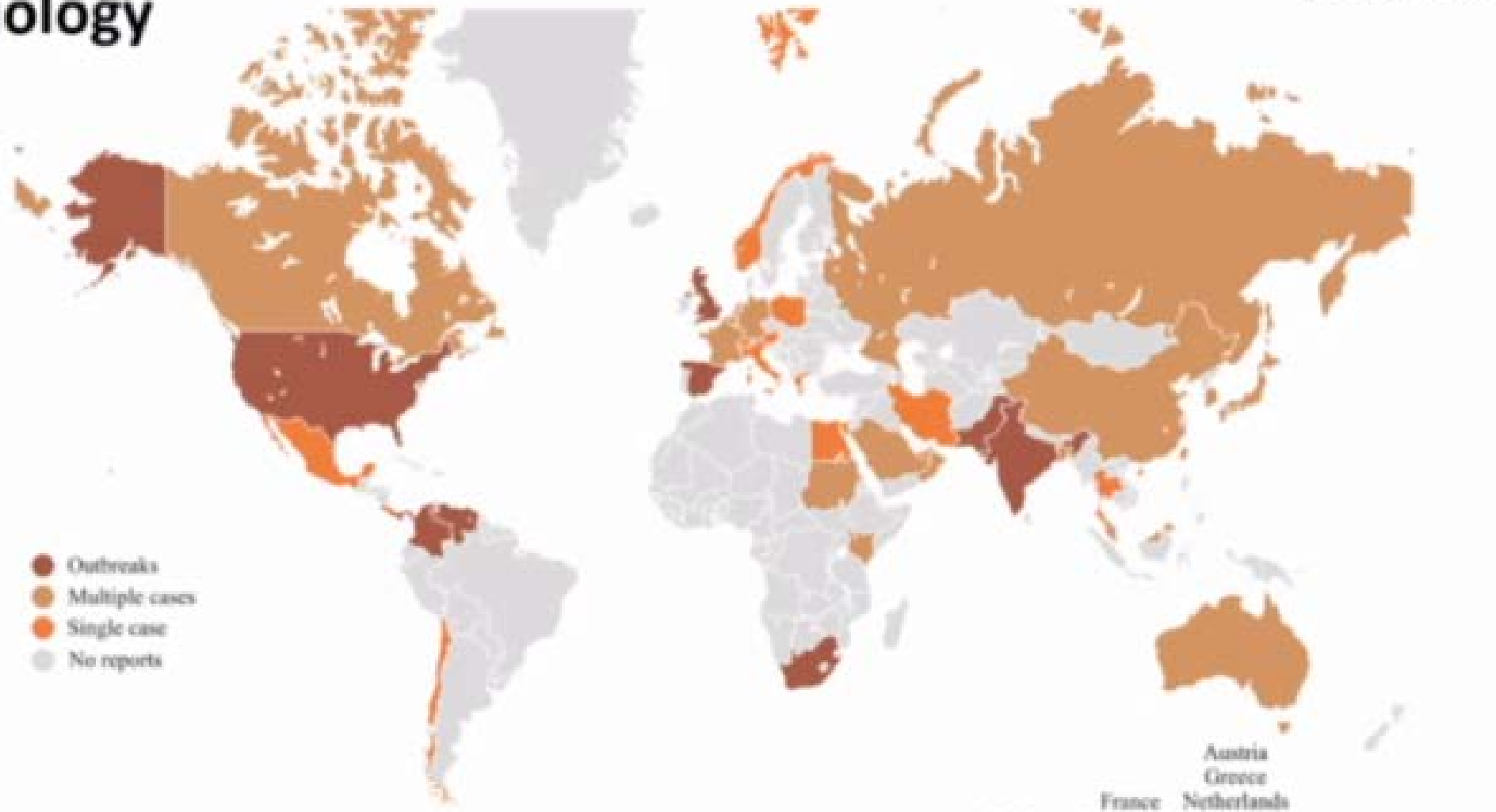
Plan prezentare

- Generalitati
- Stewardship antifungic
- Tratamentul antifungic
- Patologie fungica
  - Aspergiloza pulmonara
  - Mucormicoza
  - Candidiaza invaziva
    - *C Auris*
- Concluzii

Epidemiology

J Med Microbiol 2021; 70(3): 001318



South Korea	Japan	Pakistan	South Africa India	Kenya	China	Venezuela Singapore	Colombia USA UK	Israel Kuwait	Australia Germany	Belgium Norway Spain Russia Oman Panama	France Switzerland Canada Taiwan UAE Egypt Saudi Arabia	Austria Greece Netherlands Poland Chile Bangladesh Malaysia Thailand Iran	Italy Costa Rica Sudan	Mexico
1996	1997	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020

C. auris – o noua amenintare infectioasa

- Echinocandine / amphotericina B liposomala

Candida auris and Nosocomial Infection

Sweety Dahiya [1], Anil K Chhillar [1], Namita Sharma [1], Pooja Choudhary [1], Aruna Punia [1], Meenakshi Balhara [1], Kumar Kaushik [2], Virinder S Parmar [2]

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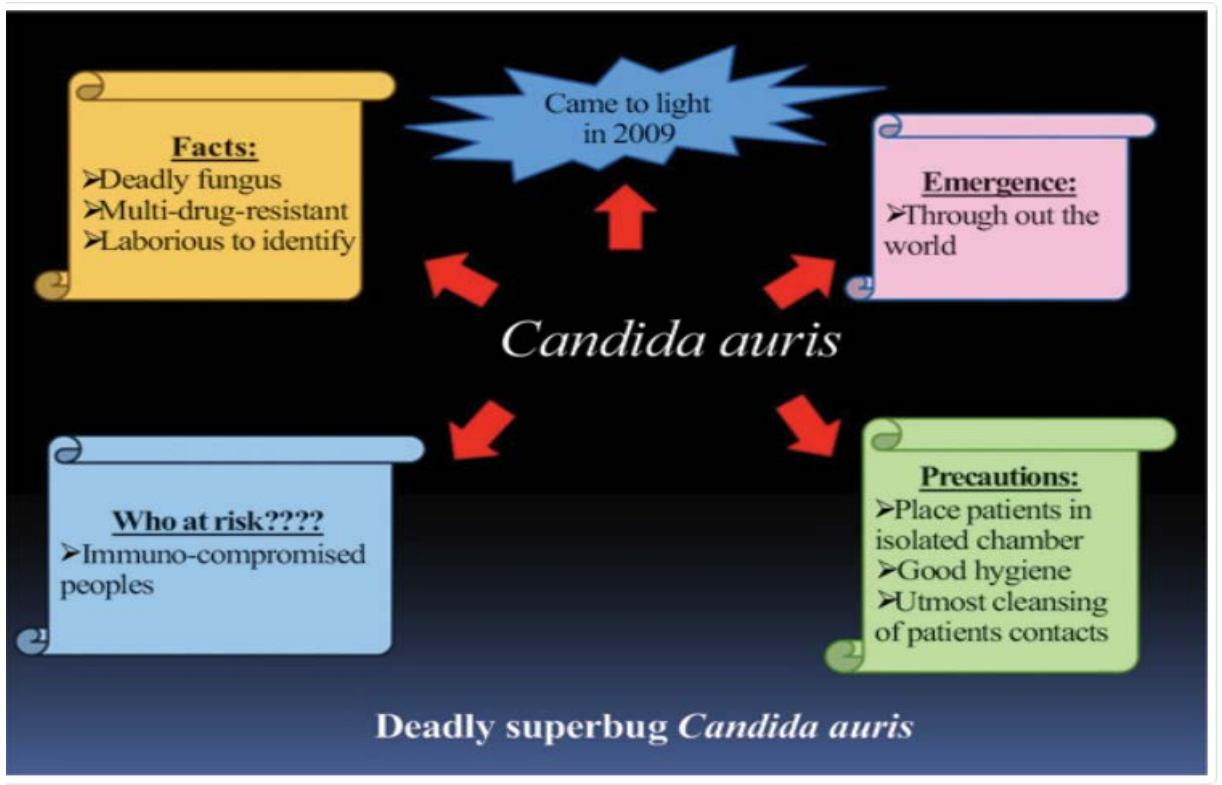
PMID: 31549952 DOI: 10.2174/1389450120666190924155631



Fluconazole	90% resistant
Voriconazole	Elevated minimum inhibitory concentration (MIC) in 50% of isolates
Amphotericin B	Variable susceptibility; 15–30% of the isolates exhibit high (>2 μg/mL) MICs
Echinocandin	2–8% resistant
Multidrug resistant	50% resistant to ≥2 antifungal classes
All classes resistant	4%
Indian intensive care units	Fluconazole, 58.1% (resistant); amphotericin B, 13.5%; caspofungin, 9.5% (high MIC); 16.2% multidrug resistant

Du H et al. PLoS Pathog. 2020

AST News Update June 2022: Hot Topic

7/11/2022

Candida auris Update: Method Variability with Amphotericin B Susceptibility Testing

Priyanka Uprety, Roche Diagnostics, Indianapolis, IN
Shawn Lockhart, Centers for Disease Control and Prevention, Atlanta, GA

Candida auris is an emerging yeast that is causing numerous outbreaks in health care settings, and life-threatening infections in patients worldwide.[1] Most isolates of *C. auris* are multidrug resistant. In the United States, 85% of isolates have fluconazole minimal inhibitory concentration (MIC) values >64 µg/mL, 33% have amphotericin B MIC values >1 µg/mL, and 1-3% have FKS mutations indicating echinocandin resistance (CDC, unpublished data). Although an echinocandin is the Infectious Diseases Society of America (IDSA)-recommended initial therapy for *Candida* bloodstream infections, echinocandin resistance is increasing in *C. auris*[2] (CDC, unpublished data). Treatment with liposomal amphotericin B could be considered when an isolate has both fluconazole MIC >32 µg/mL and an echinocandin MIC >2 µg/mL.

Amphotericin B susceptibility results for *C. auris* should be interpreted with caution, particularly for treatment of multidrug-resistant *C. auris* infections, and laboratories should share this note of caution with providers when reporting amphotericin B.

There are no breakpoints (for any antifungals) specifically for *C. auris*. Furthermore, there are no studies that show a direct correlation between MIC values and clinical outcomes for amphotericin B and any species of *Candida*

Noi agenti antifungic cu efect contra *Candida sp.*

Ibrexafungerp

- Oral, derivat semisintetic de enfumafungin – clasa triterpenoid – o noua clasa
- Inhiba sinteza de BD-glucane
- Activ si pe *Candida spp* cu R la echinocandine - inclusiv *C. auris*
- aprobat FDA – trt VVC 06/21
- Studiu cl de faza 2 ca optiune oral stepdown in candidemie, si de faza 2 si 3 (alte I)

Fosmanogepix

- Primul agent din clasa, spectru larg, inclusiv pe tulpinile rezistente de *Candida spp.* (ex *C. auris)* - nu *C.krusei*
- Mecanism de actiune nou (tintind enzyme Gwt1), ce afecteaza membrana celulara – peretele agentului fungic , cu actiune pe biofilm si previne formarea filamentelor.
- Studii cl de faza 2 pt tratamentul de 1 ln al candidemia

Rezafungin

- Echinocandin de gen 2, T1/2 lung: administrare 1 data /sapt
- Actiune rapida in-vitro pe *Candida sp* rezistente la azoli, inclusiv *C. auris*
- Studii faza 3 multicentrice randomizate

Martin Hoenigl et al, The Antifungal Pipeline: Fosmanogepix, Ibrexafungerp, Olorofim, Opelconazole, and Rezafungin, Drugs oct. 2021; 81(15): 1703–1729.

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    - *C Auris*
- Concluzii

Concluzii

- Domeniu vast – patologie a pacientului imunosupresat din diverse cauze
- Ghiduri ce trebuie adaptate la pacient
- Tratament in continua dezvoltare
- Rezistenta la medicatia antifungica in evolutie
- Emergenta agenti fungici noi cu risc mare de infectii nosocomiale
- Mortalitate crescuta

→ Necesitatea implementarii Stewarship antifungic