



Invasive aspergillosis in haematology New guidelines

ECCMID Aspergillus, IDSA Aspergillus and ECIL 2017

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Disclosures

- Gilead: travel, speaker bureau
- Basilea : travel, speaker bureau

What's new for first line IPA treatment 2 randomized trials

Annals of Internal Medicine

ORIGINAL RESEARCH

Combination Antifungal Therapy for Invasive Aspergillosis

A Randomized Trial

Kieren A. Marr, MD; Haran T. Schlamm, MD; Raoul Herbrecht, MD; Scott T. Rottinghaus, MD; Eric J. Bow, MD, MSc; Oliver A. Cornely, MD; Werner J. Heinz, MD; Shyla Jagannatha, PhD; Liang Piu Koh, MBBS; Dimitrios P. Kontoyiannis, MD; Dong-Gun Lee, MD; Marcio Nucci, MD; Peter G. Pappas, MD; Monica A. Slavin, MD; Flavio Queiroz-Telles, MD, PhD; Dominik Selleslag, MD; Thomas J. Walsh, MD; John R. Wingard, MD; and Johan A. Maertens, MD, PhD

Ann Intern Med. 2015;162:81-89.

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, Issam I Raad, Kieren A Marr, Thomas F Patterson, Dimitrios P Kontoyiannis, Oliver A Cornely, Eric J Bow, Galia Rahav, Dionysios Neofytos, Mickael Aoun, John W Baddley, Michael Giladi, Werner J Heinz, Raoul Herbrecht, William Hope, Meinolf Karthaus, Dong-Gun Lee, Olivier Lortholary, Vicki A Morrison, Ilana Oren, Dominik Selleslag, Shmuel Shoham, George R Thompson III, Misun Lee, Rochelle M Maher, Anne-Hortense Schmitt-Hoffmann, Bernhardt Zeiher, Andrew J Ullmann

Lancet. 2016;387:760-9.

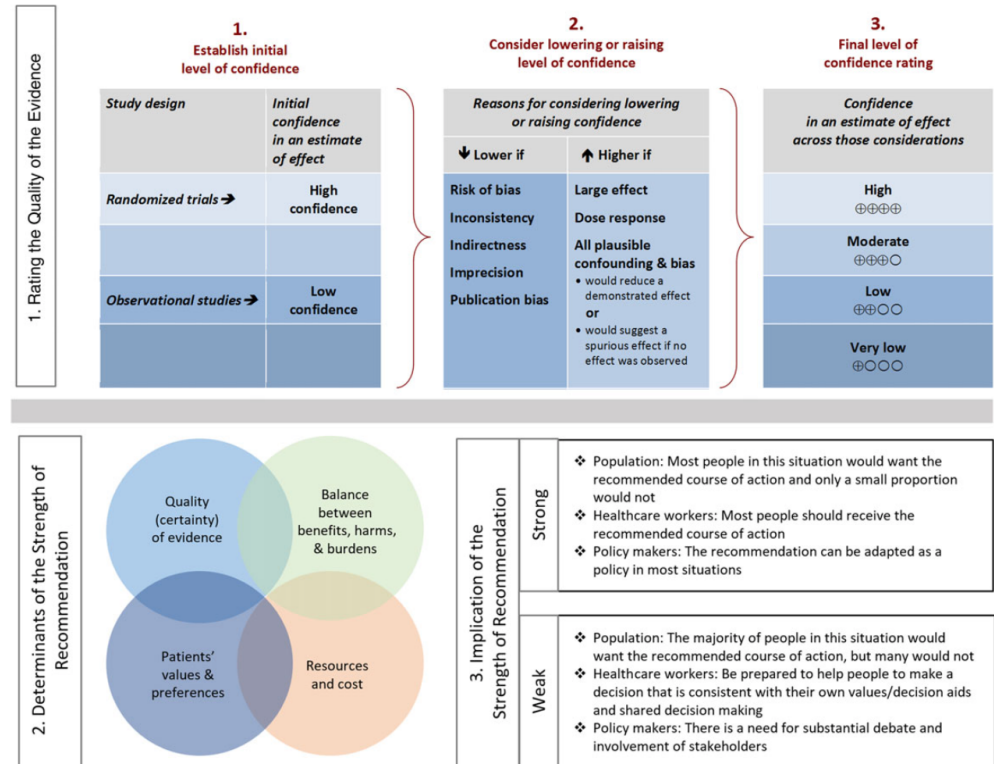
Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America

Thomas F. Patterson,^{1,a} George R. Thompson III,² David W. Denning,³ Jay A. Fishman,⁴ Susan Hadley,⁵ Raoul Herbrecht,⁶ Dimitrios P. Kontogiannis,⁷ Kieren A. Marr,⁸ Vicki A. Morrison,⁹ M. Hong Nguyen,¹⁰ Brahm H. Segal,¹¹ William J. Steinbach,¹² David A. Stevens,¹³ Thomas J. Walsh Jo-Anne H. Young,¹⁶ and John E. Bennett^{17,a}

- Infectious Diseases Society of America
- Last IDSA Aspergillus guidelines: 2008
- Literature to 2014
- 17 experts, members of IDSA: 16 adult ID physicians, 1 pediatric infectious diseases physician

Patterson T. Clin Infect Dis 2016;63:433-42.

GRADE Grading of Recommendations, Assessment, Development and Evaluation



ECIL-6 guidelines for the treatment of invasive candidiasis, aspergillosis and mucormycosis in leukemia and hematopoietic stem cell transplant patients



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Frederic Tissot,¹ Samir Agrawal,² Livio Pagano,³ Georgios Petrikkos,⁴
Andreas H. Groll,⁵ Anna Skiada,⁶ Cornelia Lass-Flörl,⁷ Thierry Calandra,¹
Claudio Viscoli⁸ and Raoul Herbrecht⁹

- **2015-update**
- ECIL: European Conference on Infections in Leukemia
- Collaboration between the EORTC, EBMT, ELN and ICHS
- 55 experts from 24 countries
- Aspergillus guidelines: ECIL-1, update in ECIL-2 and 3

Grade	Strength of evidence
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation for use

Grade	Quality of evidence
I	Evidence from at least 1 properly randomized controlled trial
II	Evidence from at least 1 well designed clinical trial, without randomization, from cohort or case-controlled analytical studies
III	Evidence from respected authorities, based on clinical experience, descriptive studies, or report or expert committees



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

A.J. Ullmann^{1, 62, 63}, J.M. Aguado^{2, 62, 63}, S. Arikan-Akdagli^{3, 62, 63}, D.W. Denning^{4, 5, 6, 63}, A.H. Groll^{7, 62, 63}, K. Lagrou^{8, 62, 63}, C. Lass-Flörl^{9, 62, 63}, R.E. Lewis^{10, 62}, P. Munoz^{11, 12, 13, 62, 63}, P.E. Verweij^{14, 62, 63}, A. Warris^{15, 62, 63}, F. Ader^{16, 17, 65}, M. Akova^{18, 62, 63}, M.C. Arendrup^{19, 62, 63}, R.A. Barnes^{20, 63}, C. Beigelman-Aubry^{21, 65}, S. Blot^{22, 23, 65}, E. Bouza^{11, 12, 13, 62, 63}, R.J.M. Brüggemann^{24, 62}, D. Buchheidt^{25, 62, 63}, J. Cadranet^{26, 65}, E. Castagnola^{27, 62}, A. Chakrabarti^{28, 63}, M. Cuenca-Estrella^{29, 62, 63}, G. Dimopoulos^{30, 65}, J. Fortun^{31, 62, 63}, J.-P. Gangneux^{32, 62, 63}, J. Garbino^{33, 62, 63}, W.J. Heinz^{1, 62, 63}, R. Herbrecht^{34, 62}, C.P. Heussel^{35, 63}, C.C. Kibbler^{36, 63}, N. Klimko^{37, 63}, B.J. Kullberg^{24, 62, 63}, C. Lange^{38, 39, 40, 65}, T. Lehrnbecher^{41, 63}, J. Löffler^{1, 62, 63}, O. Lortholary^{42, 62, 63}, J. Maertens^{43, 62, 63}, O. Marchetti^{44, 45, 62, 63}, J.F. Meis^{46, 62, 63}, L. Pagano^{47, 63}, P. Ribaud⁴⁸, M. Richardson^{4, 5, 6, 62, 63}, E. Roilides^{49, 50, 62, 63}, M. Ruhnke^{51, 62, 63}, M. Sanguinetti^{52, 62, 63}, D.C. Sheppard^{53, 62, 63}, J. Sinkó^{54, 62}, A. Skiada^{55, 62, 63}, M.J.G.T. Vehreschild^{56, 57, 58, 63}, C. Viscoli^{59, 62, 63}, O.A. Cornely^{56, 58, 60, 61, 62, 63, 64, *}

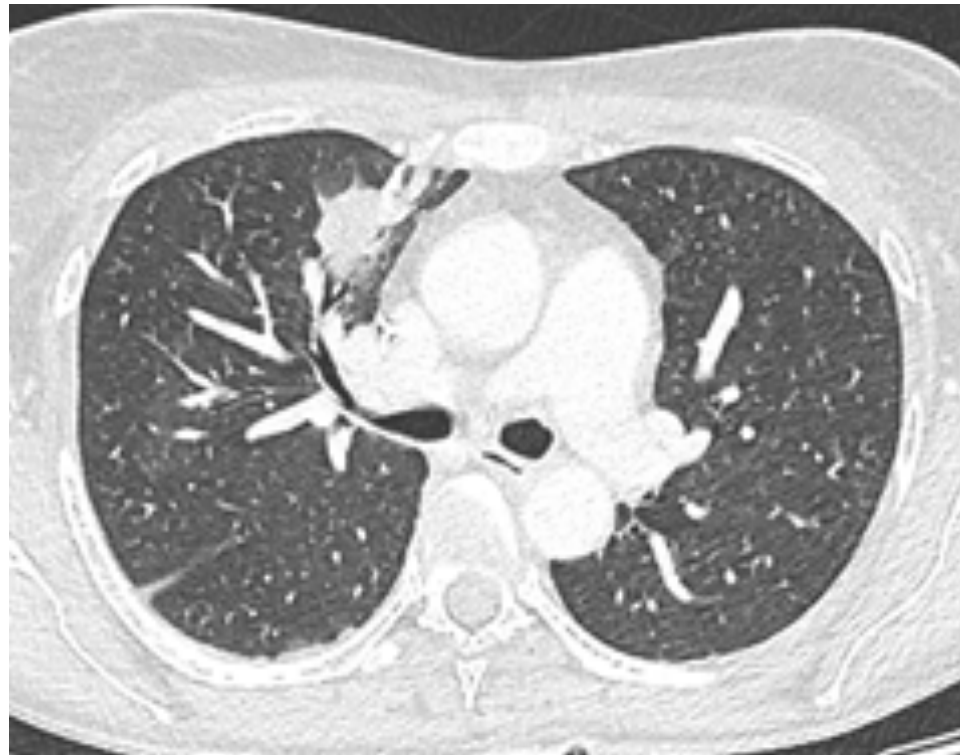
- ESCMID, ECMM and ERS
- 53 experts



Table 1
Strength of recommendation and quality of evidence

Strength of recommendation	Definition
Grade A	Societies <u>strongly</u> support a recommendation for use
Grade B	Societies <u>moderately</u> support a recommendation for use
Grade C	Societies <u>marginally</u> support a recommendation for use
Grade D	Societies support a recommendation <u>against</u> use
Quality of evidence	Definition
Level I	Evidence from at least one properly* designed randomized, controlled trial (oriented on the primary end point of the trial)
Level II	Evidence from at least one well-designed clinical trial (including secondary end points), without randomization; from cohort or case–controlled analytic studies (preferably from more than one centre); from multiple time series; or from dramatic results of uncontrolled experiments
Level III	Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies, or reports of expert committees
Added index	Source of Level II evidence
r	Meta-analysis or systematic review of randomized controlled trials
t	Transferred evidence, i.e. results from different patients' cohorts, or similar immune-status situation
h	Comparator group: historical control
u	Uncontrolled trials
a	Published abstract presented at an international symposium or meeting

First line IPA treatment



ECIL-6 recommendations for first-line treatment of invasive aspergillosis

	Grade	Comments
Voriconazole ^a	A I	Daily dose: 2x6 mg/kg on day 1 then 2x4 mg/kg (initiation with oral therapy: C III)
Isavuconazole	A I	As effective as voriconazole and better tolerated
Liposomal amphotericin B	B I	Daily dose: 3 mg/kg
Amphotericin B lipid complex	B II	Daily dose: 5 mg/kg
Amphotericin B colloidal dispersion	C I	Not more effective than d-AmB but less nephrotoxic
Caspofungin	C II	
Itraconazole	C III	
Combination voriconazole ^a + anidulafungin	C I	
Other combinations	C III	
Recommendation against use		
Amphotericin B deoxycholate	A I	Less effective and more toxic

^aMonitoring of serum levels is indicated. In the absence of sufficient data for first-line monotherapy, anidulafungin, micafungin and posaconazole have

ESCMID-ECMM-ERS guidelines for first line targeted therapy of pulmonary disease

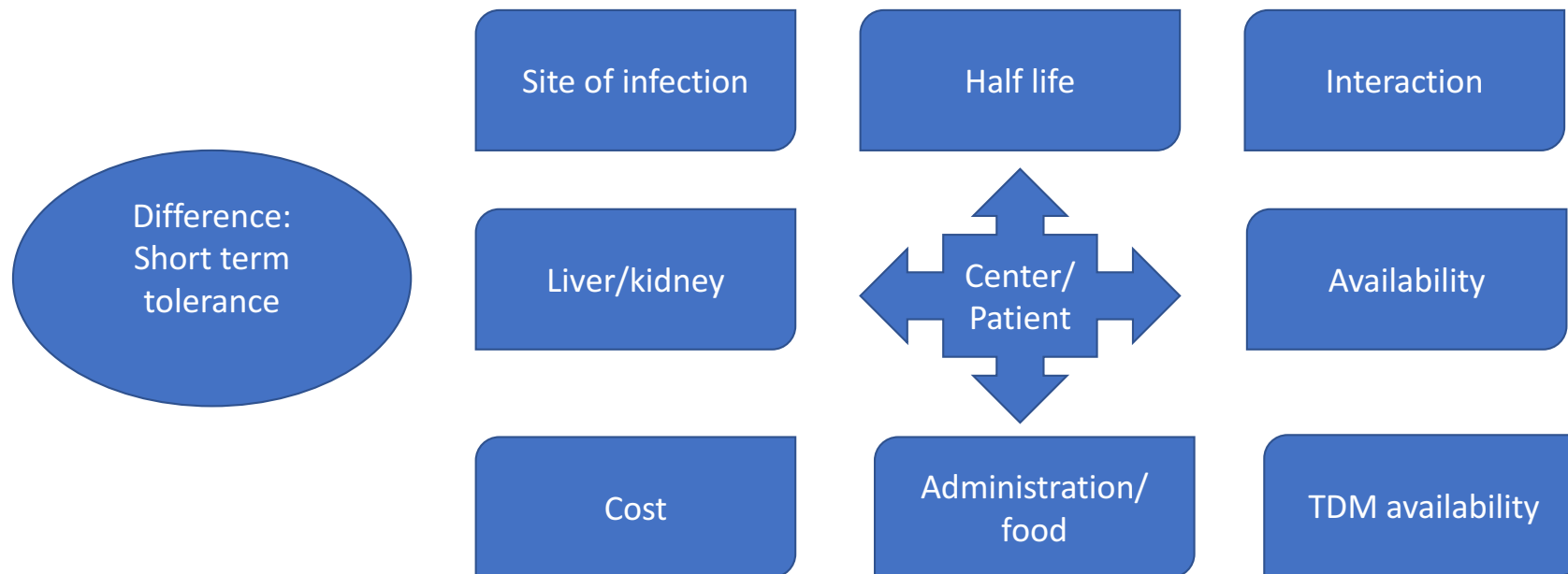
Intervention	SoR	QoE	Comment
Isavuconazole	A	I	DIII if mould active azole prophylaxis Fewer adverse events than voriconazole
Voriconazole	A	I	DIII if mould active azole prophylaxis
L-AmB	B	II	
Combination of voriconazole + anidulafungin	C	I	No significant difference compared to voriconazole In GM-positive (subgroup) better survival
Itraconazole	C	III	DIII if mould active azole prophylaxis
Caspofungin	C	II	
ABLC	C	III	
Micafungin	C	III	
ABCD	D	I	
Conventional AmB	D	I	
Other combination	D	III	

IDSA recommendations for Invasive pulmonary aspergillosis treatment

		Strength of recommendation	Quality
Primary therapy	Voriconazole	Strong	High
Alternative	L-AmB	Strong	Moderate
	Isavuconazole	Strong	Moderate
	Other lipid formulation	Weak	Low
Selected patients with documented IPA	Voriconazole and an echinocandin	Weak	Moderate
Not recommended	Echinocandin	Strong	Moderate

Voriconazole or isavuconazole?

Out of the context of frequent azole resistance/ azole antimould prophylaxis



Voriconazole dose and formulation

Guidelines		
ECIL-6	2 x 6 mg/kg on day 1 then 2 X 4 mg/kg	Initiation with oral therapy CIII
ESCMID/ECMM/ERS	2 x 6mg/kg IV (oral 400 mg bid) D1 then 2 x 4 mg/kg IV (oral 200-300mg) bid	Initiation with oral therapy CIII Consider switching to oral therapy in stable and pharmacokinetically reliable patients.
IDSA	2 x 6 mg/kg IV on day 1 Then 2 x 4 mg/kg IV oral therapy can be used at 200–300 mg bid or weight based dosing on a mg/kg basis	

Start with voriconazole IV
D1 6mg/kg bid then 4 mg/kg bid
When oral therapy 4 mg/kg bid

Voriconazole / Isavuconazole TDM

Voriconazole

Guidelines	TDM		
ECIL-6	Recommended		
ESCMID/ECM M/ERS	All IA patients	Plasma trough level after 2-5 days Repeat plasma trough level	Target 1-5.5 mg/L >2 mg/L for Aspergillus strains MIC=2 mg/mL
IDSA			➤ >1-1.5 mg/L for efficacy, < 5-6 mg/L for toxicity

Isavuconazole

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
All patients receiving isavuconazole	Improve efficacy safety and compliance	Measure serum trough level on day 5 of therapy or soon after	C	III	Limited data to support routine TDM but may be indicated in the setting of treatment failure, drug interactions, or if toxicity is suspected The long half-life of isavuconazole (130 h) may support the use of TDM in some clinical situations to confirm drug clearance before starting medications metabolized by CYP3A4, especially chemotherapy agents	FDA advisory briefing documents

Abbreviations: FDA, US Food and Drug Administration; QoE, Quality of evidence; SoR, Strength of recommendation; TDM, therapeutic drug monitoring.

Tissot F, Haematologica 2017;102:433-444, Patterson T. Clin Infect Dis 2016;63:433-42, Ullmann A, CMI 2018. Suppl 1: e1-e38

Combination Echinocandin and voriconazole

Subgroup of patients documented by positive galactomannan, 6-week all-cause mortality was lower in patients receiving combination (difference of - 11.6% in favor of combination; $P=0.037$).

Large majority felt that this subgroup analysis, that had not been originally planned, was not sufficient to give a stronger recommendation although this subgroup included 80% of the modified intent-to-treat population.

Guidelines		SoR, QoE	Comment/Recommendation
ECIL-6	Vori + Anidula	CI	
ESCMID/ECMM/ERS	Combination of voriconazole + anidulafungin	CI	No significant difference compared to voriconazole In GM-positive (subgroup) better survival
IDSA	Voriconazole and echinocandin	Weak	Selected patients with documented IPA

Documented azoles resistance

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Isolate with voriconazole MIC = 2 mg/mL	To cure IA	Voriconazole + echinocandin combination therapy or L-AmB monotherapy for IA (as well as for CPA)	A	III	The probability of voriconazole treatment failure may be higher than in voriconazole MIC <2	[529–532]
Isolate with voriconazole MIC >2 mg/mL	To cure IA	L-AmB	A	II _u		[113,114,533]
		AmB lipid complex	C	III		No reference found.
		Voriconazole & anidulafungin	B	III		[529]
		Posaconazole & caspofungin	C	III	Posaconazole not licensed for primary treatment	[534]
		Caspofungin or micafungin	C	III	Patients with contra-indications to AmB and other azoles	No reference found.

Abbreviations: AmB, Amphotericin B; CPA, chronic pulmonary aspergillosis; IA, invasive aspergillosis; L-AmB, liposomal amphotericin B; QoE, Quality of evidence; SoR, Strength of recommendation.

Extra pulmonary aspergillosis

Location		AF	SoR	QoE	Surgery
CNS	IDSA	Vori	Strong	Moderate	
	IDSA	Alternative: L AmB	Strong	Moderate	
	ESCMID/ECMM/ERS	Vori	A	II	
	ESCMID/ECMM/ERS	AmB lipid formulation	B	III	
	ESCMID/ECMM/ERS	Posa, itra, echino	D	III	
Endophthalmitis	IDSA	Systemic vori + intravitreal vori or AmB	Strong	Low	
	ESCMID/ECMM/ERS	Vori L-AmB	A A	II II	
Invasive sinusitis	IDSA	Vori or L-AmB	Strong	Moderate	
Endocarditis	IDSA	Vori or L-AmB	Strong	Low	+ Surgery
Osteomyelitis or arthritis	IDSA	Voriconazole	Strong	Moderate	+ Surgery

Patterson T. Clin Infect Dis 2016;63:433-42, Ullmann A, CMI 2018. Suppl 1: e1-e38

Salvage therapy?

- Failure definition:
 - Documentation: coinfection?
 - CT progression in not synonymous to failure
 - GM monitoring
 - Host status
 - Azoles trough level
 - Aspergillus MIC
- Rule:
 - Switch to another drug class



Table 8. ECIL-6 recommendations for salvage therapy of invasive aspergillosis.

	Grade	Comments
Liposomal amphotericin B	B II	No data on voriconazole failure
Amphotericin B lipid complex	B II	No data on voriconazole failure
Caspofungin	B II	No data on voriconazole failure
Itraconazole	C III	Insufficient data
Posaconazole ^a	B II	No data on voriconazole failure
Voriconazole ^a	B II	If not used in first-line
Combination	B II	Various studies and conflicting results

^aMonitoring of serum levels is indicated, especially if posaconazole oral suspension is used.

Treatment duration

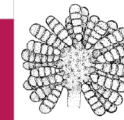
Guidelines		
ESCMID/ECMM/ERS	Clinical response, immune reconstitution	No persistent imaging, mycological evidence of disease 3-50 w Close monitoring after AF discontinuation
IDSA	Minimum of 6-12 w	Depends on immunosuppression, Site of disease Disease improvement

New guidelines

- Isavuconazole / Voriconazole first line: personalized choice
- Higher voriconazole oral dose/ early TDM
- Recommendation for resistant *Aspergillus*
- No place for first line combination except some cases: to be defined
- Breakthrough/Salvage and duration: lack of data

SAVE THE DATE

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