Mercoledì 8 ottobre

Infezioni: Ricerca e clinica

Chair: L.Dalfino, G. Montrucchio

14:30 – 15:10 Infezioni da Muffe in terapia intensiva: pandemia silente *B. Viaggi*

15:10 – 15:30 Candida Auris: sfide emergenti nella sanità italiana *R. Fumagalli*

15:30 – 16:10 Malattie infettive e Terapia intensiva a braccetto. Risultati degli studi su PROSAFE: BLOOD-ICU, VAP study, Candidemie, e Infezioni addominali complesse *M. Colaneri, E. Palomba, M. Offer*

16:10 – 16:30 Dati Prosafe: Multiresistenze ed outcome di VAP da pseudomonas *S. Bettoni, I. Magnesa*

Coffee Break

Progetti di ricerca e collab. internazionali

Chair: L. Pisani

17:00 – 17:15 S/F - P/F *D.Magatti, T. Tonetti*

17:15– 17:30 ETT ARDS *S.Finazzi, M. Ranieri*

17:30 – 17:45 Validazione score SOFA *J. Salluh*

17:45 – 18:00 Validazione score SMS – ICU *A. Tracy*

18:00 – 18:15 The differences in ICU efficiency between The Netherlands and Italy A registry-based observational study *D.Dongelmans*

18:15 - 18:30 Dashboard MargheritaTre *D.Magatti*

Progetti di ricerca Regionali

Chair: C. Olivieri, S.Finazzi

18:30 – 18:45 Nuovi indicatori *S. Conti, A. Lavetti*

18:45 – 19:00 Progetto StART *S. Conti, A. Lavetti*

Cena

21:00 – 22:30 Assemblea dei Soci - O.D.G: Gestione del consenso informato negli studi GiViTi

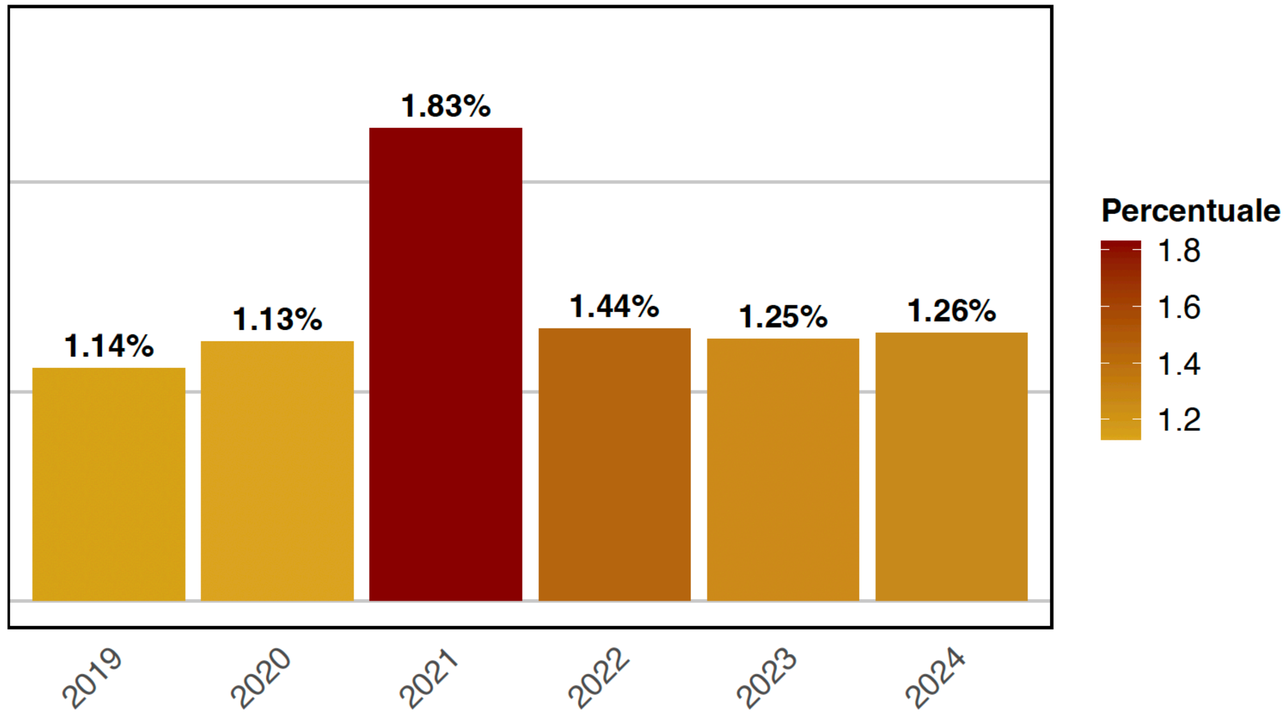
Sara Bettoni
Laboratory of Clinical Data Science
Mario Negri Institute

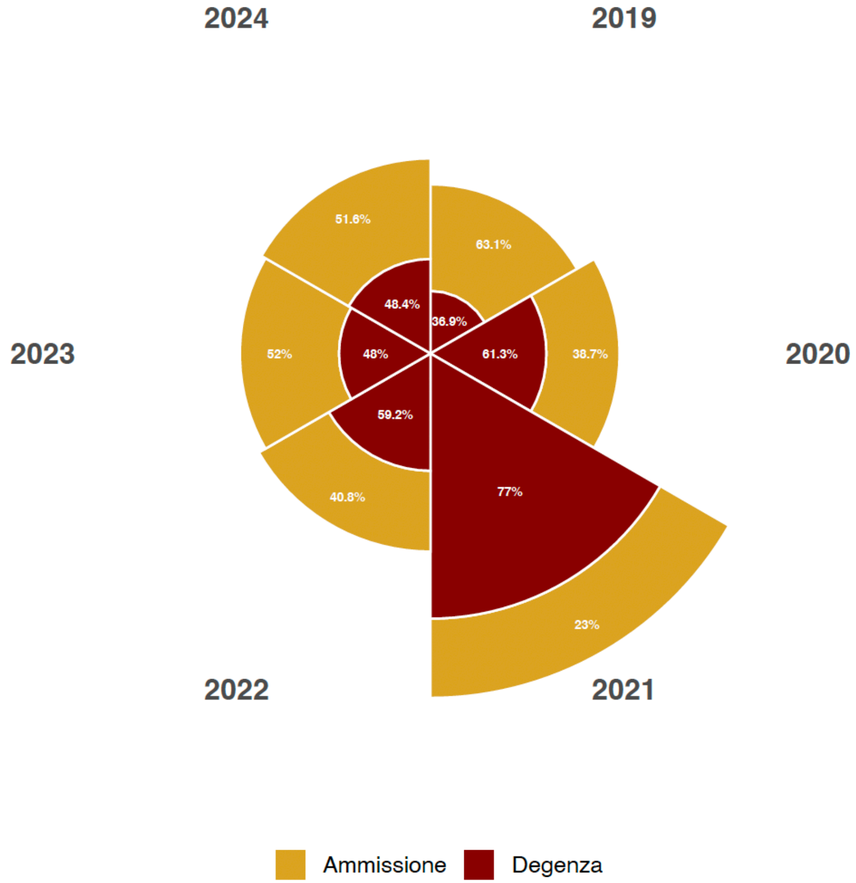
Bruno Viaggi
Unit Infezioni Correlate all'assistenza
del Paziente Critico
Dipartimento di Anestesia
NeuroRianimazione AOU Careggi

Dichiarazione su potenziali conflitti di interesse
Consulenze, partecipazione advisory boards, speaker's bureau, contratti/ contributi di ricerca e di eventi studio:

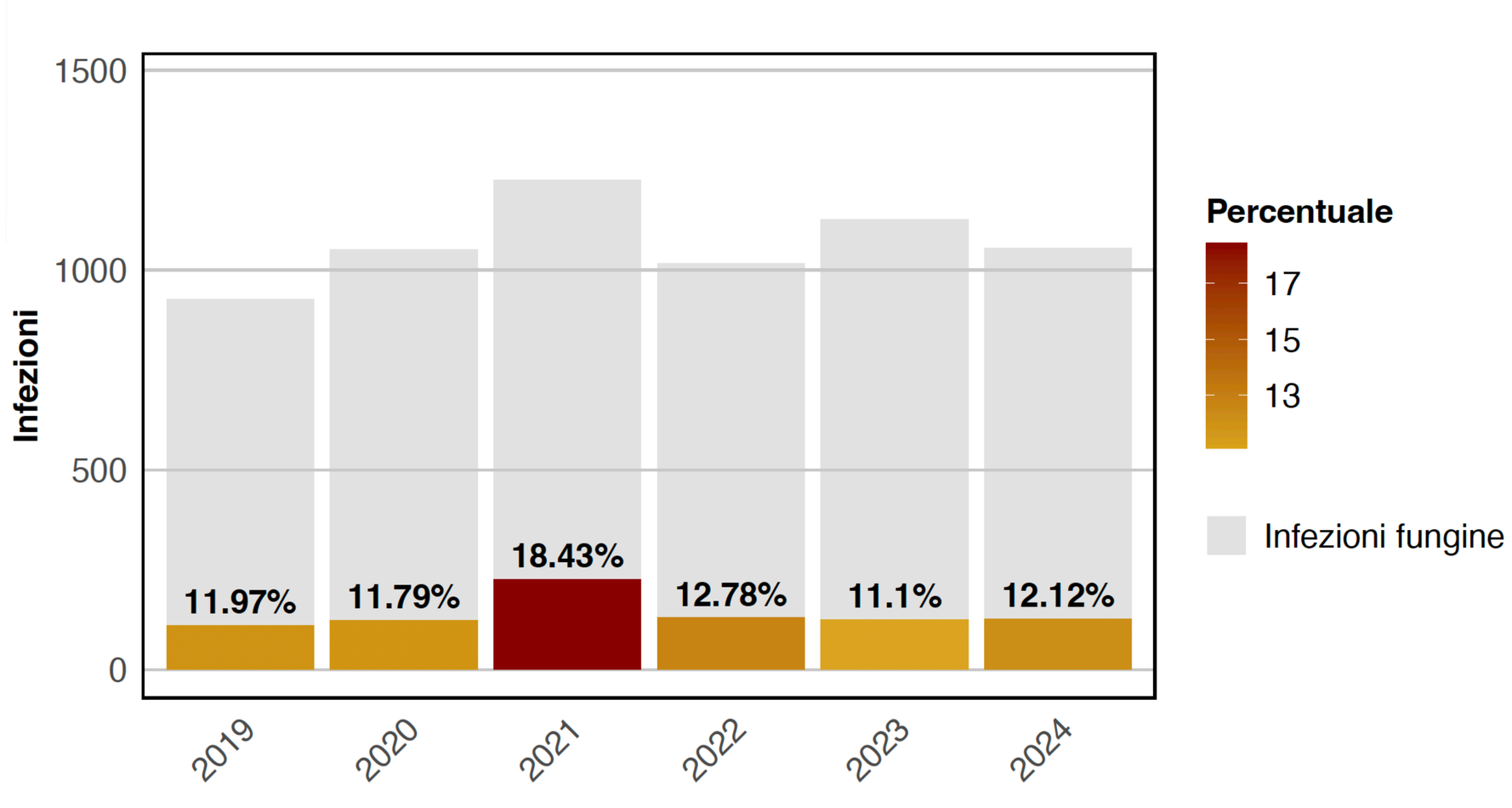
Abbott, Accelerate Diagnostics, Ada, Advanz Pharma, Alifax, Angelini, Becton Dickinson, Bellco, Biomerieux, Biotest, Cepheid, Correvio, Dasit, Diasorin, Emmegi Diagnostica, Gilead, InfectoPharm, Menarini, MercK Sharp & Dohme, Nordic Pharma, Pfizer, Shionogi, Thermofischer Scientific, Viatris

Infezioni da Aspergillo 2019-2024

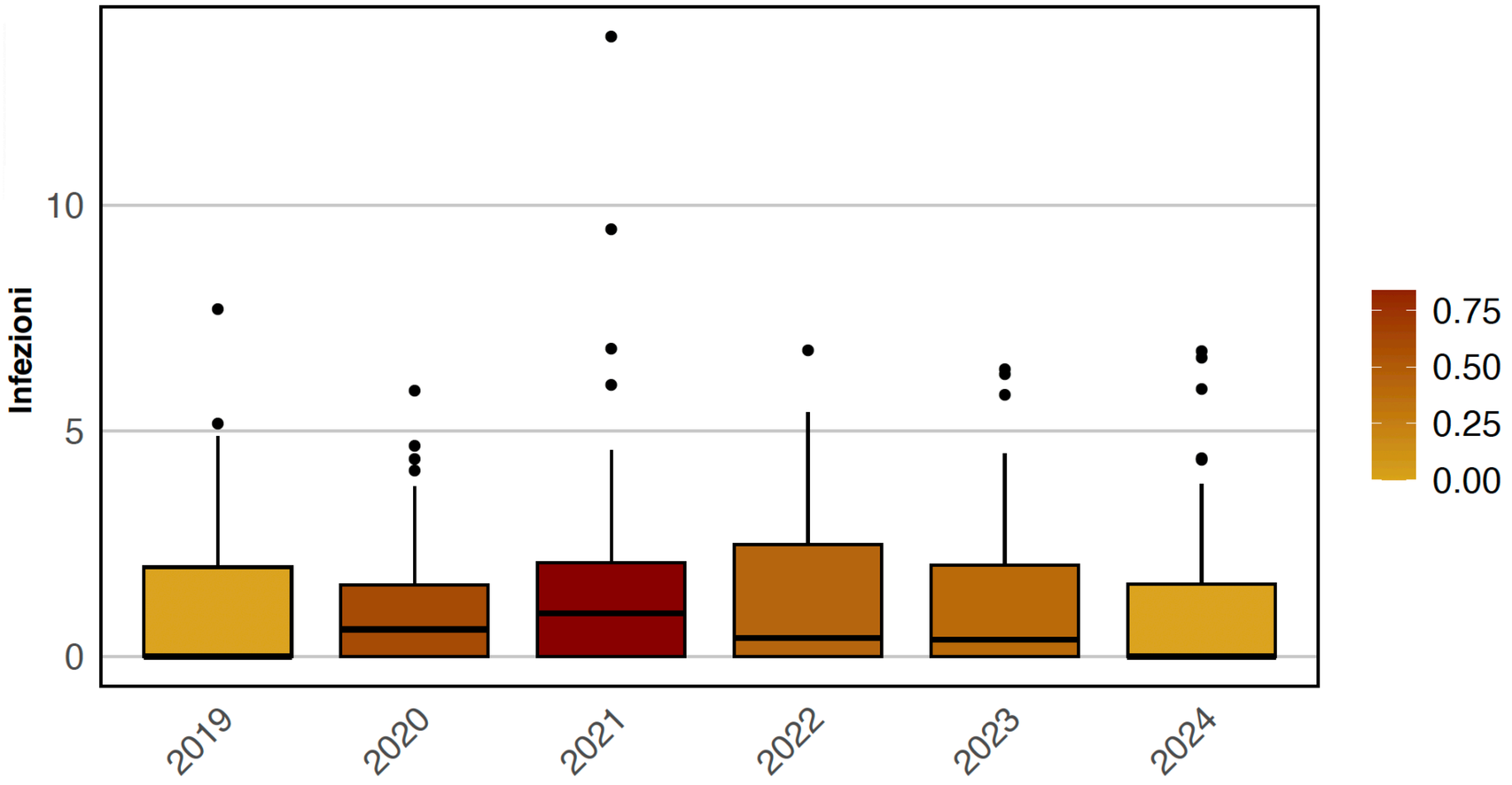




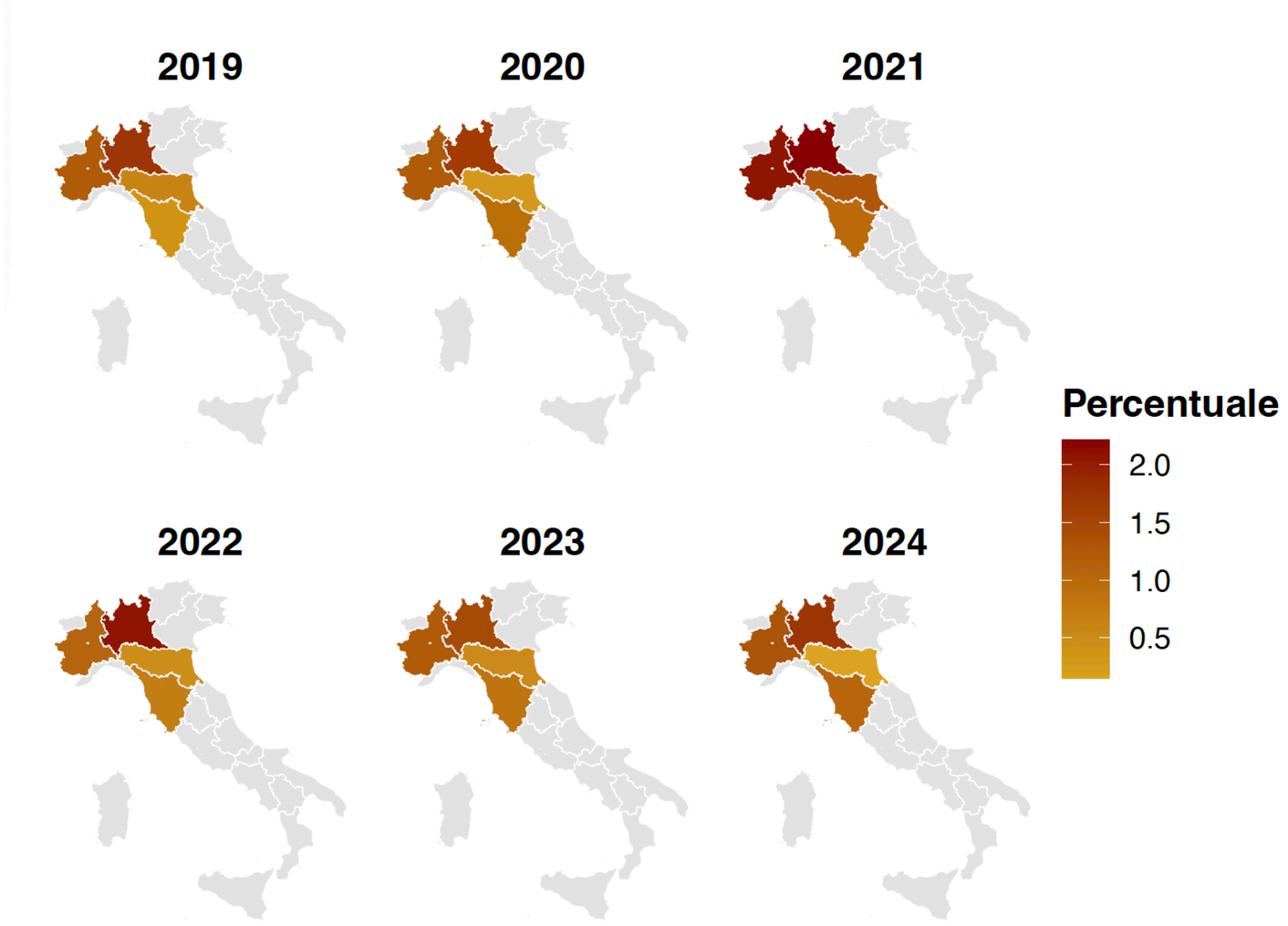
Infezioni da Aspergillo 2019-2024



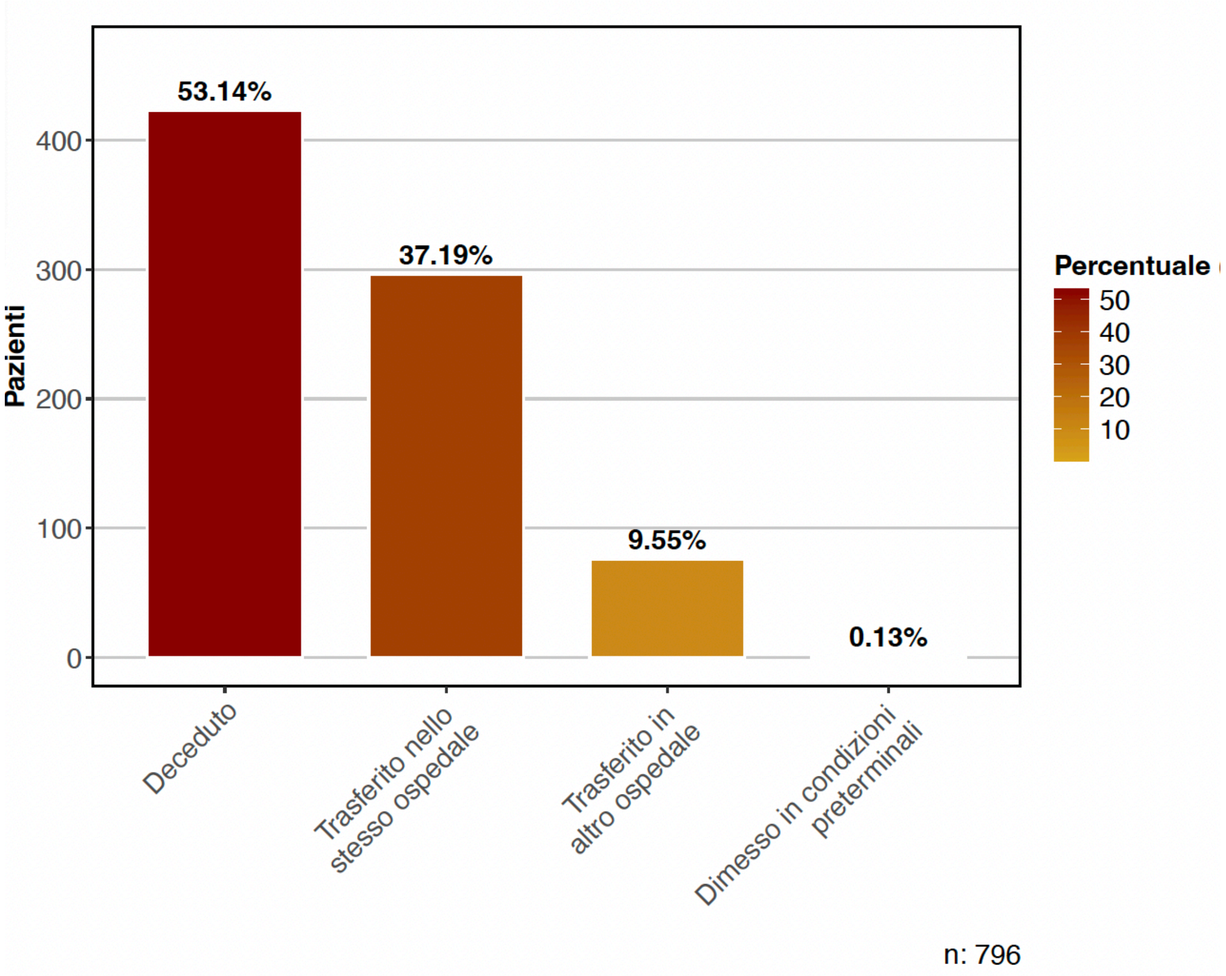
Distribuzioni delle infezioni da Aspergillo per centro



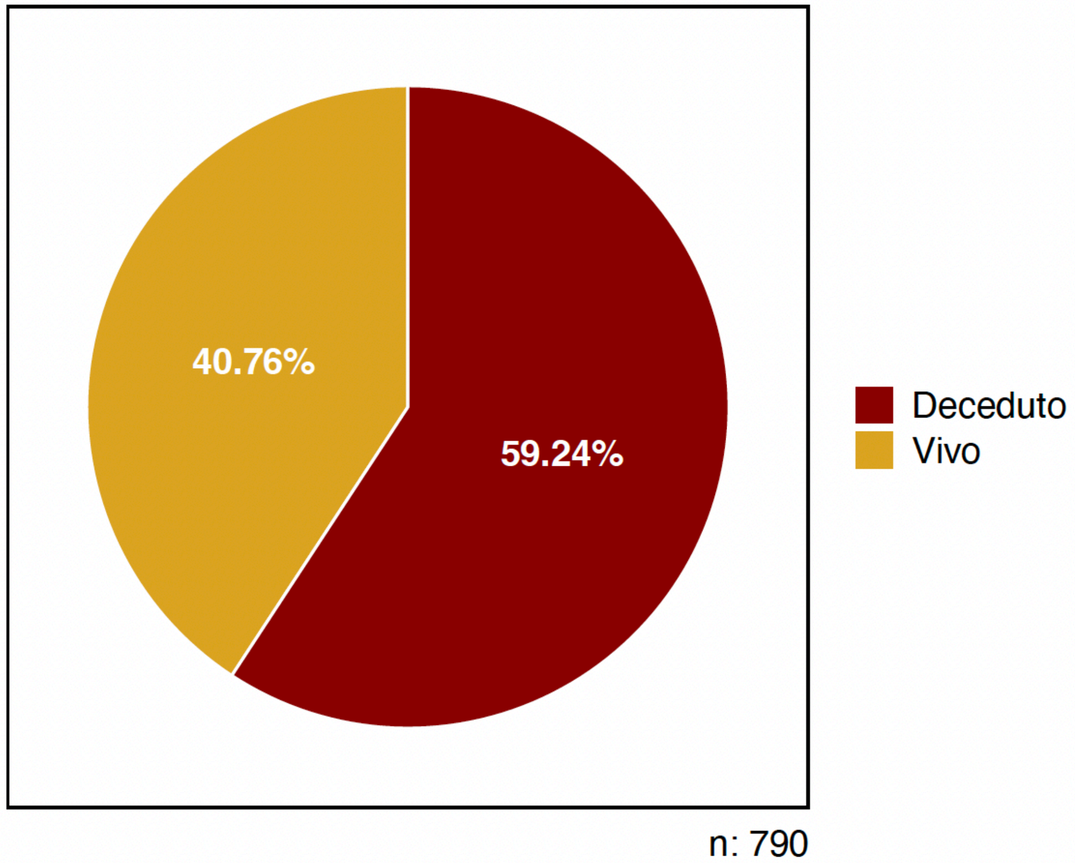
Infezioni da Aspergillo per regione



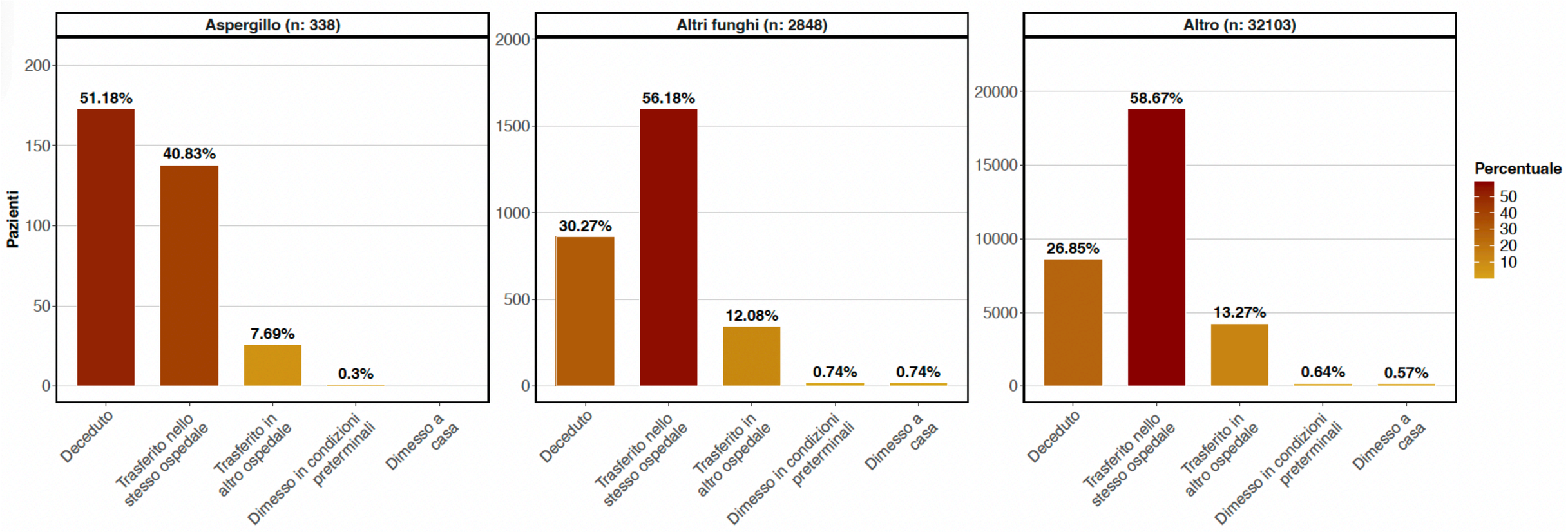
Outcome TI pazienti infetti da Aspergillo



Outcome ospedaliero pazienti infetti da Aspergillo

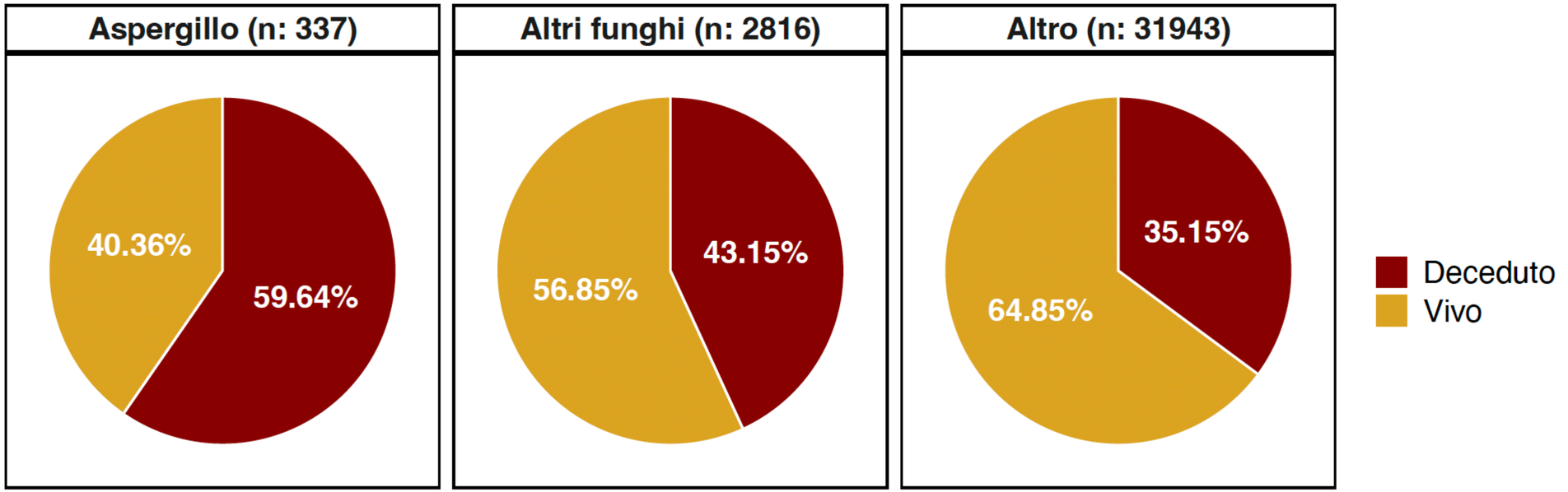


Outcome TI pazienti infetti in ammissione



Aspergillo (n=*339*)	Altri funghi (N=*2854*)	Altro (N=*32155*)
Almeno un'infezione in ammissione da *Aspergillo*	Non infetto in ammissione da *Aspergillo*, ma con almeno un'infezione da un altro fungo (*Candida* spp, Altri funghi, *Pneumocystis jirovecii*)	Non infetto in ammissione da funghi, ma con almeno un'infezione accertata in ammissione da batteri/virus

Outcome ospedaliero pazienti infetti in ammissione



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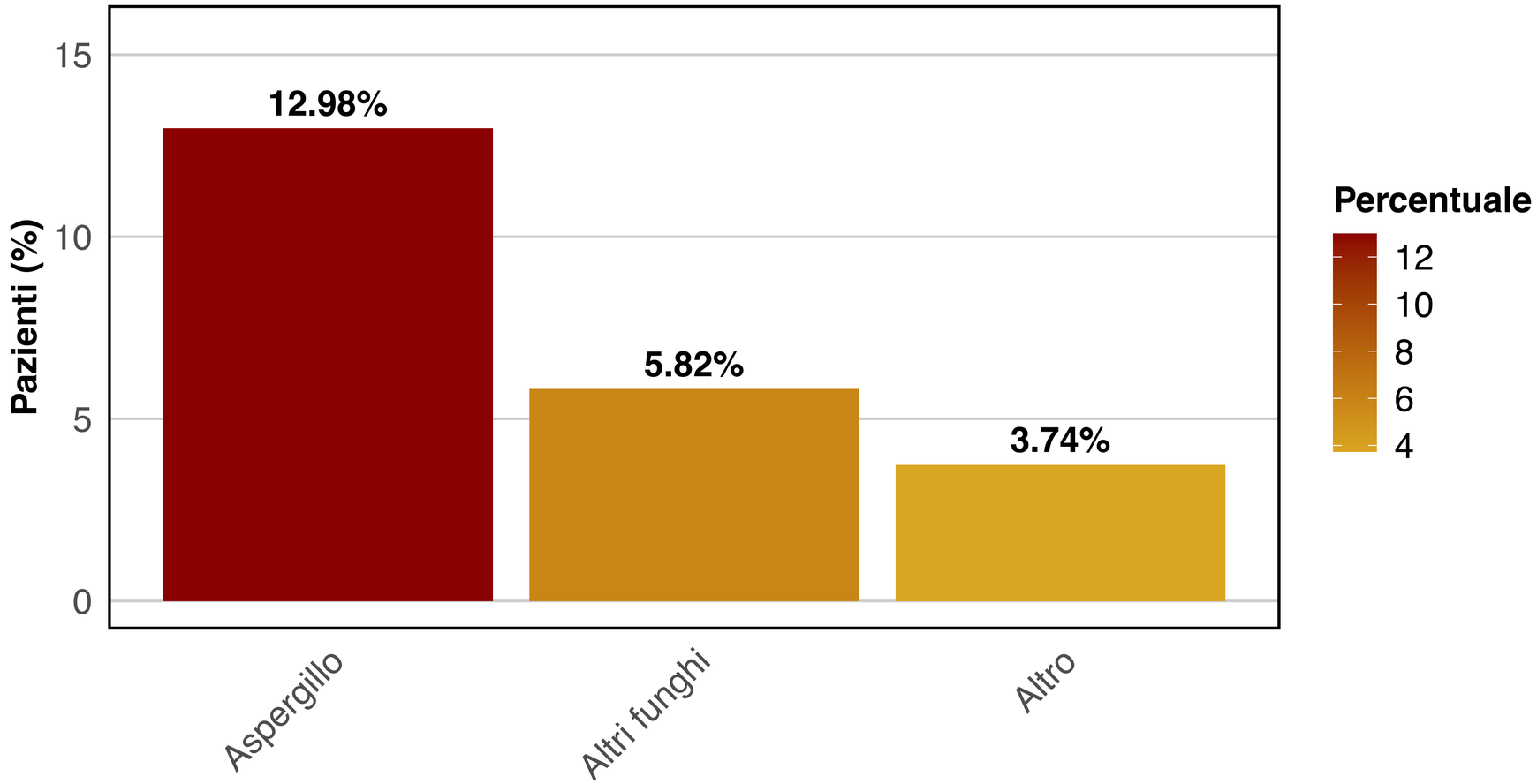
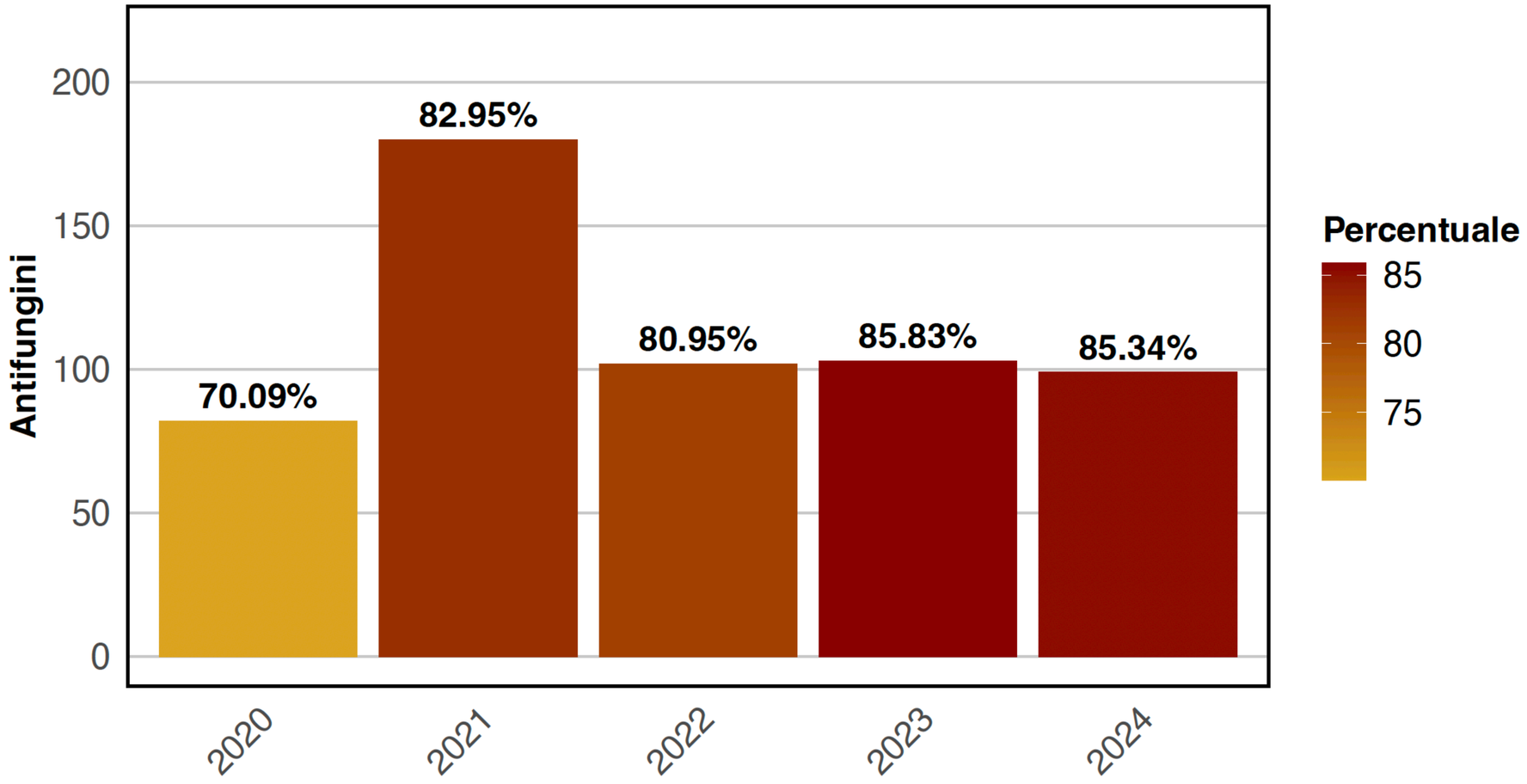
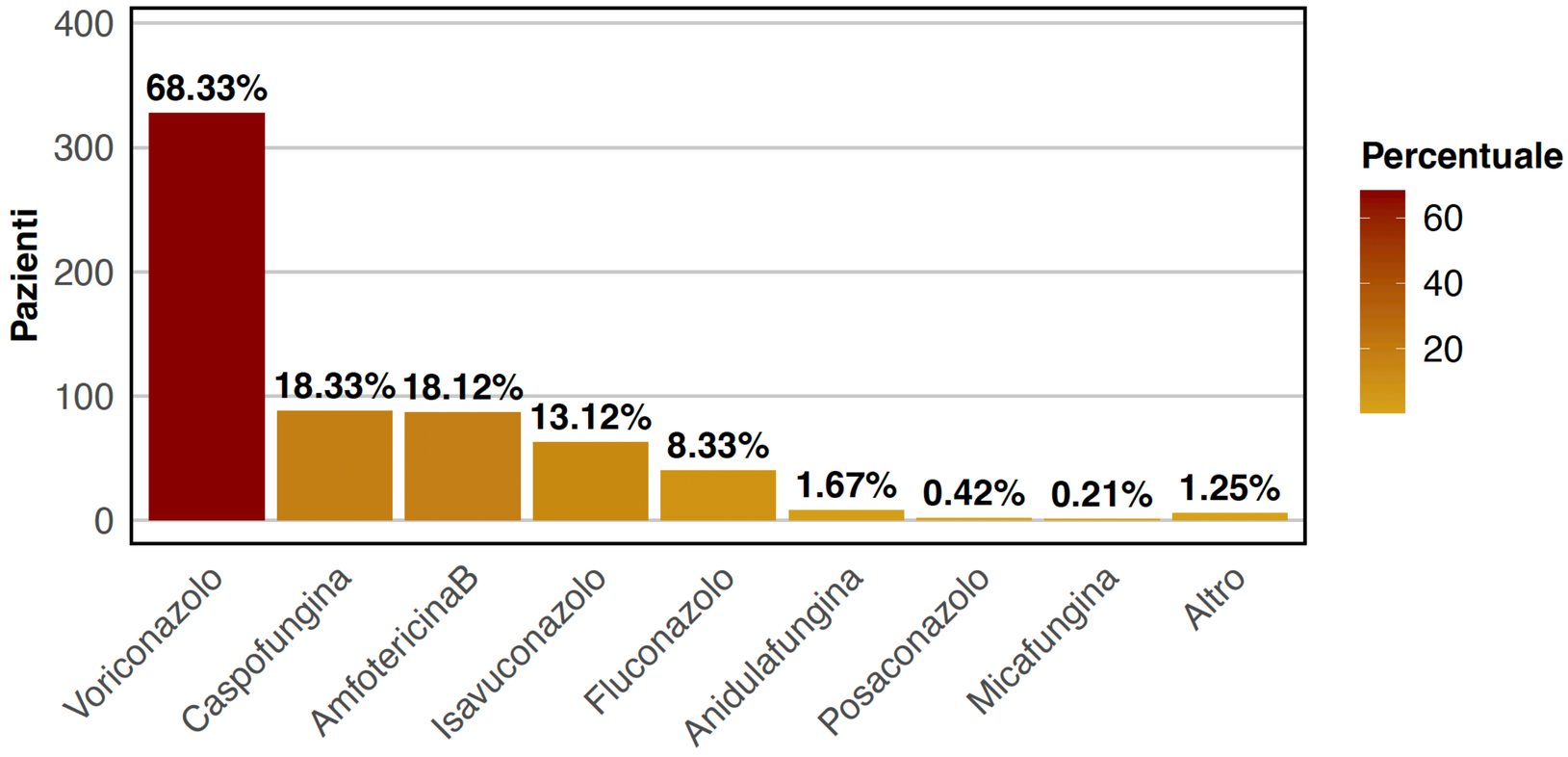
Immunosoppressione nei pazienti infetti in ammissione



Somministrazione antifungini dal 2020 al 2024

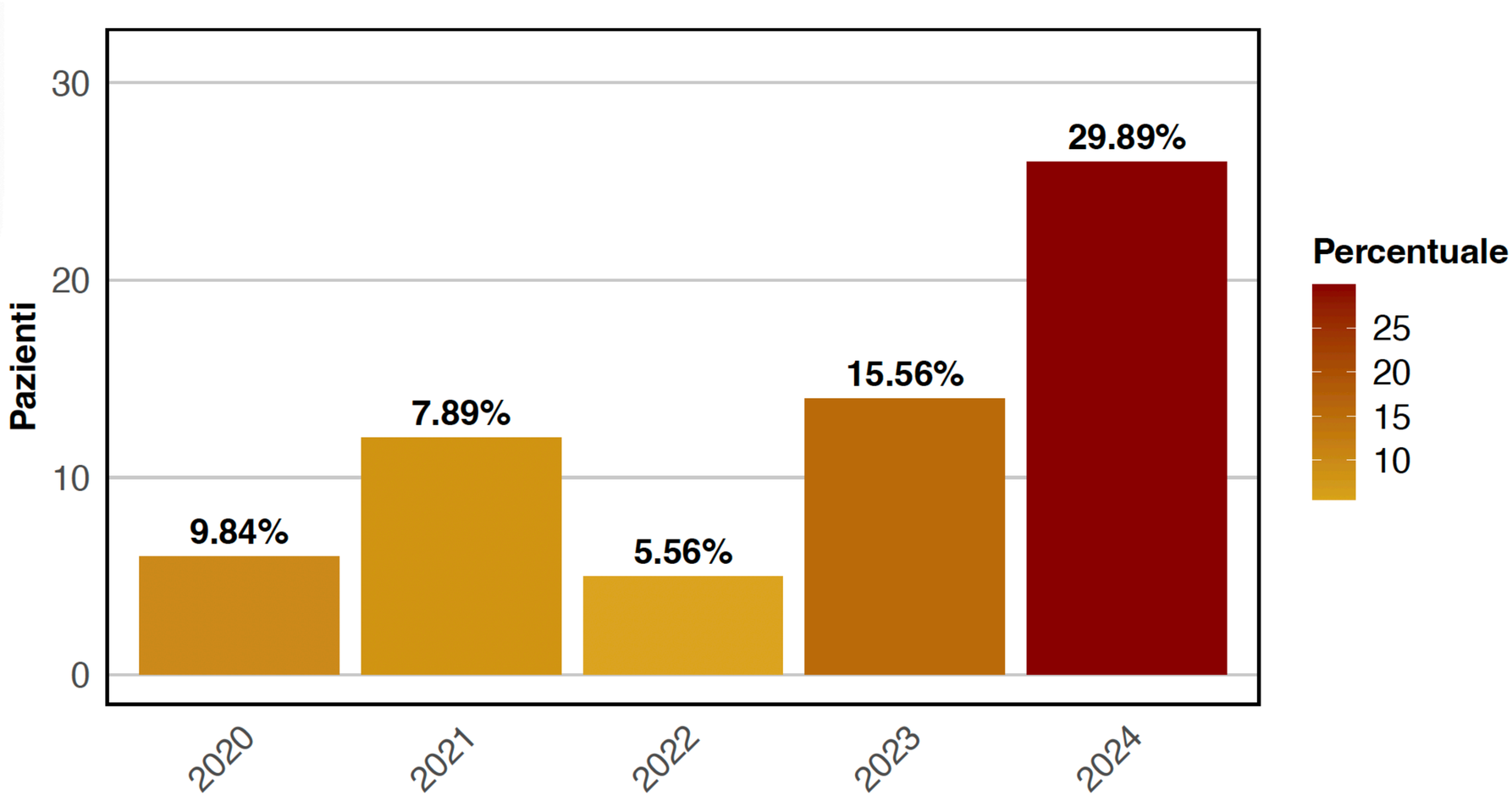


Tipologia antifungino



Nota: i pazienti possono ricevere più antifungini. (n: 480)

Isavuconazolo



64aa

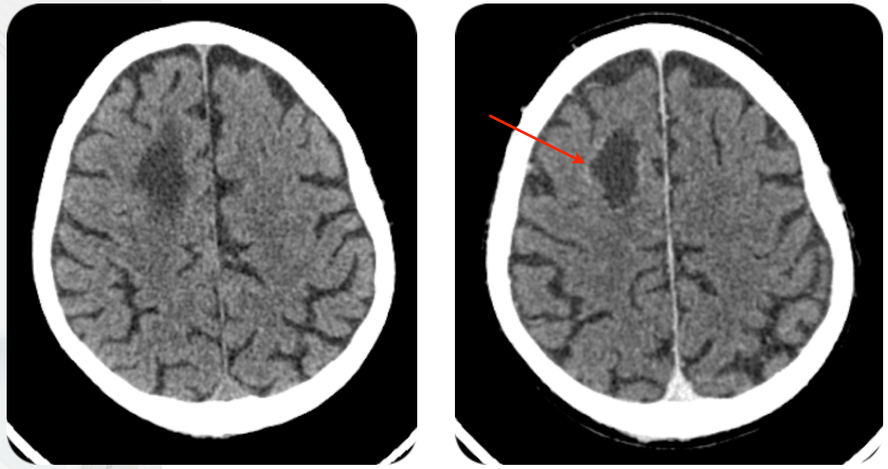
ipertensione arteriosa, diabete mellito in tp, artrite psoriasica in tp (ciclosporina, sulfalazina)

EMILATO SX gamba>braccio

WHAT DO YOU THINK?

TAC cranio basale e dopo somministrazione di contrasto

*L'**ascesso da Aspergillus** è tipicamente ipodenso e con scarso enhancement, che si esprime in genere come un sottile rima di captazione periferica. Anche i segni di massa sono generalmente contenuti*



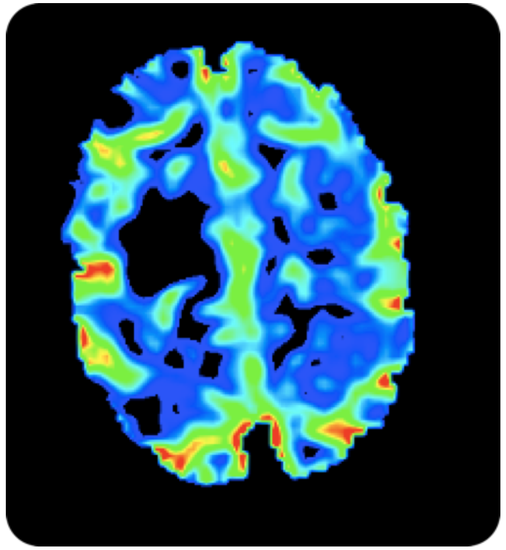
*Tali lesioni, normalmente si trovano, **A CAVALLO DELLA GIUNZIONE** tra la sostanza bianca e grigia. Altra caratteristica radiologica è la tendenza di Aspergillus ad occludere anche piccole arterie perforanti con ischemie a carico dei **NUCLEI DELLA BASE**, dei **TALAMI**, del **CORPO CALLOSO** e del **TRONCO**, tutte aree che vengono raramente colpite da altri organismi responsabili di infezioni del SNC*

*Stesso caso, **RMN encefalo**. Immagini assiali **T1** dipendenti senza e con contrasto.*

*Immagine coronale in **T2** dipendente, da notare gli scarsi effetti di massa*

*Stesso caso, **RMN encefalo**. Immagini assiali **T1** dipendenti senza e con contrasto. Immagine coronale in **T2** dipendente, da notare gli scarsi effetti di massa*

RMN di ***perfusione ematica cerebrale***. In particolare la tecnica usata misura gli indici di volume ematico cerebrale per voxel. Questo studio dimostra che le lesioni da *Aspergillus* sono ***completamente avascolarizzate***

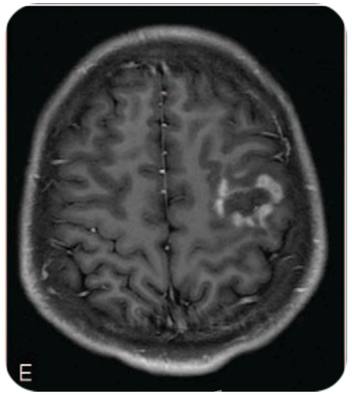


Observational Study > Medicine (Baltimore). 2020 Oct 30;99(44):e22911

Central nervous system *ASPERGILLOSIS* in immunocompetent patients: case series and literature review

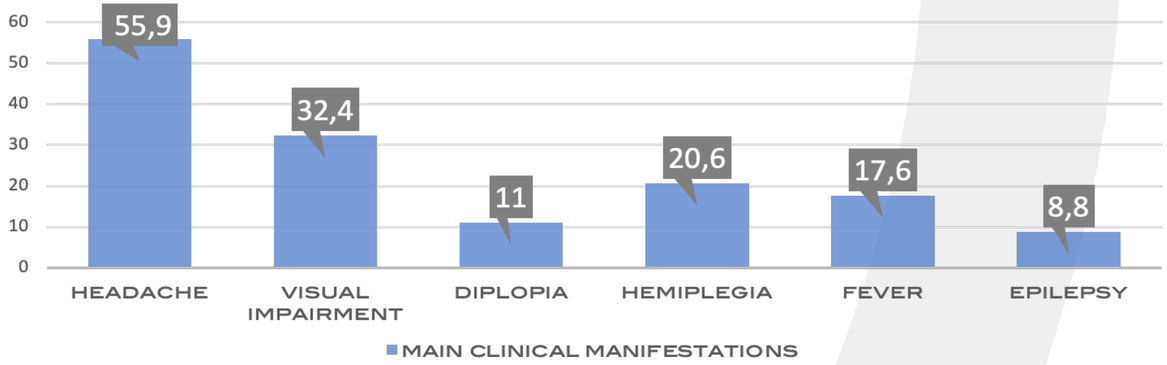
Yubao Ma [1], Wanjun Li, Ran Ao, Xiaoyang Lan, Yang Li, Jiatang Zhang, Shengyuan Yu

This study enrolled ***six*** immunocompetent patients diagnosed with CNS aspergillosis. Additionally, we reviewed the clinical profiles for ***28*** cases reported in the literature

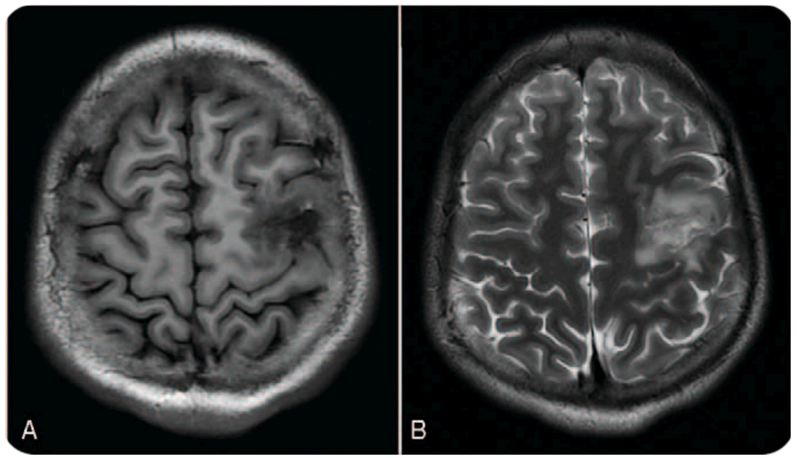


Imaging

Contrast-enhanced imaging demonstrated petal-like enhancement

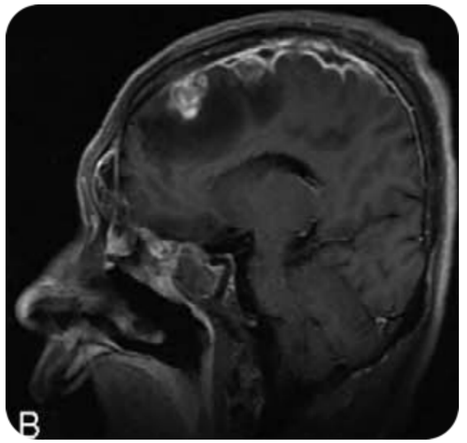


According to the radiological features, CNS aspergillosis lesions were divided into ***TWO SUBTYPES***: parenchymal lesions in the cerebral lobes (n=11), and meningeal lesions in the meninges (n=23



Brain magnetic resonance imaging showed a lesion in the left frontal lobe with hypointensity on T1-weighted imaging (A) and hyperintensity on T2-weighted imaging (B)

Brain magnetic resonance imaging showed lesions in the bilateral frontal sinuses, superior sagittal sinus, and left meninges with remarkable enhancement



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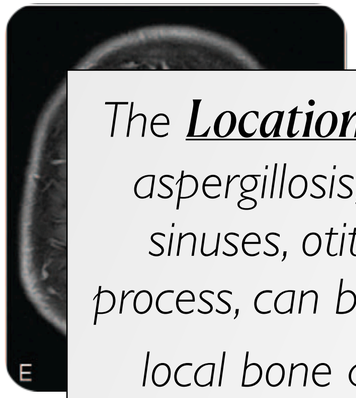
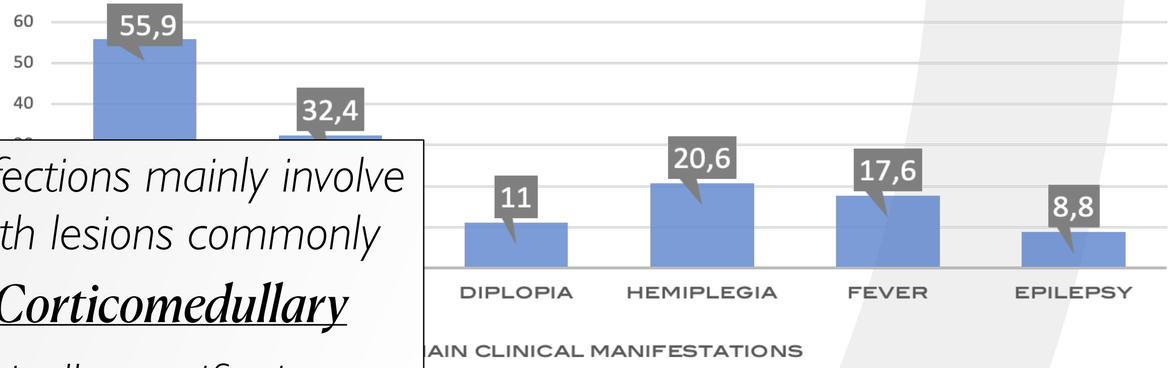


Imaging

*The **Location** of **Primary Infection** of aspergillosis, such as the paranasal sinuses, otitis media, and mastoid process, can be identified based on the local bone destruction. **Meningeal Lesions Usually Occur** in the cavernous sinus, the retroorbital region, and the frontotemporal areas*

*Hematogenous infections mainly involve cerebral lobes, with lesions commonly located at the **Corticomedullary Junction** and clinically manifesting as localization-related symptoms*



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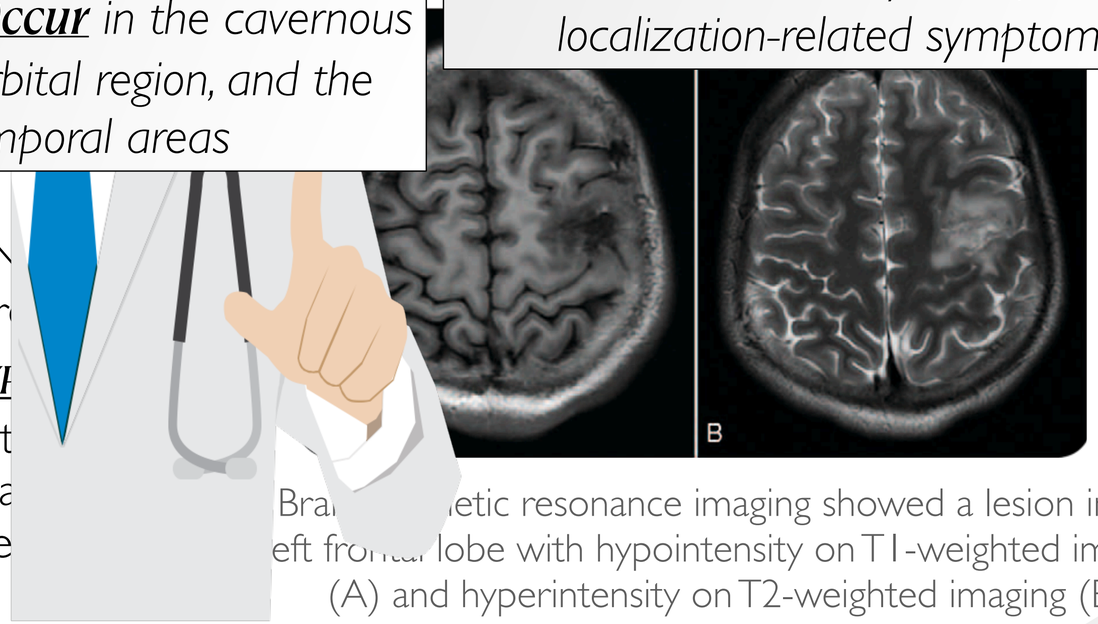

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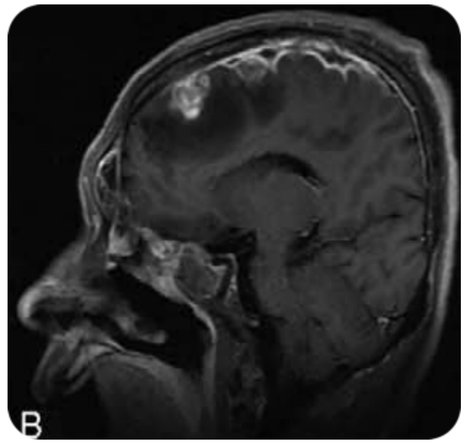
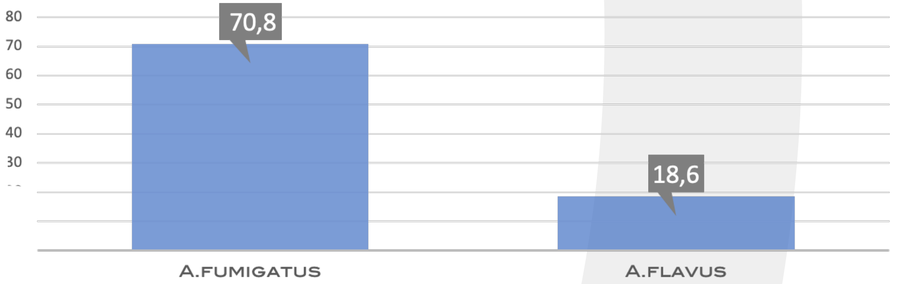


Infect Dis Now. 2021 Nov;51(8):654-660. doi: 10.1016/j.idnow.2021.04.002

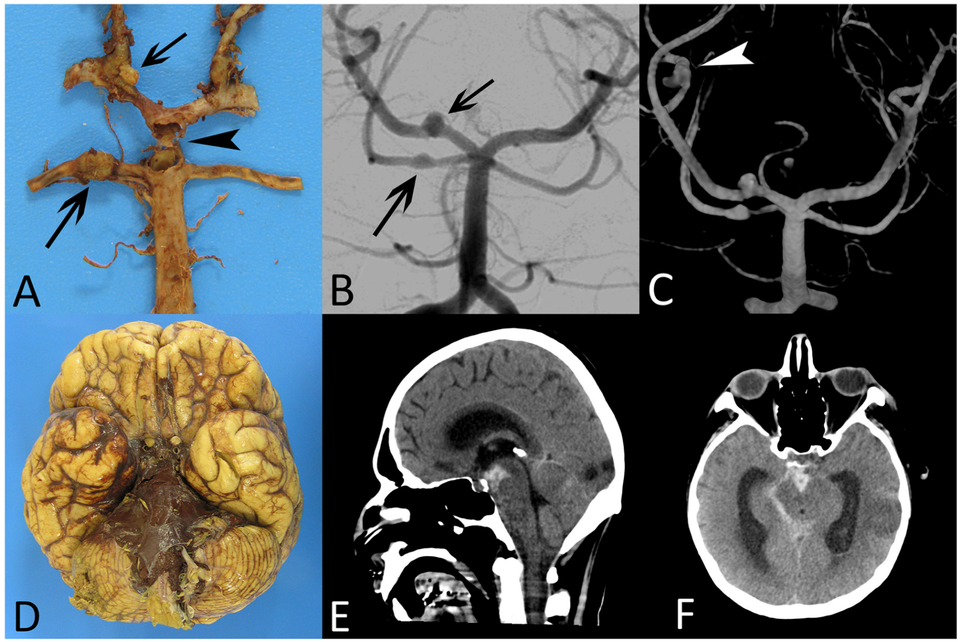
Clinical manifestations, diagnosis, and treatment outcome of *CNS ASPERGILLOSIS:* A systematic review of 235 cases

Durga Shankar Meena [1], Deepak Kumar [2], Gopal Krishana Bohra [3], Gaurav Kumar



poglycorrhachia (48.1% vs 22.2%, P: 0.001) and 0.05), were the factors associated with poor

Marzolf G. et al. *PLOSone* **2016**



Gross examination (A) and cerebral angiogram (B) show aneurysmal lesions on superior cerebellar artery, posterior cerebral artery (arrows) and a ruptured aneurysm of the distal part of the basilar artery (arrowhead). The 3D angiography (C) shows an additional distal fusiform aneurysm on the middle cerebral artery (arrowhead). Massive cerebral hemorrhage into the basal cisterns (interpeduncular and pontine cisterns) visualized on gross examination (D) and non-enhanced CT scan (E and F)

Sundaram C. et al. *W J Clin Neurosci* **2007**
Guermazi A. et al. *Eur Radiol* **2003**
Rhodes IC. et al. *Diagn Microbiol Infect Dis* **1988**

Vascular invasion by Aspergillus can lead to thrombus formation and development of cerebral infarct, necrotizing arteritis, formation of mycotic aneurysm, and subarachnoid hemorrhage.

Angioinvasion by aspergillosis is explained by ***an Ability*** *to produce* ***Elastase Enzyme****, which can degrade the arterial wall elastin, contributing to the breakdown of anatomical barrier and resulting in the growth of fungal hyphae in vessel wall and in aneurysm formation*

› Infect Dis Now. 2021 Nov;51(8):654-660. doi: 10.1016/j.idnow.2021.04.002

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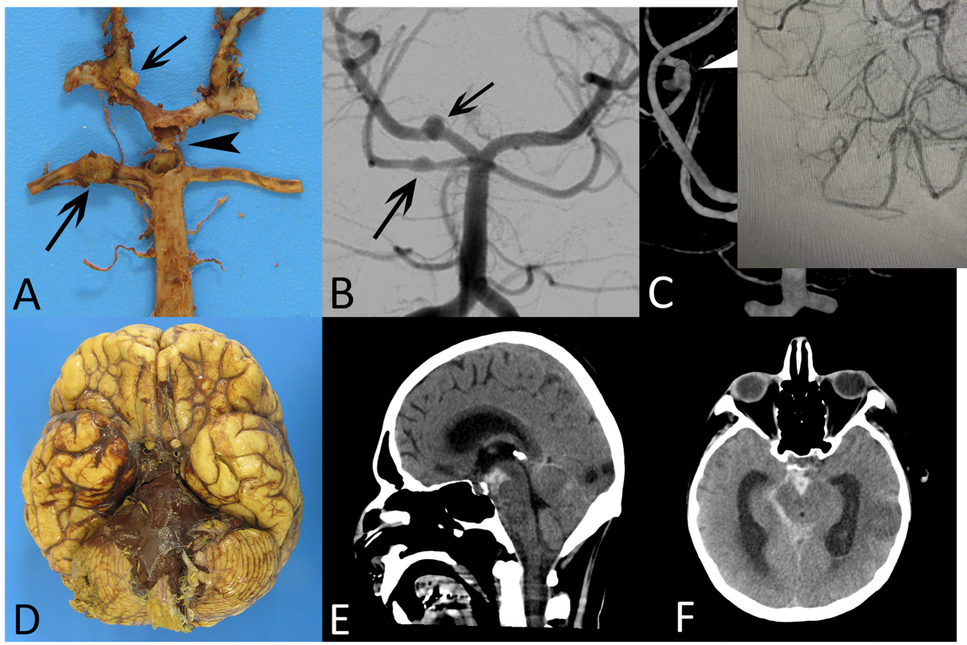

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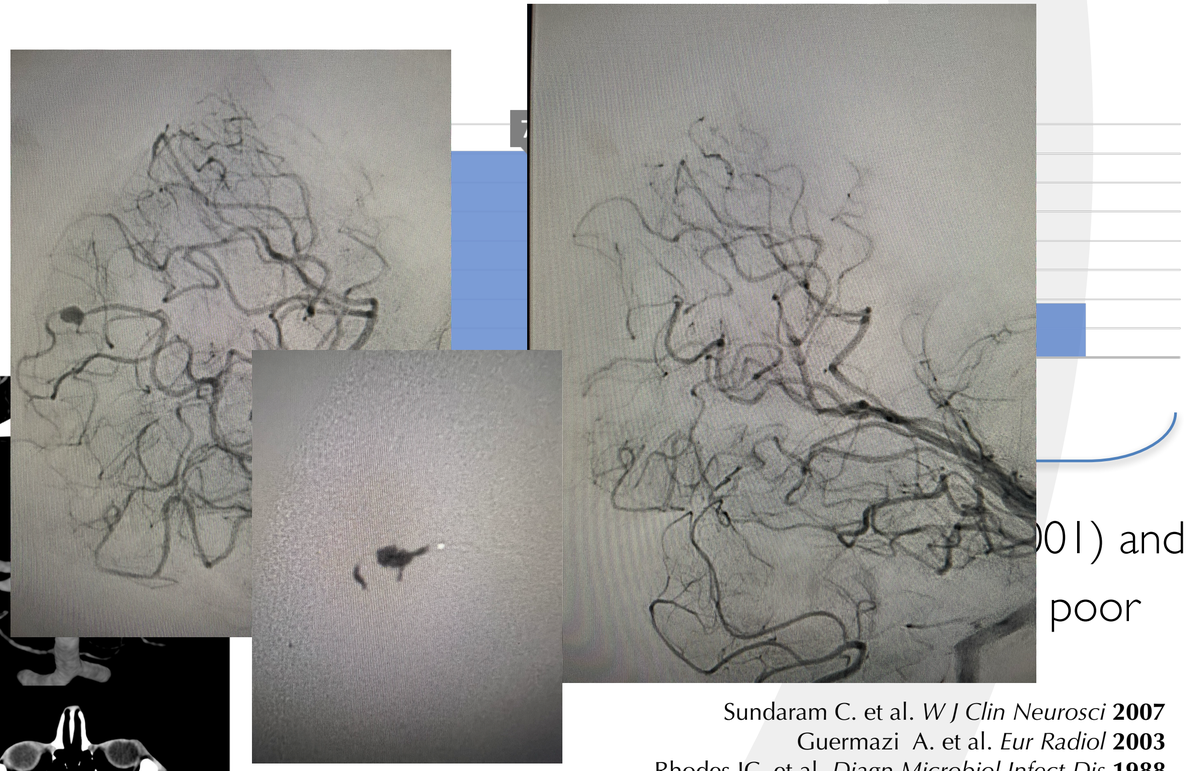

001) and

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Clin Infect Dis. 2024 Jan 25;78(1):11-14. doi: 10.1093/cid/ciad520

Emerging Roles of (1→3)-β-D-glucan in Cerebrospinal Fluid for Detection and Therapeutic Monitoring of Invasive Fungal Diseases of the Central Nervous System

Thomas J Walsh [1] [2], Sean X Zhang [3]

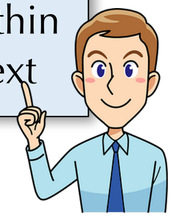
Background: early detection and prompt initiation of antifungal therapy are essential to a successful outcome of IFDs of the CNS

There is a paucity of biomarkers for detection of non-cryptococcal IFDs of the CNS. Diagnosis of non-cryptococcal IFDs of the CNS, such as ***Hematogenous Candida Meningoencephalitis*** (HCME), ***Cerebral Aspergillosis*** and ***Other Mold Infections of the CNS*** is clinically and microbiologically challenging

The potential clinical utility of (1→3)-β-D-glucan is predicated on the unique structural characteristics of this cell wall polysaccharide being present in fungal cells but not that of mammalian cells

The ***use of CSF (1.3)-β-D-glucan*** for therapeutic monitoring of response to antifungal therapy ***permits personalizing individual treatment*** until resolution of the biomarker, particularly with respect to length of therapy

In summary: CSF (1.3)-β-D-glucan ***Is a Valuable Biomarker*** for detection and monitoring of therapeutic response of HCME and a promising indicator for *Aspergillus* and non-*Aspergillus* mold infections of the CNS within the appropriate clinical context



64aa

ipertensione arteriosa, diabete mellito in tp, artrite psoriasica in tp (ciclosporina, sulfalazina)

EMILATO SX gamba>braccio

Rapporto glucosio liquor/plasma 32%

GM liquor 2.6 **GM** BAL 2

1. Voriconazolo
2. L-AmB
3. Caspofungina
4. Isavuconazolo

THERAPY?

Clinical Infectious Diseases

IDSA GUIDELINE

Practice Guidelines for the Diagnosis and Management of *ASPERGILLOSIS*: 2016 Update by the Infectious Diseases Society of America

Patterson TF. et al. *Clin Infect Dis* **2016**

L-Amb 5 mg/Kg/die

20 feb

Condition	Therapy: Primary	Therapy: Alternative	Comments
Invasive syndromes of *Aspergillus*			
IPA	Voriconazole (6 mg/kg IV every 12 h for 1 d, followed by 4 mg/kg IV every 12 h; oral therapy can be used at 200–300 mg every 12 h or weight based dosing on a mg/kg basis); see text for pediatric dosing	Primary: Liposomal AmB (3–5 mg/kg/day IV), isavuconazole 200 mg every 8 h for 6 doses, then 200 mg daily Salvage: ABLC (5 mg/kg/day IV), caspofungin (70 mg/day IV × 1, then 50 mg/day IV thereafter), micafungin (100–150 mg/day IV), posaconazole (oral suspension: 200 mg TID; tablet: 300 mg BID on day 1, then 300 mg daily, IV: 300 mg BID on day 1, then 300 mg daily, itraconazole suspension (200 mg PO every 12 h)	Primary combination therapy is not routinely recommended; addition of another agent or switch to another drug class for salvage therapy may be considered in individual patients; dosage in pediatric patients for voriconazole and for caspofungin is different than that of adults; limited clinical experience is reported with anidulafungin; dosage of posaconazole in pediatric patients has not been defined
Aspergillosis of the CNS	Similar to IPA	Similar to IPA Surgical resection may be beneficial in selected cases	This infection is associated with the highest mortality among all of the different patterns of IA; drug interactions with anticonvulsant therapy

WHY? COULD YOU HAVE CHOSEN OTHER OPTIONS?

LG?

VORICONAZOLE VERSUS AMPHOTERICIN B FOR PRIMARY THERAPY OF INVASIVE ASPERGILLOSIS

Herbrecht R. et al. *NEJM* **2002**

Methods In this ***Randomized, Unblinded Trial,*** patients received either intravenous voriconazole (two doses of 6 mg per kilogram of body weight on day 1, then 4 mg per kilogram twice daily for at least seven days) followed by 200 mg orally twice daily or intravenous ***Amphotericin B Deoxycholate*** (1 to 1.5 mg per kilogram per day)

Clinical Infectious Diseases

IDSA GUIDELINE

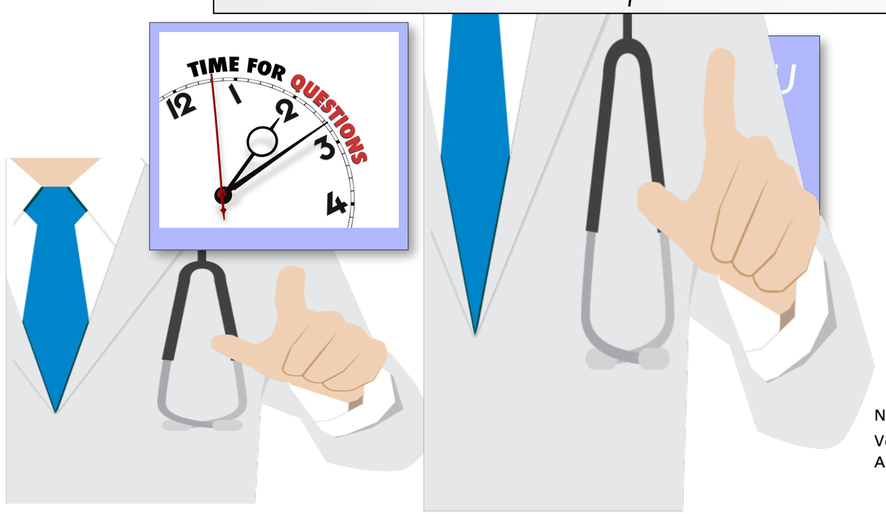
Practice Guidelines for the Diagnosis and Management of ***ASPERGILLOSIS***: 2016 Update by the Infectious Diseases Society of America

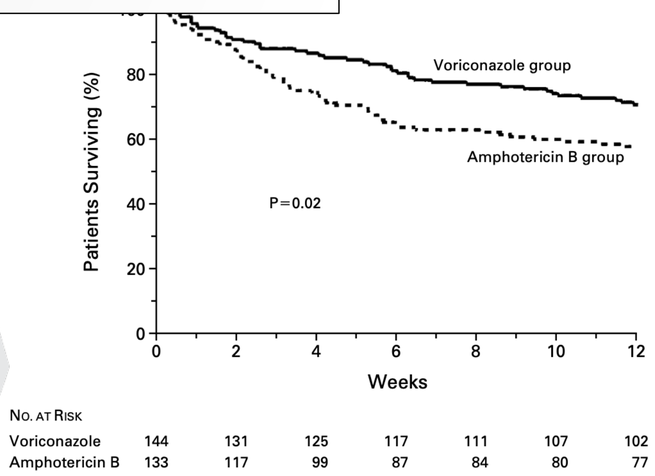
Patterson TF. et al. *Clin Infect Dis* **2016**

L-Amb 5 mg/Kg/die

CONCLUSION: *In patients with invasive aspergillosis, initial therapy with* ***Voriconazole*** *led to better responses and improved survival and resulted in fewer severe side effects than the standard approach of initial therapy with amphotericin B*

Condition	Therapy: Primary	Therapy: Alternative	Comments
Invasive syndromes of *Aspergillus*			
	…llowed by 4 mg/kg …sing on a mg/kg	Primary: Liposomal AmB (3–5 mg/kg/day IV), isavuconazole 200 mg every 8 h for 6 doses, then 200 mg daily Salvage: ABLC (5 mg/kg/day IV), caspofungin (70 mg/day IV × 1, then 50 mg/day IV thereafter), micafungin (100–150 mg/day IV), posaconazole (oral suspension: 200 mg TID; tablet: 300 mg BID on day 1, then 300 mg daily, IV: 300 mg BID on day 1, then 300 mg daily, itraconazole suspension (200 mg PO every 12 h)	Primary combination therapy is not routinely recommended; addition of another agent or switch to another drug class for salvage therapy may be considered in individual patients; dosage in pediatric patients for voriconazole and for caspofungin is different than that of adults; limited clinical experience is reported with anidulafungin; dosage of posaconazole in pediatric patients has not been defined
		Similar to IPA Surgical resection may be beneficial in selected cases	This infection is associated with the highest mortality among all of the different patterns of IA; drug interactions with anticonvulsant therapy





No. at Risk

Voriconazole	144	131	125	117	111	107	102
Amphotericin B	133	117	99	87	84	80	77

VORICONAZOLE VERSUS AMPHOTERICIN B FOR PRIMARY THERAPY OF INVASIVE ASPERGILLOSIS

Herbrecht R. et al. *NEJM* **2002**

Methods In this ***Randomized, Unblinded Trial,*** patients received either intravenous voriconazole (two doses of 6 mg per kilogram of body weight on day 1, then 4 mg per kilogram twice daily for at least seven days) followed by 200 mg orally twice daily or intravenous ***Amphotericin B Deoxycholate*** (1 to 1.5 mg per kilogram per day)

Clinical Infectious Diseases

IDSA GUIDELINE

L-Amb 5 mg/Kg/die

20 feb

ISAV and **VORICO** are the preferred agents for first-line treatment of pulmonary IA, whereas liposomal amphotericin B is moderately supported. Combinations of antifungals as primary treatment options are not recommended

WHY? COULD YOU HAVE CHOSEN OTHER OPTIONS?

LG?

Practice Guidelines for the Diagnosis and Management of *ASPERGILLOSIS*

Clinical Microbiology and Infection 24 (2018) e1–e38

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Diagnosis and management of *Aspergillus* diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline

mg daily, itraconazole suspension (200 mg PO every 12 h) has not been defined

Similar to IPA. Surgical resection may be beneficial in selected cases. This infection is associated with the highest mortality among all of the different patterns of IA; drug interactions with anticonvulsant

Targeted therapy of extrapulmonary disease—first line

Population	Intention	Intervention	SoR	QoE	Comment
Suspected or proven IA of the central nervous system	To increase response and survival rate	Surgical debridement, if surgically possible	A	II_u	
		Voriconazole	A	II_u	$n = 5/5$ $n = 81$, 48 proven cases, 33 probable cases, TDM recommended targeting trough concentration of 2–5.5 mg/L
		Posaconazole	D	III	8 patients documented in studies (5 failures)
		Itraconazole	D	III	
		Lipid formulations of AmB	B	III	Case collections, animal data
		cAmB	D	I	Renal toxicity
		Echinocandins	D	III	Insufficient tissue penetration
Patients with clinical suspicion of or proven invasive sinus aspergillosis	To cure	Surgery	A	III	Need to be considered on an individual basis and decision
Patients with invasive sinus aspergillosis (all levels of certainty: suspected through proven)		Local antifungal therapy	C	III	
		Voriconazole	A	II_t	$n = 8/7$, TDM recommended
		L-AmB	A	II_t	Active against mucormycosis as well since mixed infections occur or cannot be differentiated
		Posaconazole, itraconazole, echinocandins	C	III	Not well specified in studies, TDM recommended for posaconazole and itraconazole

TABLE 3 Antifungal agents for the treatment of pulmonary aspergillosis

Antifungal class	Drugs	Dosage	Therapeutic use	Comments
Polyenes	Deoxycholate amphotericin B	1–1.5 mg·kg^{-1} once daily (intravenous only)	Should be avoided (privilege lipid formulations of amphotericin B if available)	
	Liposomal amphotericin B	3–5 mg·kg^{-1} once daily (intravenous only)	Treatment of IPA (second choice after triazoles; first choice in areas with high prevalence of azole-resistant *Aspergillus fumigatus* isolates if no culture/fungigram available)	Monitor kidney function and electrolytes (K^+) Consider co-administration of paracetamol if fever and/or rigors
	Amphotericin B lipid complex	5 mg·kg^{-1} once daily (intravenous only)	Treatment of IPA (privilege liposomal amphotericin B if available)	Consider alternative therapy for *Aspergillus terreus*
	Amphotericin B colloidal dispersion	6 mg·kg^{-1} once daily (intravenous only)	Treatment of IPA (privilege liposomal amphotericin B if available)	
Triazoles	Itraconazole	200 mg once daily or twice daily (intravenous or oral) TDM recommended (target: C_{trough}: 1–4 mg·L^{-1})	Treatment of CPA	
	Voriconazole	Intravenous: 6 mg·kg^{-1} twice daily (D1), then 4 mg·kg^{-1} twice daily Oral: 400 mg twice daily (D1), then 200–300 mg twice daily TDM recommended (target: C_{trough}: 1–5 mg·L^{-1})	Treatment of IPA (first choice) Treatment of CPA	Monitor hepatic tests (ALT, AST, ALP, GGT, bilirubin) Monitor ECG (QT interval, in particular voriconazole)
	Posaconazole	Intravenous or oral tablets: 300 mg twice daily (D1), then 300 mg once daily Oral suspension: 200 mg three times daily TDM recommended (target: C_{trough}: >1 mg·L^{-1} for therapy and >0.7 mg·L^{-1} for prophylaxis)	Prophylaxis or treatment of IPA Treatment of CPA (privilege itraconazole or voriconazole) Oral suspension should be avoided or limited to prophylaxis (privilege intravenous formulation or oral tablets)	DDIs (in particular voriconazole) Consider alternative therapy for *Aspergillus calidoustus* or cryptic species of section Fumigati (*e.g. Aspergillus lentulus*)
	Isavuconazole	200 mg three times daily (D1–2), then 200 mg once daily TDM not routinely recommended (may be considered)	Treatment of IPA Treatment of CPA (privilege itraconazole or voriconazole)	
Echinocandins	Caspofungin	70 mg (D1), then 50 mg once daily (intravenous only)	Treatment of IPA as monotherapy (third choice after triazoles and lipid formulations of amphotericin B) Treatment of IPA in combination with triazoles (severe cases and/or positive GM; azole-resistant *Aspergillus fumigatus* isolates)	
	Anidulafungin	200 mg (D1), then 100 mg once daily (intravenous only)		
	Micafungin	100 mg once daily (intravenous only)		

ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CPA: chronic pulmonary aspergillosis; D1: day 1; DDI: drug–drug interaction; GGT: gamma glutamyltranspeptidase; GM: galactomannan; IPA: invasive pulmonary aspergillosis; TDM: therapeutic drug monitoring, W1: week 1.

SUPPLEMENT ARTICLE

Pulmonary aspergillosis: diagnosis and treatment

Frederic Lamoth[1,2] and Thierry Calandra[1]

Number 7 in the Series "Respiratory infections"
Edited by Antoni Torres and Michael S. Niederman

Eur Respir Rev 2022; 31: 220114

breakthrough
ole therapy/

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improved outcomes
positive

ered in severe disease
ole dosing based on
7

Antifungal TDM in the management of IA **IS RECOMMENDED** during treatment with voriconazole or posaconazole (Strong recommendation, Level II evidence)

WHAT IS THE ROLE OF TDM IN MANAGING IA?

SUPPLEMENT ARTICLE

EUROPEAN RESPIRATORY REVIEW
SERIES
F. LAMOTH AND T. CALANDRA

Pulmonary aspergillosis: diagnosis and treatment

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	Voriconazole	Intravenous: 6 mg·kg^{-1} twice daily (D1), then 4 m twice daily	Treatment of IPA (first choice)	
		Oral: 400 mg twice d then 200–300 mg twi TDM recommended C_{trough}: 1–5 mg·L		
	Posaconazole	Intravenous or oral 300 mg twice daily (D 300 mg once da		
		Oral suspension: 200 times daily TDM recommended C_{trough}: >1 mg·L^{-1} for and >0.7 mg·L^{-1} prophylaxis)		
	Isavuconazole	200 mg three times (D1–2), then 200 mg o TDM not routin recommended (m considered)		
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	Micafungin	100 mg once daily (int only)		

ALP: alkaline phosphatase; ALT: alanine aminotransferas drug–drug interaction; GGT: gamma glutamyltranspeptic monitoring, W1: week 1.

- Therapeutic drug monitoring for ***Invasive Mould Infections*** and disease: pharmacokinetic and pharmacodynamic considerations

Stott KE. et al. *J Antimicrob Chemother* **2017**

Voriconazole … exits ***Highly Variable Inter-Individual Pharmacokinetics*** … undergoes ***Extensive Hepatic Metabolism*** via CYP3A4, CYP2C9 and CYP2C19

Antifungal TDM in the management of IA **IS RECOMMENDED** during treatment with voriconazole or posaconazole (Strong recommendation, Level II evidence)

WHAT IS THE ROLE OF TDM IN MANAGING IA?

Antimicrob Agents Chemother. 2014;58(1):424-31. doi: 10.1128/AAC.01558-13.

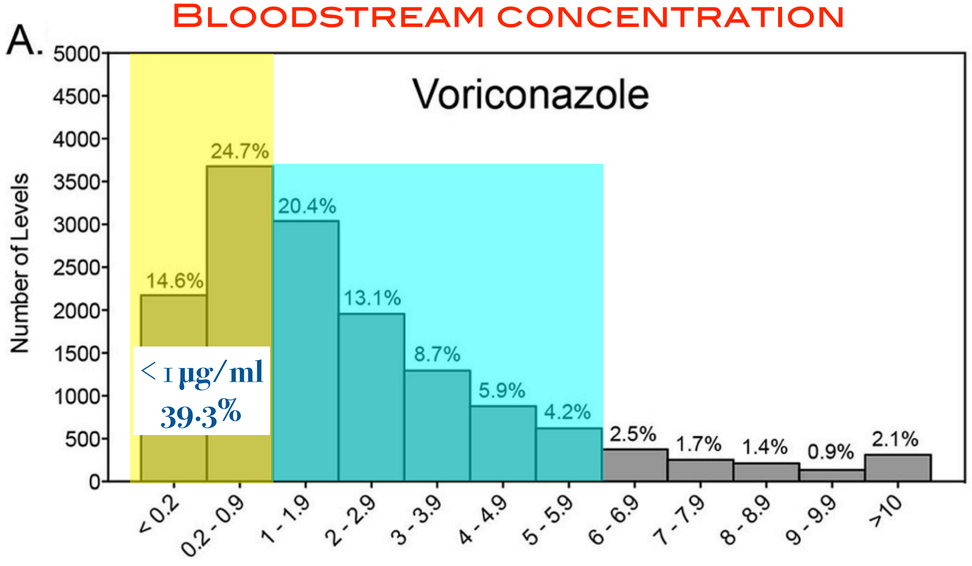
A Reference Laboratory Experience of Clinically Achievable *Voriconazole*, *Posaconazole*, and *Itracc*... Bloodstream and Cerebral Spinal Fluid

Nathan P Wied... hic...
James S Lewis... D...

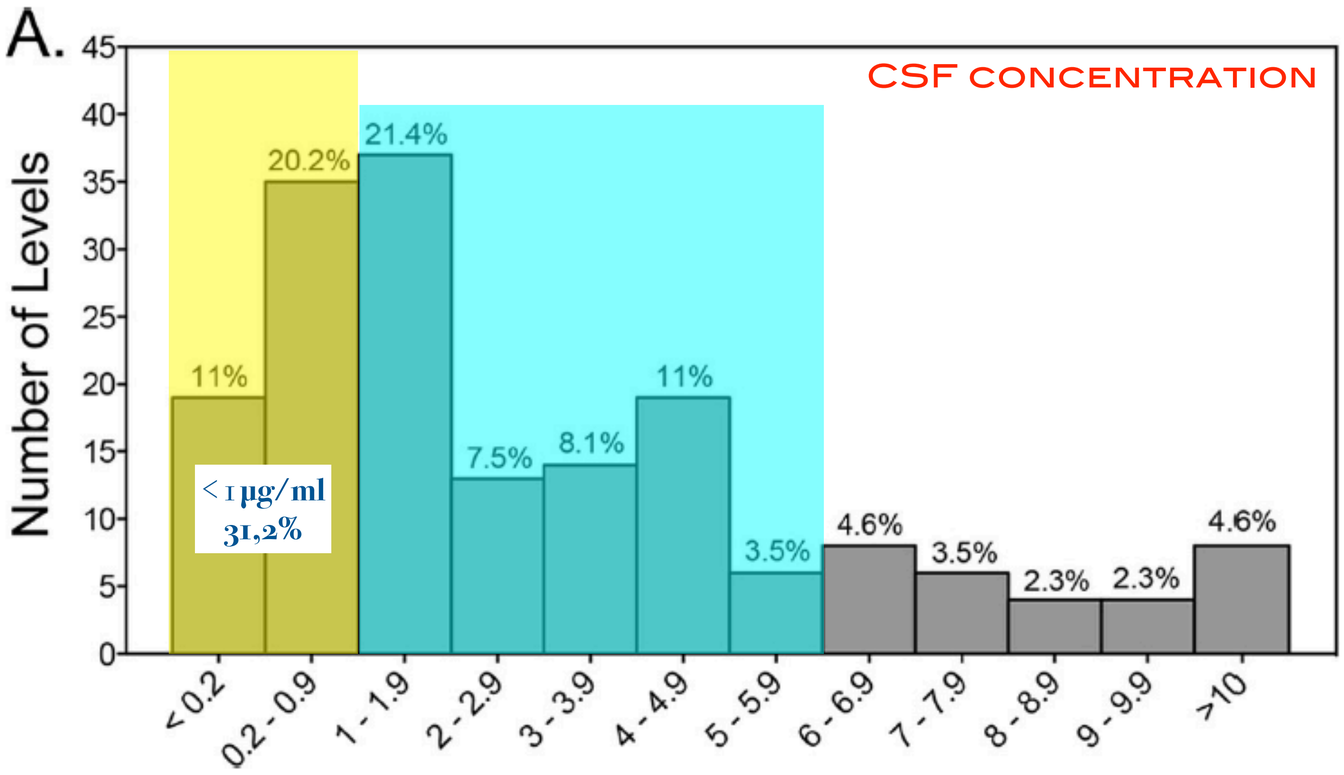
What do you think about ISAV brain penetration ?

...were found for voriconazole (14,370 and *173*, respectively). ...dstream concentrations within the range of 1 to 5.5 µg/ml represented *50.6%* of samples. Levels below ...antification (0.2 µg/ml) were observed in *14.6%* of samples, and *10.4%* of samples had levels of >5.5 ...e levels ranged *from undetectable to 15.3 µg/ml* and were *<0.2 µg/ml* in *11%* of samples

Bloodstream concentration



CSF concentration



J Antimicrob Chemother. 2019 Jun 1;74(6):1751-1753. doi: 10.1093/jac/dkz050

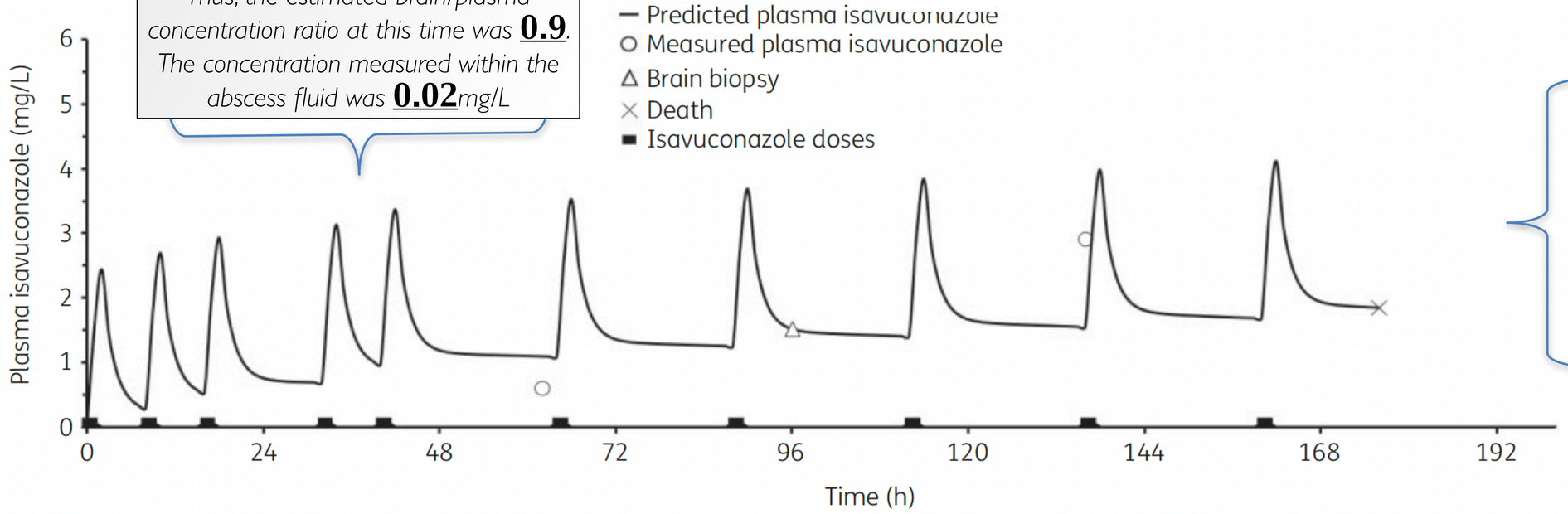
ISAVUCONAZOLE brain penetration in cerebral aspergillosis

F Lamoth [1 2], T Mercier [3], P André [3], J L Pagani [4], O Pantet [4], R Maduri [5], B Guery, L A Decosterd [3]

Cerebral aspergillosis is a rare, but often fatal, infection in immunocompromised patients

We report data of ***Isavuconazole*** concentrations within the brain lesion of a patient with cerebral aspergillosis. The patient developed IA during the neutropenic phase following induction chemotherapy for AML. The diagnosis initially relied on a positive galactomannan in serum, a positive PCR for *Aspergillus fumigatus* in a bronchial aspirate and nodular chest CT lesions. Cerebral CT and MRI showed a frontoparietal abscess consistent with cerebral aspergillosis. Initial amphotericin B therapy was switched to intravenous isavuconazole (200mg q8h for days 1 and 2, then 200mg q24h). This latter drug was preferred over voriconazole because of severe cholestasis and renal failure requiring continuous haemofiltration. After 4 days of isavuconazole therapy, a biopsy of the brain lesion was performed by craniectomy

The estimated curve showed that the expected plasma concentration on day 4 (timing of brain biopsy) was **1.7** *mg/L with an estimated accumulation of* ***44%****. Thus, the estimated brain/plasma concentration ratio at this time was* **0.9**. *The concentration measured within the abscess fluid was* **0.02** *mg/L*



Trough plasma concentrations of isavuconazole (24 h after last dose) on day 3 and day 6 of therapy were **0.6** *and* **2.9** *mg/L, respectively. Isavuconazole concentration in the brain tissue measured 6 h after the end of the administration of the drug on day 4 was* **1.46** *mg/kg*

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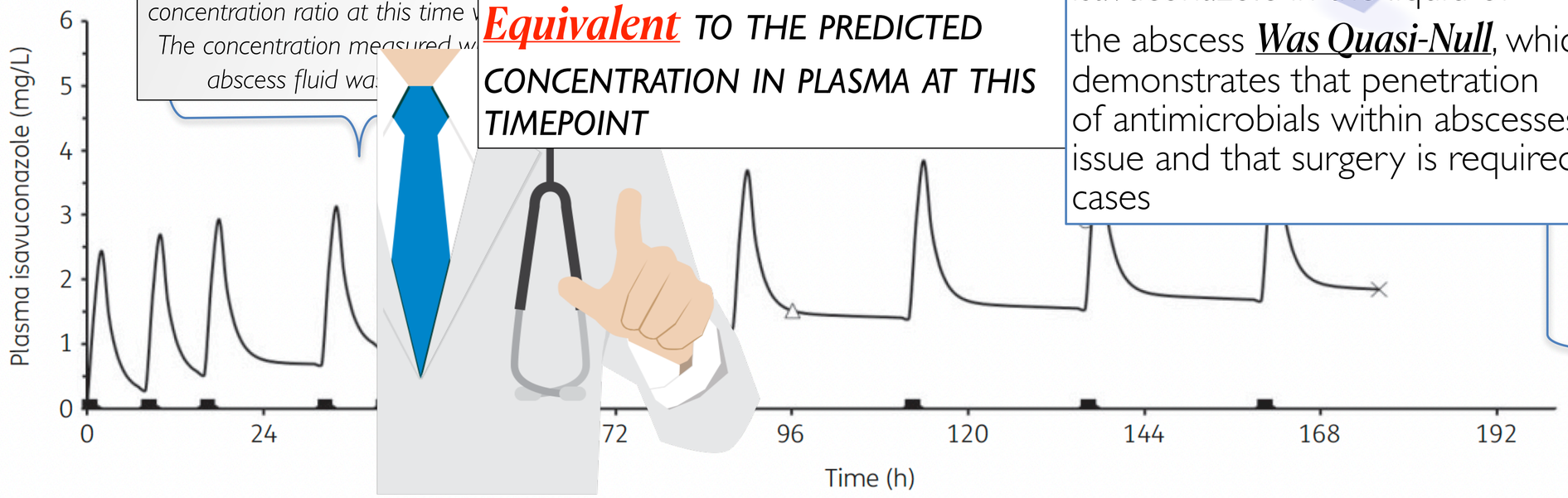
OUR RESULTS SHOW THAT THE ISAVUCONAZOLE CONCENTRATION MEASURED IN THE INFLAMMATORY BRAIN TISSUE SURROUNDING THE ABSCESS **Was Equivalent** TO THE PREDICTED CONCENTRATION IN PLASMA AT THIS TIMEPOINT

However, the concentration of isavuconazole in the liquid of the abscess **Was Quasi-Null**, which further demonstrates that penetration of antimicrobials within abscesses is an issue and that surgery is required in such cases



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2.9 *mg/L, respectively.*
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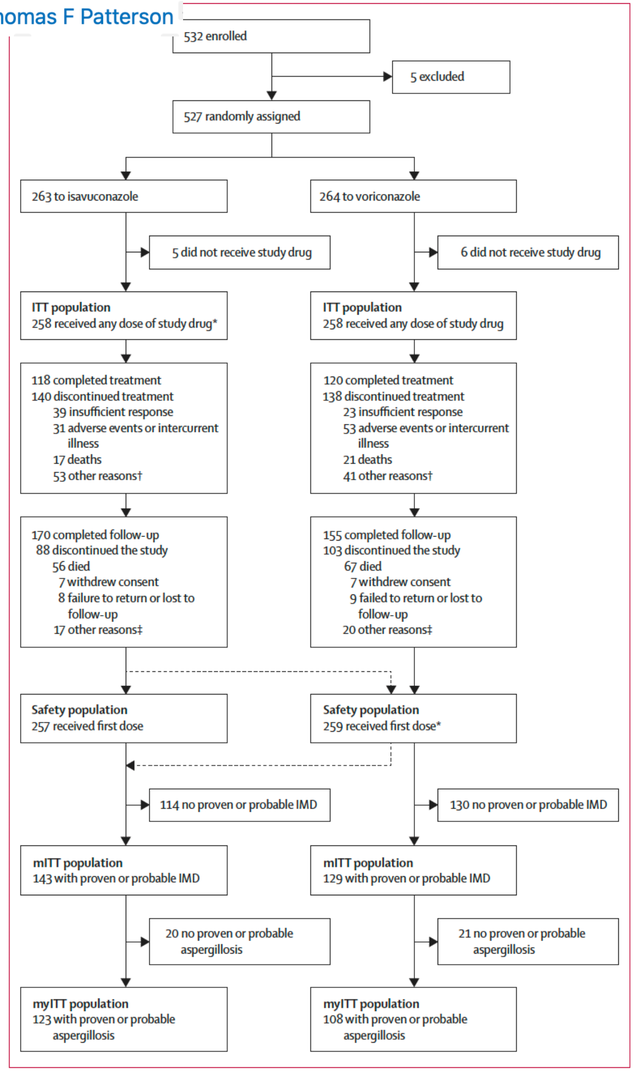
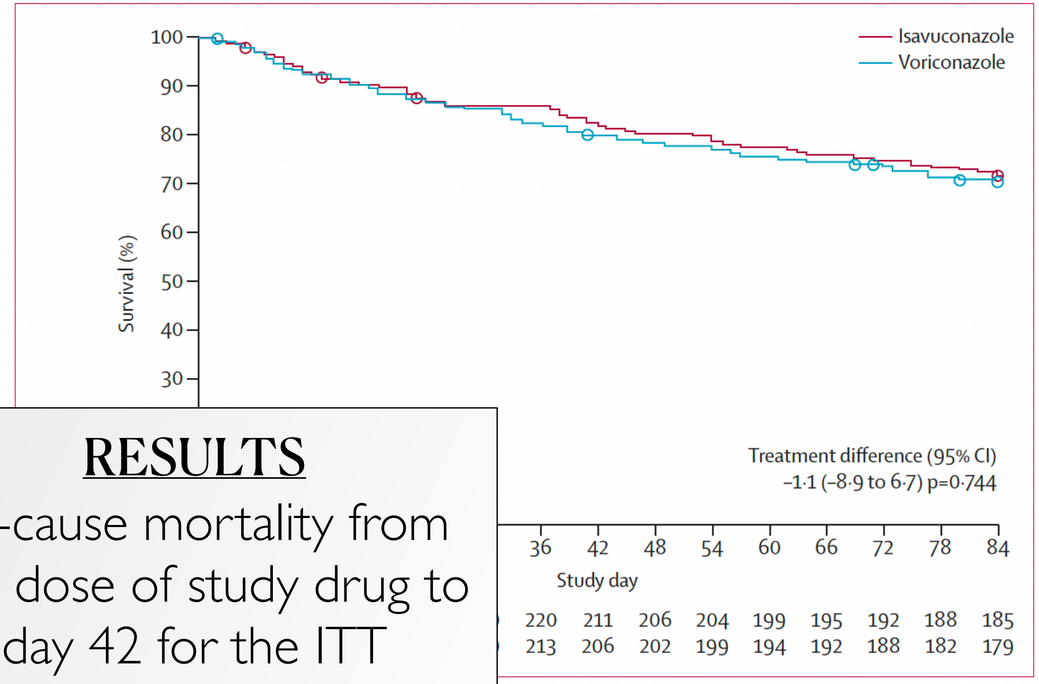
Clinical Trial > Lancet. 2016 Feb 20;387(10020):760-9. doi: 10.1016/S0140-6736(15)01159-9

ISAVUCONAZOLE versus VORICONAZOLE for primary treatment of invasive mould disease caused by *Aspergillus* and other filamentous fungi (SECURE): a phase 3, randomised-controlled, non-inferiority trial

Johan A Maertens [1], Issam I Raad [2], Kieren A Marr [3], Thomas F Patterson

Methods: This was a phase 3, double-blind, global multicentre, comparative-group study. Patients with suspected invasive mould disease were randomised in a 1:1 ratio **to receive** isavuconazonium sulfate **372 mg** (prodrug; equivalent to 200 mg isavuconazole; intravenously three times a day on days 1 and 2, then either intravenously or orally once daily) or voriconazole (**6 mg/kg** intravenously twice daily on day 1, **4 mg/kg** intravenously twice daily on day 2, then intravenously **4 mg/kg** twice daily or orally **200 mg** twice daily from day 3 onwards)





RESULTS

All-cause mortality from first dose of study drug to day 42 for the ITT population was **19**% with isavuconazole (48 patients) and **20**% with voriconazole (52 patients)

myITT=mycological intention to treat

Clinical Trial > Lancet. 2016 Feb 20;387(10020):760-9. doi: 10.1016/S0140-6736(15)01159-9

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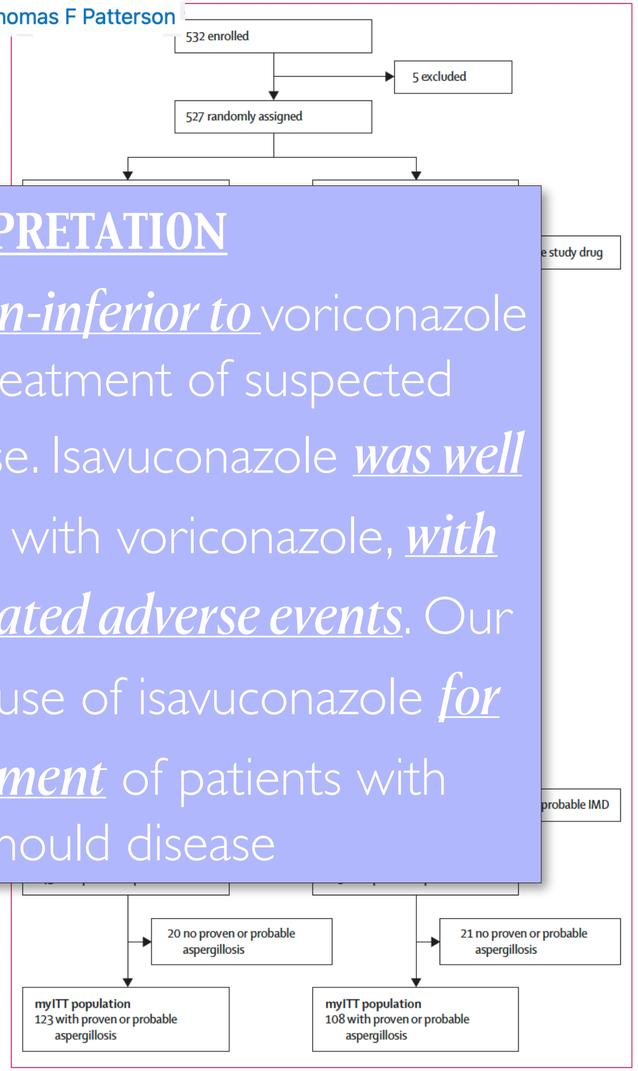
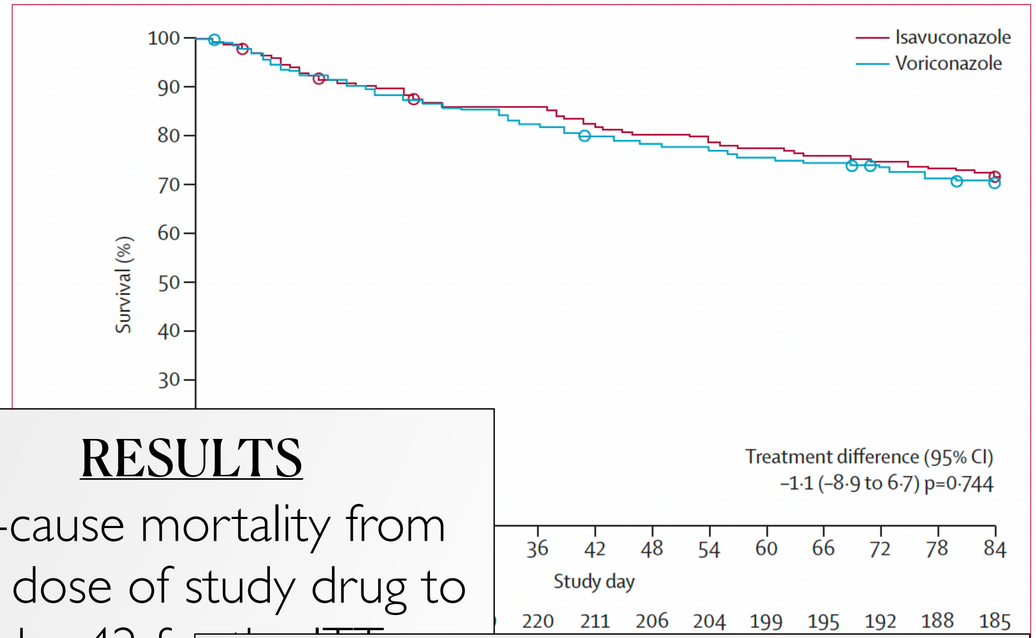
INTERPRETATION

Isavuconazole ***was non-inferior to*** voriconazole for the primary treatment of suspected invasive mould disease. Isavuconazole ***was well tolerated compared*** with voriconazole, ***with fewer study-drug-related adverse events***. Our results support the use of isavuconazole ***for the primary treatment*** of patients with invasive mould disease





RESULTS

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population
with isavuco
patients) an
voriconazole

*Proportions of patients with treatment-emergent adverse events by system organ class were similar overall. However, **ISV**-treated patients had a lower frequency of hepatobiliary disorders 9% vs 16%, eye disorders 15% vs 27%, and skin or subcutaneous tissue disorders 33% vs 42%. Drug-related adverse events were reported in 109 (42%) patients receiving **ISV** and 155 (60%) receiving **VOR** (p<0·001)*

myITT=mycological intention to treat

Multicenter Study > Clin Infect Dis. 2024 Oct 15;79(4):936-943. doi: 10.1093/cid/ciae371

European Study of Cerebral Aspergillosis treated with Isavuconazole (ESCAI): A study by the ESCMID Fungal Infection Study Group

Alexandra Serris,[1] Riina Rautemaa-Richardson,[2,3,a] Joana D. Laranjinha,[4,a] Anna Candoni,[5,a] Carolina Garcia-Vidal,[6,b] Ana Alastruey-Izquierdo,[7,8,b] Helena Hammarström,[9,10,b] Danila Seidel,[11,12] Jan Styczynski,[13] Raquel Sabino,[14,15] Frederic Lamoth,[16,17] Juergen Prattes,[18] Adilia Warris,[19,20] Raphaël Porcher,[21,22] Fanny Lanternier[1,23]; and the ESCAI Study Group

40 PATIENTS FROM 10 COUNTRIES WERE INCLUDED. THE MAIN UNDERLYING CONDITIONS WERE HEMATOLOGICAL MALIGNANCIES (53%) AND SOLID-ORGAN TRANSPLANTATION (20%)

CONCLUSIONS: ISAVUCONAZOLE APPEARS TO BE A WELL-TOLERATED TREATMENT. MORTALITY OF CA TREATED WITH ISAVUCONAZOLE IS SIMILAR TO THAT REPORTED WITH VORICONAZOLE

ISAVUCONAZOLE WAS ADMINISTERED AS A FIRST-LINE TREATMENT TO 10 PATIENTS, PRIMARILY IN COMBINATION THERAPY, RESULTING IN CONTROL OF CA IN 70% OF THESE CASES. THIRTY PATIENTS RECEIVED ISAVUCONAZOLE AFTER A MEDIAN OF 65 DAYS ON ANOTHER THERAPY, MOSTLY BECAUSE OF SIDE EFFECTS (50%) OR THERAPEUTIC FAILURE (23%) OF THE PREVIOUS TREATMENT PREDOMINANTLY GIVEN AS MONOTHERAPY, IT ACHIEVED CONTROL OF CA IN 73% OF THE PATIENTS. SEVENTEEN PATIENTS (43%) UNDERWENT NEUROSURGERY

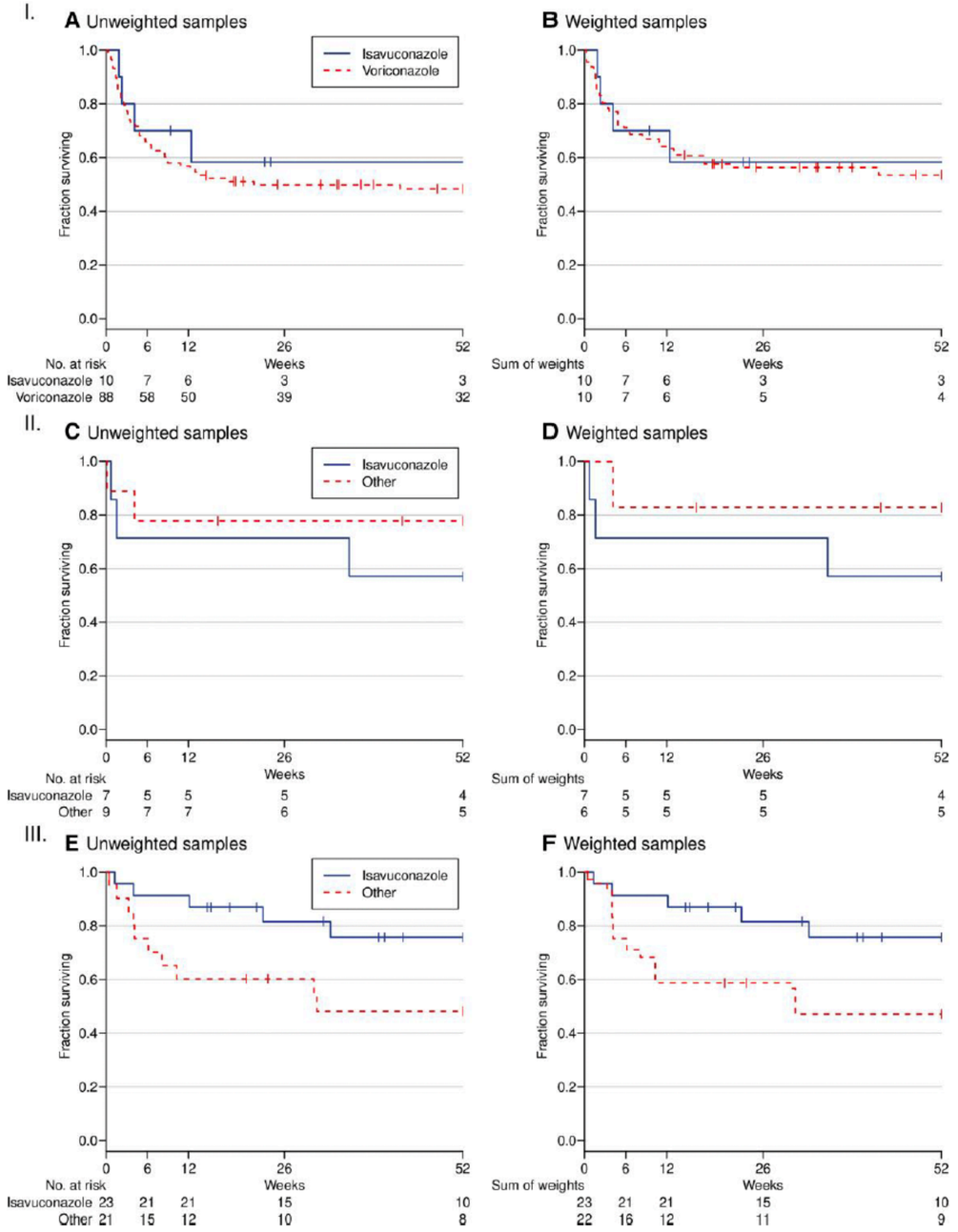

Figure 1. Survival comparison between ESCAI and CEREALS patients. I. Survival during the first year after first-line antifungal therapy. Unweighted sample (*A*) and weighted sample (*B*). II. Survival during the first year after second-or-more-line antifungal therapy, after switch for treatment failure. Unweighted sample (*C*) and weighted sample (*D*). III. Survival during the first year after second-or-more-line antifungal therapy, after switch for reasons other than treatment failure. Unweighted sample (*E*) and weighted sample (*F*). Abbreviations: CEREALS, Cerebral Aspergillosis Lesional Study; ESCAI, European Study of Cerebral Aspergillosis treated With Isavuconazole.

Multicenter Study > Clin Infect Dis. 2024 Oct 15;79(4):936-943. doi: 10.1093/cid/ciae371

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When measured, isavuconazole levels were low in cerebrospinal fluid but adequate in serum and brain tissue. Isavuconazole toxicity led to treatment interruption in 7.5% of the patients

Isavuconazole levels were low in CSF but adequate in serum and brain tissue in the few patients tested, which is in accordance with previously published data. Aspergillus brain infection is thought to follow angioinvasion of small or large brain vessels (depending on the route of dissemination) by hyphal elements, leading to cerebral infarction and the formation of brain abscesses rather than primary meningeal involvement. This might explain the efficacy of isavuconazole despite its low CSF penetration

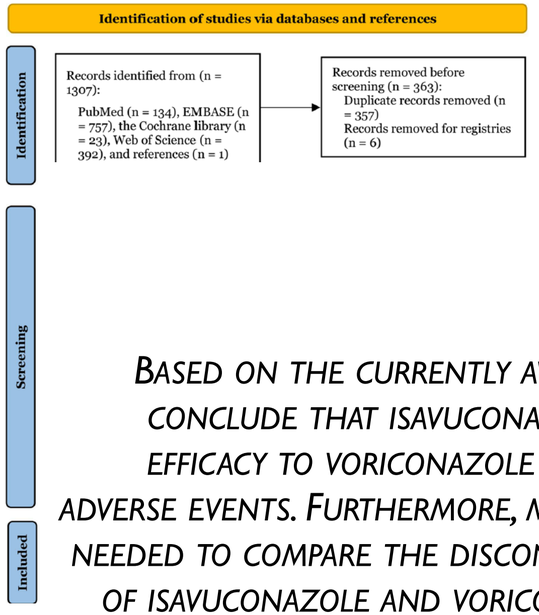
Schmitt-Hoffmann AH.et al. Tissue distribution and elimination of isavuconazole following single and repeat oral-dose administration of isavuconazonium sulfate to rats. *Antimicrob Agents Chemother* **2017**; 61: e01292–17
Rouzaud C. et al. Isavuconazole diffusion in infected human brain. *Antimicrob Agents Chemother* **2019**; 63:e02474–18
Lamoth F. et al. Isavuconazole brain penetration in cerebral aspergillosis. *J Antimicrob Chemother* **2019**; 74:1751–3

Candoni A. et al. Fungal infections of the central nervous system and paranasal sinuses in onco-haematologic patients. Epidemiological study reporting the diagnostic-therapeutic approach and outcome in 89 cases. *Mycoses* **2019**; 62:252–60.
Serris A. et al. Cerebral aspergillosis in the era of new antifungals: the CEREALS national cohort study. Nationwide CEREbral Aspergillosis Lesional Study (CEREALS). *J Infect* **2022**; 84:227–36
Schwartz S. et al. Improved outcome in central nervous system aspergillosis, using voriconazole treatment. *Blood* **2005**; 106:2641–5

The overall 12-week mortality of 18% was lower than what is commonly reported in the literature (51%–70%). This can be explained by a selection bias: 75% of the patients included in this study received isavuconazole as a second- or-later-line treatment, indicating a potentially less severe form of CA as they survived long enough to be switched to isavuconazole. However, the mortality rate of 30% among patients receiving isavuconazole as a first-line

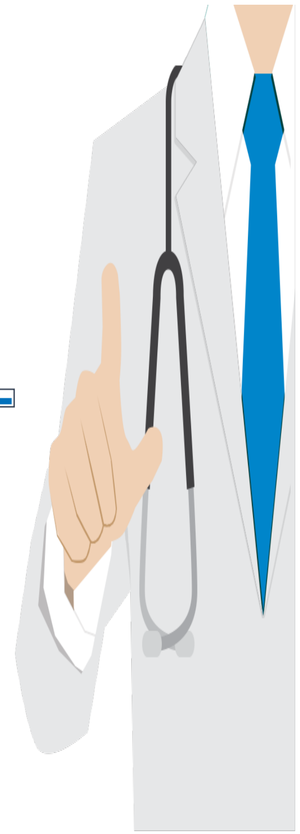
Efficacy and safety of *ISAVUCONAZOLE* versus *VORICONAZOLE* for the treatment of invasive fungal infections: a meta-analysis with trial sequential analysis

Jianzhen Weng [1], Xiaoman Du [1], Baomin Fang [1], Yanming Li [1], Lixue Huang [1], Yang Ju



CONCLUSIONS

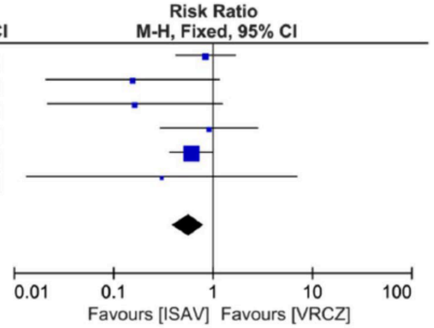
BASED ON THE CURRENTLY AVAILABLE DATA, WE CONCLUDE THAT ISAVUCONAZOLE HAS SIMILAR EFFICACY TO VORICONAZOLE BUT WITH FEWER ADVERSE EVENTS. FURTHERMORE, MORE STUDIES ARE NEEDED TO COMPARE THE DISCONTINUATION RATES OF ISAVUCONAZOLE AND VORICONAZOLE, AS A NO DEFINITIVE CONCLUSION CAN BE DRAWN. DESPITE THIS, OUR FINDINGS SUPPORT THE USE OF ISAVUCONAZOLE AS THE PRIMARY THERAPY FOR INVASIVE FUNGAL INFECTIONS



a

Study or Subgroup	ISAV Events	ISAV Total	VRCZ Events	VRCZ Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bongomin et al., 2019	8	20	10	21	15.0%	0.84 [0.42, 1.69]
Cheng et al., 2018	1	29	8	36	11.0%	0.16 [0.02, 1.17]
Cheng et al., 2020	1	28	7	32	10.0%	0.16 [0.02, 1.25]
Kohno et al., 2023	7	52	4	27	8.1%	0.91 [0.29, 2.83]
Maertens et al., 2016	21	257	35	259	53.5%	0.60 [0.36, 1.01]
Stull et al., 2019	0	22	1	20	2.4%	0.30 [0.01, 7.07]
Total (95% CI)		**408**		**395**	**100.0%**	**0.56 [0.39, 0.82]**
Total events	38		65			

Heterogeneity: Chi² = 5.14, df = 5 (P = 0.40); I² = 3%
Test for overall effect: Z = 3.01 (P = 0.003)



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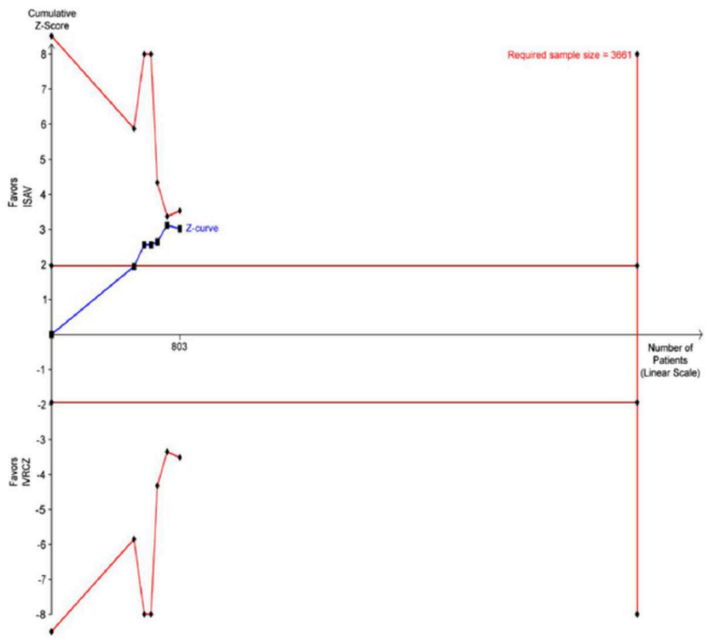


Fig. 5 Meta-analysis (**a**) and trial sequential analysis (**b**) showing difference in the rate of discontinuation due to drug-related adverse events between isavuconazole and voriconazole

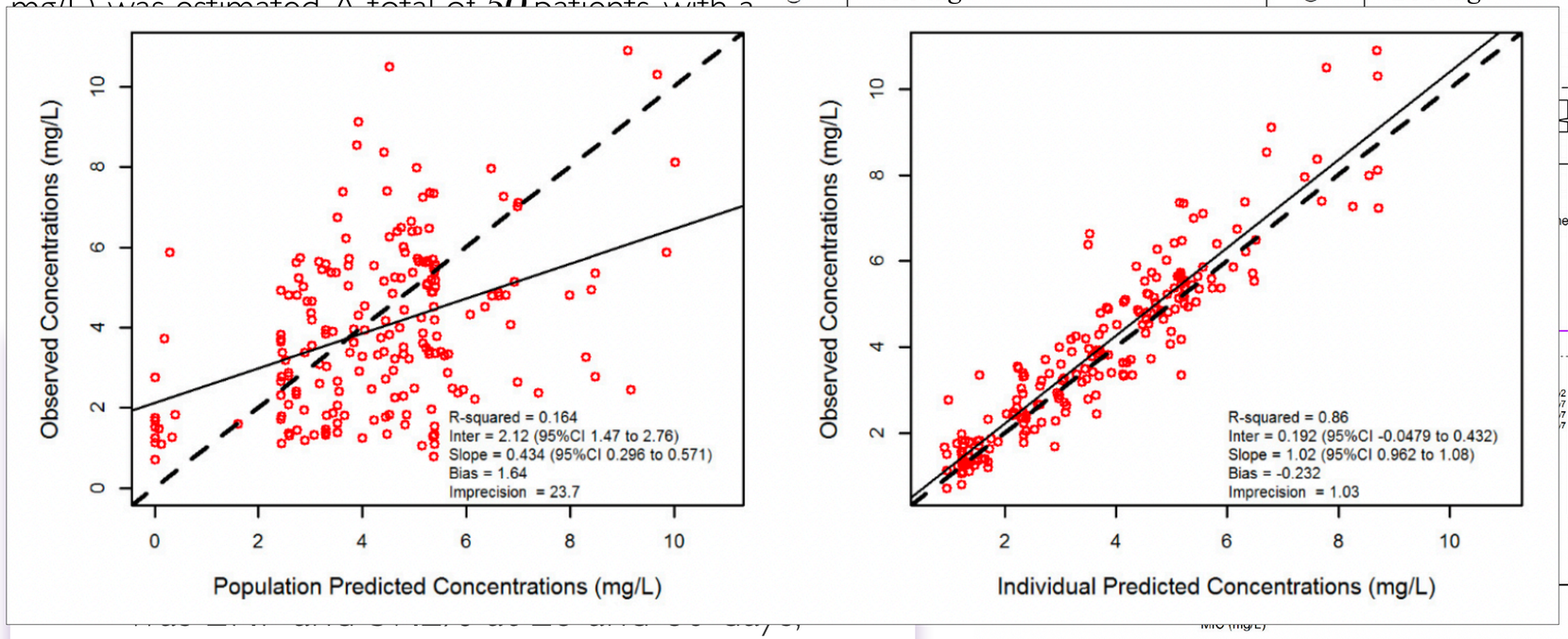
Pharmaceutics. 2021 Dec 6;13(12):2099. doi: 10.3390/pharmaceutics13122099.

Population PK and PD Target Attainment of *ISAVUCONAZOLE* against *Aspergillus fumigatus* and *Aspergillus flavus* in Adult Patients with Invasive Fungal Diseases: Should Therapeutic Drug Monitoring for Isavuconazole Be Considered as Mandatory as for the Other Mold-Active Azoles?

Pier Giorgio Cojutti [1,2], Alessia Carnelutti [3], Davide Lazzarotto [4], Emanuela Sozio
Anna Candoni [4], Renato Fanin [4,5], Carlo Tascini [3,5], Federico Pea [2,6]

The objective of this study was to conduct a population PK and PD analysis of ***Isavuconazole*** in a retrospective cohort of hospitalized patients

The proportion of trough concentrations (C_{trough}) exceeding a defined threshold of toxicity (>5.13 mg/L) was estimated. A total of 50 patients with a



respectively, due to isavuconazole accumulation over time

CFR=cumulative fraction of response

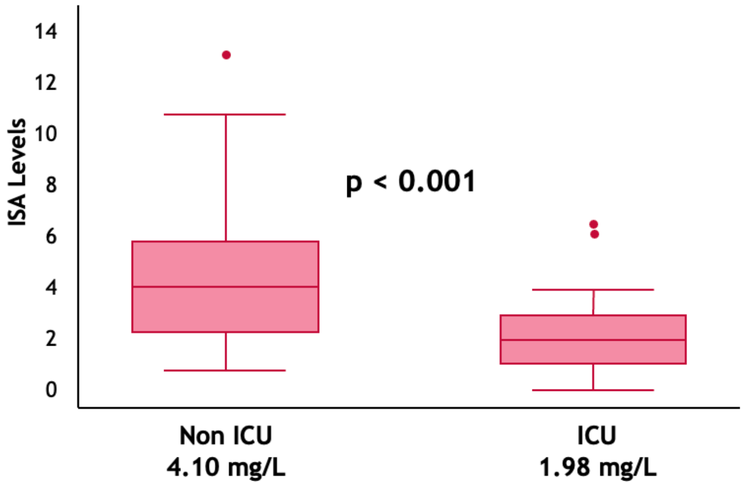
Figure 5. Probability of target attainment (PTA) of $AUC_{24\,h}$/MIC > 33.4 after loading and on Day 7 associated with isavuconazole maintenance doses of 100, 200 and 300 mg daily (solid lines) against the EUCAST MIC distribution (histograms) of *A. fumigatus* (**a**) and *A. flavus* (**b**). Horizontal dotted lines identify the threshold for optimal PTA (90%).

Our findings suggest that TDM for isavuconazole ***should not be considered*** as mandatory as for the other mold-active azoles voriconazole and posaconazole

Lower Blood Levels of Isavuconazole in ICU Patients

Restrospective analysis of TDM results for ICU patients versus non-ICU patients receiving standard ISA dose

Median ISA levels for non-ICU and ICU Patients



188 ISA determinations; median of 2 samples per patient

Patients with subtherapeutic ISA levels

	Non-ICU (n=39)	ICU (n=33)
Patients with all determinations <2 mg/L	3/39 (8%)	11/33 (33%)
Patients with at least 1 determination <1 mg/L	2/39 (5%)	9/33 (27%)
Patients that never achieved 1 mg/L	0	4/33 (12%)

Factors associated with lower ISA levels (univariate analysis)

BMI >25 p<0.001

CRRT p<0.001

Calcineurin inhibitors p=0.001

Factors associated with lower ISA levels (multivariate analysis)

BMI >25 p=0.05

ICU admission p<0.001

A high rate of ICU patients did not achieve therapeutic levels (>1-2 mg/L) of isavuconazole and had significantly lower levels compared to non-ICU patients, TDM should be considered in patients admitted to ICU, in patients with high BMI and in patients undergoing CCRT.

BMI, body mass index; CRRT, continuous renal replacement therapy; ICU, Intensive Care Unit; ISA, Isavuconazole; TDM: Therapeutic Drug Monitoring.
Melchio M, et al. ECCMID 2023. Oral O0217.

- Lower blood levels of ***ISAVUCONAZOLE*** in critically ill patients compared with other populations: possible need for therapeutic drug monitoring

Mikulska M. et al. *J Antimicrob Chemother* **2024**; 79:835-845

PREDICTORS OF LOWER ISV LEVELS WERE ADMISSION TO THE ICU, BMI > 25 KG/M², BILIRUBIN > 1.2 MG/DL AND THE ABSENCE OF HAEMATOLOGICAL DISORDER

J Antimicrob Chemother. 2025 Jun 3;80(6):1702-1706.

ISAVUCONAZOLE therapeutic drug monitoring and association with adverse events

Emily Huang [1], Rebecca Wittenberg [1], Joy Vongspanich Dray [1], Jeffrey Fine [2], Elizabeth Robison [3], Machelle Wilson [2], Kate Trigg [3], Derek J Bays [3], Melissa Chee George R Thompson 3rd [3 4]

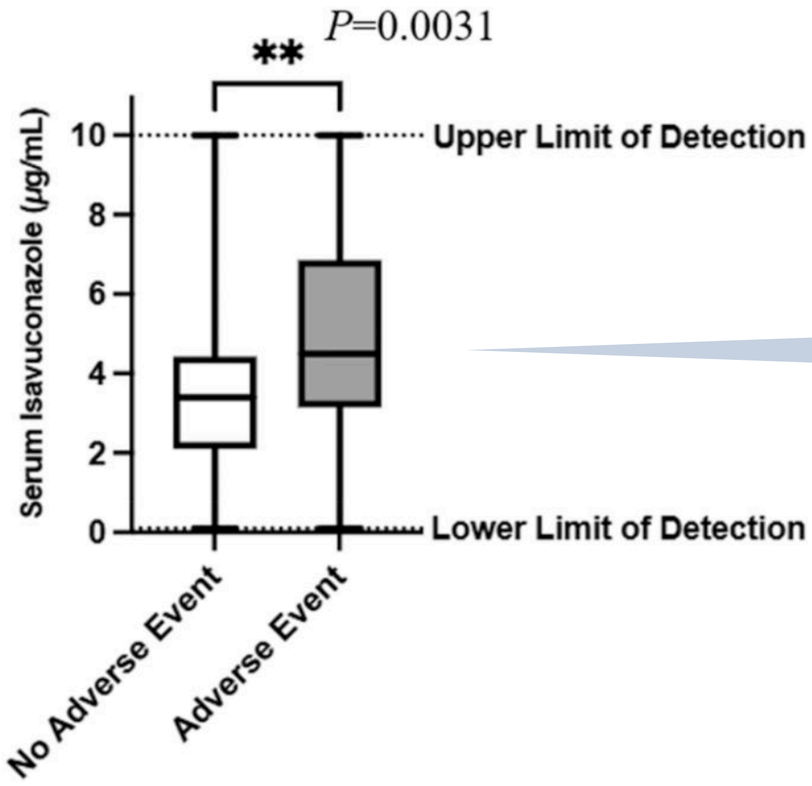


Figure 1. Isavuconazole serum drug levels between patients with and without adverse events.

OUR FINDINGS IDENTIFIED AN EXPOSURE-TOXICITY RELATIONSHIP FOR ISAVUCONAZOLE. THERAPEUTIC DRUG MONITORING MAY BE BENEFICIAL FOR THOSE ON ISAVUCONAZOLE THERAPY WHO DEVELOP SIGNS OR SYMPTOMS OF POTENTIAL TOXICITY. ADDITIONALLY, IN PATIENTS WITH ADVERSE EVENTS ATTRIBUTED TO ISAVUCONAZOLE, DOSE REDUCTION OFTEN LED TO RESOLUTION

Ninety-five patients, corresponding to 219 serum levels total, were analysed. Thirty-seven (*38.9*%) developed adverse events, most commonly transaminitis (*29.7*%), diarrhoea (24.3%), and nausea (*18.9*%). All 24 patients undergoing isavuconazole dose reduction demonstrated resolution of symptoms

Table 2. Types of adverse event in isavuconazole-treated patients with serum drug levels available

Adverse event type	Number of patients
Transaminitis, *n* (%)	12 (32.4%)
Diarrhoea, *n* (%)	9 (24.3%)
Nausea, *n* (%)	7 (18.9%)
Constipation, *n* (%)	4 (10.8%)
Dyspnoea, *n* (%)	4 (10.8%)
Fatigue, *n* (%)	4 (10.8%)
Skin rash, *n* (%)	4 (10.8%)
Hair loss, *n* (%)	4 (10.8%)
Vomiting, *n* (%)	3 (8.11%)
Headache, *n* (%)	3 (8.11%)
Elevated alkaline phosphatase, *n* (%)	3 (8.11%)
Peripheral neuropathy, *n* (%)	2 (5.41%)

Multicenter Study > Clin Pharmacokinet. 2023 Dec;62(12):1701-1711.

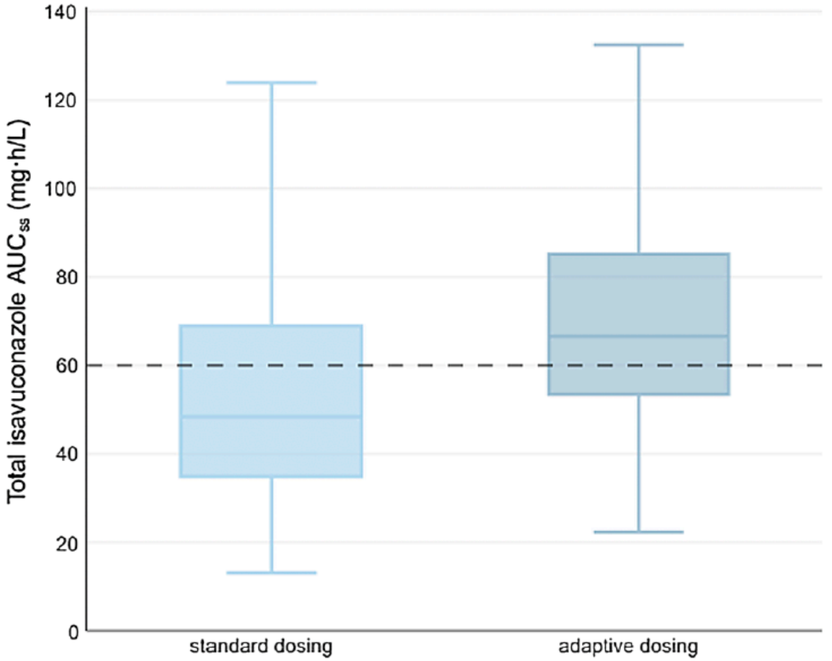
Population PK of Total and Unbound *ISAVUCONAZOLE* in Critically Ill Patients: Implications for Adaptive Dosing Strategies

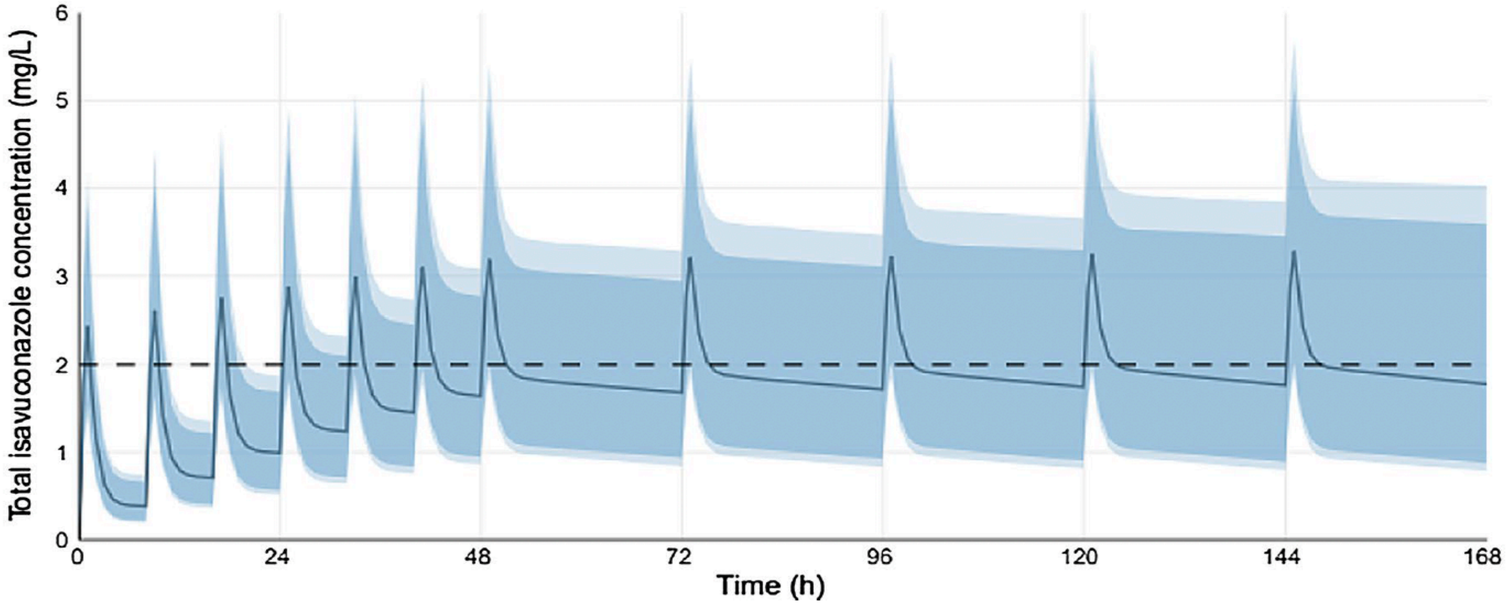
Anouk M E Jansen [1 2], Beatrijs Mertens [3 4], Isabel Spriet [3 4], Paul E Verweij, Jeroen Schouten [7], Joost Wauters [8], Yves Debaveye [8], Rob Ter Heine [9], Roger J M Brüggemann [9 5]

Dosing adjustments were made as follows: when C_{min} at 24 h after the start of therapy was below 1.0 mg/L, between 1.0 and 1.5 mg/L, or above 5.0 mg/L, daily maintenance doses were adjusted to 400 mg, 300 mg and 100 mg, respectively. Our strategy resulted in an increase of patients at adequate exposure on steady state from 35.8 to 62.3% compared with standard dosing

The dashed horizontal line represents the threshold total ISV trough concentration of 2 mg currently recommended by international guidelines

ADAPTATIVE DOSING





Clin Drug Investig. 2025 Mar 28. doi: 10.1007/s40261-025-01432-z

An Overview of *ISAVUCONAZOLE* Clinical Use: A Multicentre Analysis of Indications, Exposure and Hepatic Safety

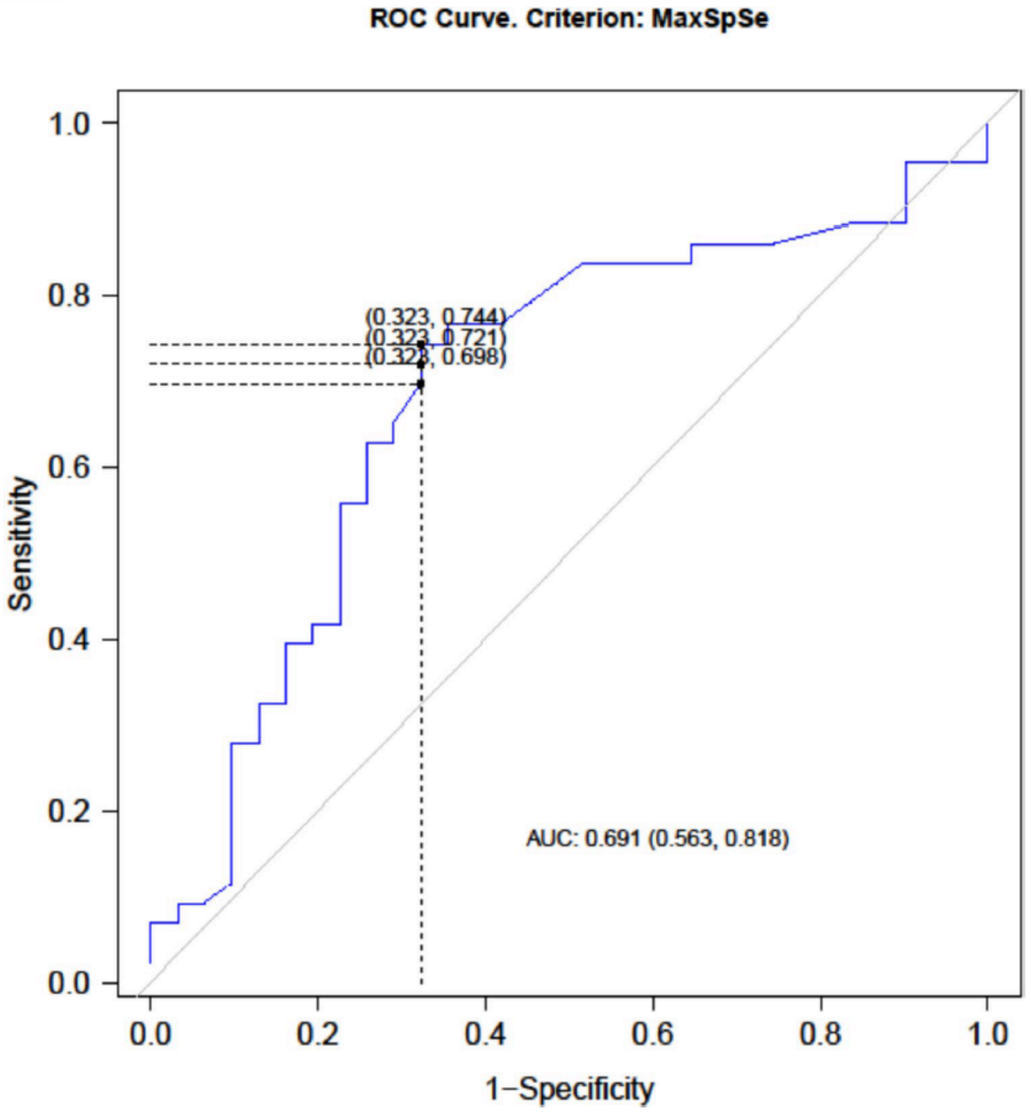
Anne-Lise Bienvenu [1 2], Alexandra Duffour [3], Claire Chatron [4], Natacha Mrozek [5], Luc Foroni [6], Aurélien Millet [7], Anne-Claire Lukaszewicz [8], Claire Merveilleux-du-Vignaux Philippe Portran [10], François Parant [7], Thierry Vial [11], Hélène Labussière-Wallet [12], Cécile Moluçon-Chabrot [13], Pauline Rascle [14], Agnès Henry [3], Pierre Pradat [15], Sylvain Goutelle [16 17]

Fig. 3 Receiver operating characteristic (ROC) curve analyses to predict albumin cut-off needed to achieve an optimal isavuconazole exposure > 2 mg/L. The AUC was statistically significant and the albumin cut-off was 26.5 mg/L (Se = 0.74; Sp = 0.68; PPV = 0.76; NPV = 0.66). *AUC* area under the curve, *NPV* negative predictive value, *PPV* predictive positive value, *Se* sensitivity, *Sp* specificity, *TDM* therapeutic drug monitoring

Therefore . . .

ALBUMIN ON THE DAY OF TDM APPEARED TO BE AN IMPORTANT FACTOR DRIVING ISAVUCONAZOLE EXPOSURE, ESPECIALLY IN ICU PATIENTS

ISV IF HYPOALBUMINEMIC < 2.5 IT IS ADVISABLE TO INCREASE THE DOSAGE - THEREFORE GO FROM 200 MG TO 300 MG



J Antimicrob Chemother. 2023 Dec 1;78(12):2902-2908. doi: 10.1093/jac/dkad328

Early attainment of *ISAVUCONAZOLE* target concentration using an increased loading dose in critically ill patients with ECMO

Stefan Hatzl [1 2 3], Lisa Kriegl [4], Florian Posch [5], Gernot Schilcher [1], Philipp Eller
Alexander Reisinger [1], Yvonne Grinschgl [6], Tina Muhr [7], Andreas Meinitzer [8],
Martin Hoenigl [4 9], Robert Krause [4 9]

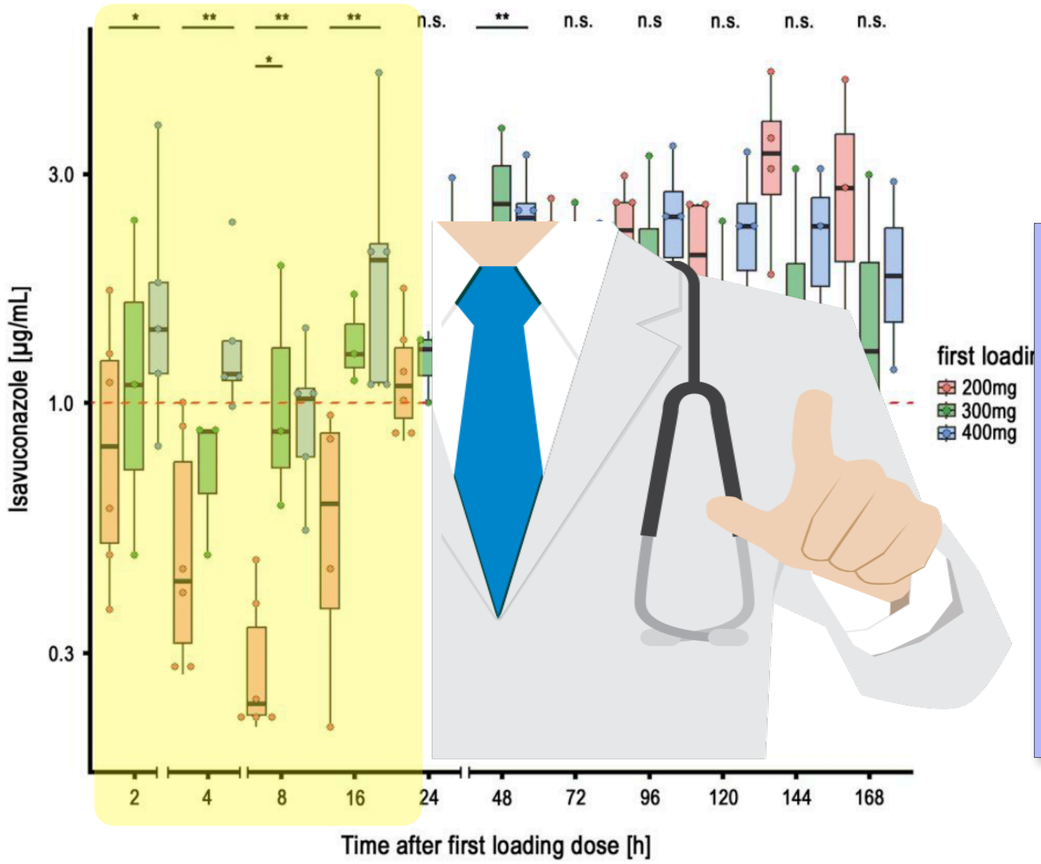


Figure 1. Isavuconazole plasma concentrations in ECMO patients at given timepoints after the first isavuconazole dose (200 mg, 300 mg or 400 mg as the first loading dose). At dedicated isavuconazole administration timepoints samples were obtained just before the scheduled isavuconazole infusions. *Denotes significantly higher isavuconazole concentrations in patients receiving 400 mg isavuconazole as the first loading dose compared with patients receiving 200 mg; **denotes significantly higher isavuconazole concentrations in patients receiving 400 mg isavuconazole as the first loading dose compared with patients receiving 200 mg or 300 mg; n.s. denotes no significant difference.

METHODS: 15 patients were included in this study, and isavuconazole concentrations were measured at several timepoints starting 2 h after the first isavuconazole dose up to 168 h. By interim analysis of isavuconazole concentrations and meticulous screening for adverse events, the ***first loading dose*** was stepwise increased from 200 to 300 mg, and finally to 400 mg

CONCLUSIONS

In critically ill patients with **ECMO** the **400 MG** loading dose of isavuconazole resulted in immediate median isavuconazole plasma concentrations **≥1 MG/L** and remained constant above this threshold after the first loading dose

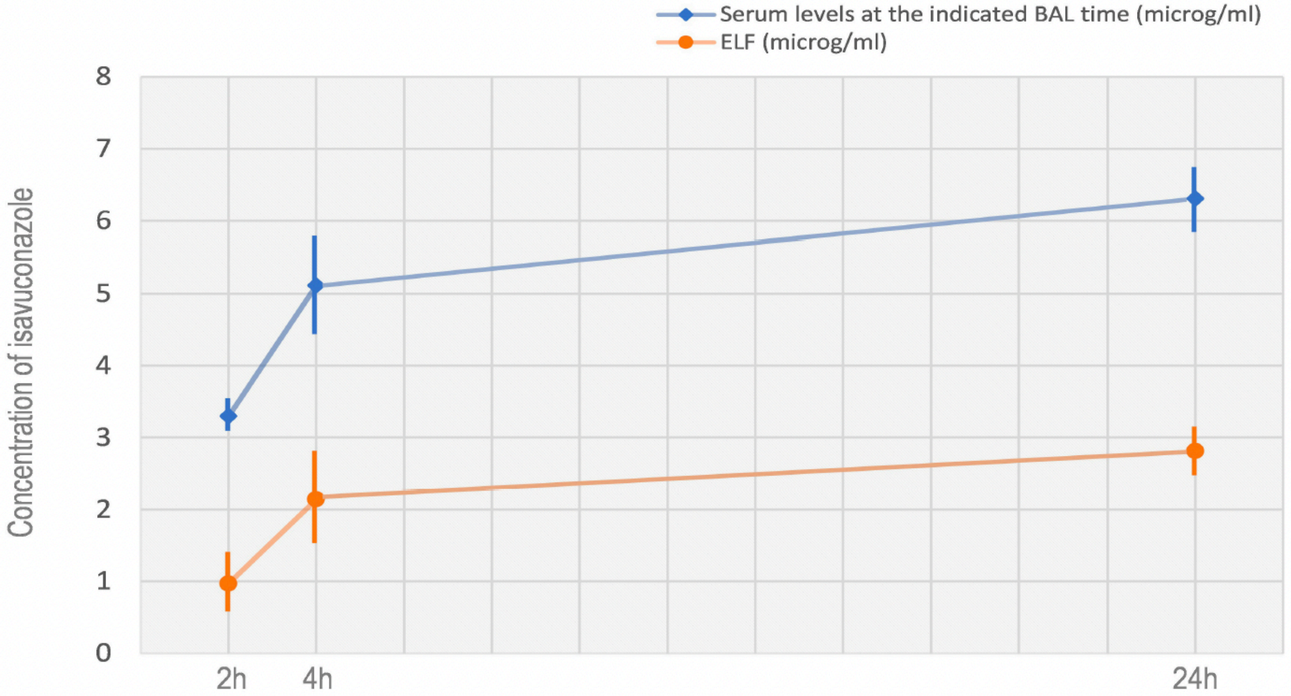
15 patients (***47%***) received standard ading dosage with 200 mg as the first ved 300 mg, and 5/15 (***33%***) received vuconazole as the first dose, followed ndard dosing in all patients. In patients ***mg*** as the first dose all isavuconazole ***gnificantly higher*** at timepoints ***up to*** higher proportions of isavuconazole L compared with patients with other loading dosages. In timepoints ***≥24 h*** after isavuconazole initiation all patient groups reached comparable plasma concentrations, regardless of the first loading dose regimen. We did not observe concentrations above ≥5 mg/L or any adverse events related to isavuconazole administration

› Antimicrob Agents Chemother. 2023 Oct 18;67(10):e0061323. doi: 10.1128/aac.00613-23

Bronchopulmonary penetration of *ISAVUCONAZOLE* in lung transplant recipients

Antonio F Caballero-Bermejo [# 1 2], Ignacio Darnaude-Ximénez [# 1], Myriam Aguilar-Pérez

This study included ***13*** patients and showed mean serum concentrations of ***3.30*** (standard deviation [SD] 0.45), ***5.12*** (SD 1.36), and ***6.31*** (SD 0.95) at ***2 h***, ***4 h***, and ***24 h*** respectively. Mean concentrations in the epithelial lining fluid were ***0.969*** (SD 0.895), ***2.141*** (SD 1.265), and ***2.812*** (SD 0.693) at the same time points



	Groups by BAL time (h)		
Mean (SD)	2h (N=3)	4h (N=5)	24h (N=2)
Serum levels at the indicated BAL time (microg/ml)	3.30 (0.46)	5.12 (1.36)	6.31 (0.95)
ELF (microg/ml)	0.969 (0.895)	2.141 (1.265)	2.812 (0.694)

FIG 1 Concentrations of ISA in serum and ELF at the time of BAL (mean and IQR concentrations).

In ***conclusion***, ISA adequately penetrated the ELF, with a relative concentration lower than that of blood. It is a drug with a tolerable safety profile that achieves ***adequate concentrations in the lung.*** These data support the use of ISA for the treatment of invasive aspergillosis

Antimicrob Agents Chemother. 2019 Sep 9;63(12):e01085-19. doi: 10.1128/AAC.01085-19

Pharmacokinetics and Dialytic Clearance of *ISAVUCONAZOLE* during In Vitro and In Vivo Continuous Renal Replacement Therapy

M Biagi [1], D Butler [1], X Tan [1], S Qasmieh [1], K Tejani [1], S Patel [1 2], R M Rivosecchi
M H Nguyen [4], C J Clancy [4 4], R K Shields [4 4], E Wenzler [5]

The pharmacokinetics (PK) and dialytic clearance of ***Isavuconazole*** in vitro and in 7 solid-organ transplant patients undergoing continuous renal replacement therapy (CRRT) were evaluated

TABLE 3 Plasma pharmacokinetic parameters of isavuconazole in solid-organ transplant patients receiving CRRT, healthy subjects, and patients with invasive fungal infection[a]

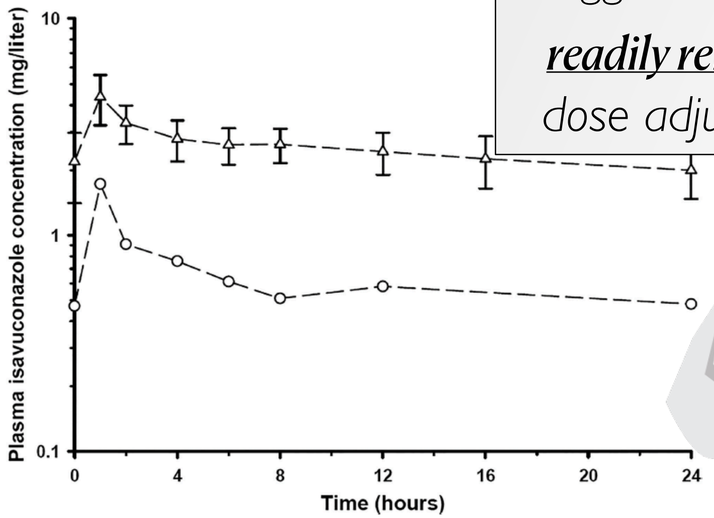
Group	C_{max} (mg/liter)	C_{min} (mg/liter)	$t_{1/2}$ (h)	AUC_{0-24} (mg · h/liter)	CL_{SS} (liters/h)	V_{SS} (liters)
CVVH ($n = 1$)	1.73	0.47	29.33	15.03	13.31	564.95
CVVHDF ($n = 6$)	4.38 ± 1.15	1.97 ± 0.54	51.53 ± 31.30	60.51 ± 13.18	3.44 ± 0.73	242.75 ± 148.33
Healthy subjects ($n = 6$)[b]	2.55 ± 0.88		117 ± 17.6[c]	33.6 ± 9.67	3.19 ± 0.90	542 ± 229[c]
IFI patients ($n = 136$)[d]				87.1 ± 41		

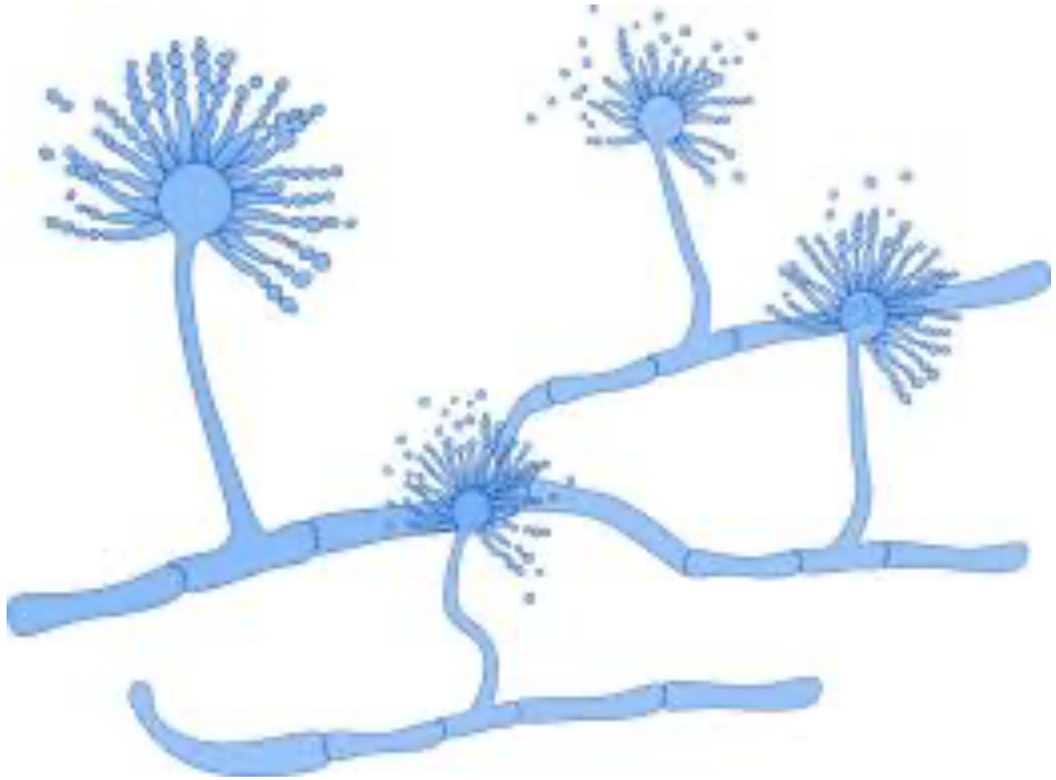
[a]Data are presented as means ± SDs.
[b]Subjects received a single i.v. loading dose equivalent to 200 mg isavuconazole followed by daily i.v. maintenance dose
14 days. All doses were infused over 1 h (28).
[c]$n = 4$.
[d]Patients received i.v. or oral (p.o.) dose of isavuconazole equivalent to 200 mg every 8 h for 48 h followed by i.v. or p.o.

Transmembrane clearance represented just 0.7% of the total isavuconazole clearance. These data suggest that isavuconazole ***is not readily removed*** *by CRRT and no dose adjustments are necessary*

In vivo, the mean plasma PK ameters of isavuconazole were as follows: maximum concentration of drug in serum (Cmax), 4.00±1.45 mg/liter; imum concentration of drug in um (Cmin), 1.76±0.76 mg/liter; half-life ($t_{1/2}$), 48.36±29.78 h; volume of distribution at steady state (Vss), 288.78±182.11 liters, clearance at steady state (CLss), 4.85±3.79 liters/h; and area under the concentration-time curve (AUC), 54.01±20.98 mg · h/liter

Prefilter plasma concentration-time profiles of isavuconazole in solid-organ transplant patients receiving either **CVVH** (dashed line, open circles) or **CVVHDF** (dashed line, open triangles)





Thank You

For Your Attention