Invasive Aspergillosis in 2018: An Update in Diagnosis and Management

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  - Merck, Inc
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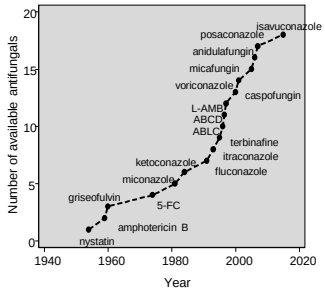
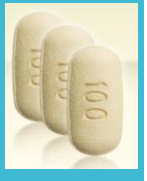
  - Gilead, Inc
  - Cidara, Inc
  - Amplyx, Inc

A congested field of antifungals for treatment of IA





Posaconazole gastro-resist tablet (100 mg)

New posaconazole formulation

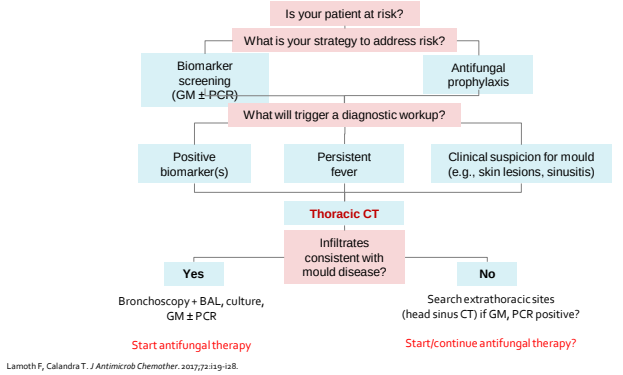
- Delays the release of posaconazole until the tablets reach the small intestine [pH -hypromellose acetate succinate]
- Improves oral bioavailability, and avoids requirement of multiple daily dosing with high fat meal
- No dosage adjustments are required when used concomitantly with antacids, H_2-receptor antagonists, and PPIs

Recent ECIL guidelines

Antifungal Prophylaxis	Pre-Engraftment Low Risk for Moulds	Pre-Engraftment High Risk for Moulds	GVHD
Fluconazole	A-I	A-III against	A-III against
Itraconazole	B-I	B-I	B-I
Voriconazole	B-I	B-I	B-I
Posaconazole oral/tablet	B-II	B-II	A-I
Micafungin	B-I	C-I	C-II
Caspofungin/anidulafungin	No data	No data	No data
Liposomal amphotericin B	C-II	C-II	C-II
Aerosolised amphotericin B plus fluconazole	C-III	B-II	No data

AML/MDS: POSA A-I

Maertens J et al. JAC 2018



Lamoth F, Calandra T. *J Antimicrob Chemother*. 2017;72:i19-i28.

Where d we stand with the galactomannan assay?

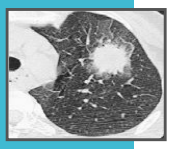
- Suboptimal performance of serum GM in the setting of mold-active prophylaxis (high false positive rate, high false negative rate)
- Suboptimal performance in immunosuppressed, non-immunosuppressed patients (e.g., SOTs, CGD)
- Good as adjunctive diagnostic
- Serial measurements of galactomannan important
- Test should be interpreted with other clinical indicators of infection

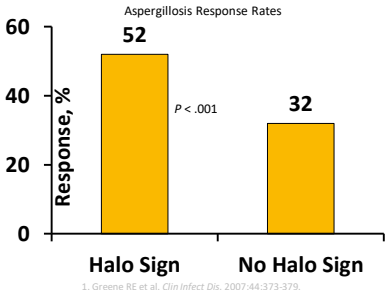
2016 IDSA Guideline for Treatment of Aspergillosis

Condition	Primary therapy	Alternative	Comments
Invasive Pulmonary	**Voriconazole** (6 mg/kg IV every 12 hours x 1 day; then 4 mg/kg every 12 hours)	**Primary:** Isavuconazole 200 mg Q8 x 6 doses, then 200mg daily L-AMB (3-5 mg/kg/day) **Salvage:** ABLC (5 mg/kg/day) Caspofungin (70 mg/day x 1, then 50 mg/day) Micafungin (100-150 mg/day) Posaconazole tablet 300 mg BID x 1, then 300 mg daily Itraconazole suspension (200 mg PO every 12 hours)	***Primary Combination therapy*** Not routinely recommended; addition of another agent or switch to another drug class for salvage therapy may be considered in individual patients.

Herbrecht R, et al. NEJM. 2002 Aug 8;347(6):408-15. Patterson TF, Thompson GR, Denning DW, et al. Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2016 Aug 15;63(4):e1-e60.

Initiating Therapy Early Makes a Difference![1]





1. Greene RE et al. *Clin Infect Dis.* 2007;44:373-379.

Looking to the future

Breakthrough IA

Definition, diagnosis, management

Guidelines (e.g., IDSA, NCCN, etc)-endorsed primary prophylaxis with a mold-active azole the norm in hematology centers-AML in US

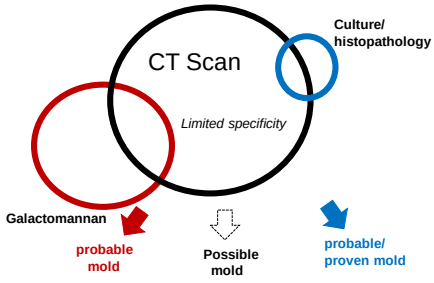
Primary prophylaxis for AML patients

Institution	NCI Cancer Designation	Primary Prophylaxis
MD Anderson Cancer Center	Yes	posaconazole
Roswell Park Cancer Institute	Yes	posaconazole
Memorial Sloan Kettering	Yes	posaconazole
University of Pennsylvania	Yes	voriconazole
Mayo Clinic	Yes	voriconazole*
University of Kentucky	Yes	posaconazole
University of Michigan	Yes	voriconazole
Mount Sinai Hospital	Yes	voriconazole
Georgia Regents Medical Center	No	posaconazole
Wake Forest Baptist	Yes	posaconazole/ fluconazole (for hypomethylating agent therapy)
Fred Hutchinson Cancer Center	Yes	fluconazole
Virginia Commonweath University	Yes	fluconazole
Dana Farber Cancer Institute	Yes	None
Saint Louis University	No	fluconazole

*Posaconazole if: voriconazole-specific ADR; require reinduction at day 14; if neutropenia lasts>30 days;

Thanks to C Raush, PharmD & Lydia Benitez, PharmD

Antifungal therapy typically triggered by symptomatic or radiographic evidence of breakthrough infection (presumed IA)



Nivoix et al. Clin Infect Dis 2008;47:1176.85
Kohno Clin Infect Dis 2008;47:1185-7

…There is a spectrum of definitions on what constitutes breakthrough IA

Table 1. Patterns of invasive fungal disease in pratice, based on 2008 EORTC-MSG criteria.

	A	B	C				D	E
	-	-	I	II	III	IV	-	
Radiological signs and clinical symptoms	No	Persistent febrile neutropenia	No	Clinical (any new infiltrate not fulfilling the EORTC/MSG criteria)		Radiological signs on CT (dense, well-circumscribed lesions(s) with or without a halo sign, air-crescent sign, or cavity)		Not considered necessary
Mycology results	Negative	Negative	Positive biomarker or microscopy or culture	Negative	Positive biomarker or microscopy or culture	Negative	Positive biomarker or microscopy or culture	Positive tissue or specimen from a sterile site
Clinical evidence of IFD	No	No	No	No	No	Yes	Yes	Yes
Mycological evidence of IFI	No	No	Yes	No	Yes	No	Yes	Yes
Final diagnosis	Unclassified					Possible IMD	Probable IMD	Proven IMD
Management	Prophylaxis	Empirical therapy	Diagnostic-driven (pre-emptive) therapy				Targeted therapy	

Maertens JA et al. Hematologica 2012

Another look at the pivotal recent IA trials and their relevance in 2018

- **Prospective randomized trial (VRC+placebo vs VRC+ ANF)** (Marr K et al. AIM 2015)
- RCT in 93 centers 2008-2011
- High risk pts (leukemia, alloSCT), well balanced demographics
- **Only 8% of pts received mold-active prophylaxis**
- Pts with major co-morbidities or advanced underlying disease were excluded
- Most (75-79%) had diagnosis based on CT and serum/BAL GM
- Mortality rates at 6 weeks were 19.3% (for combination therapy and 27.5% for monotherapy (P = 0.087)

Another look at the pivotal recent IA trials and their relevance in 2018

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 (Maertens J et al. Lancet 2016), RCT in 102 centers, 007-2013

High risk pts(leukemia, alloSCT, well balanced demographics

CT and BAL/serum Gm based dx in most (75-80%)

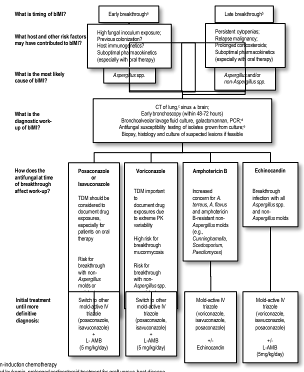
Pts with major co-morbidities or advanced underlying disease were excluded

All-cause mortality (day 42, ITT population) 19% ISA vs 20% with VRC (P=NS)

No info provided regarding prior mold active prophylaxis

Systematic approach to breakthrough mould infection?

Lionakis MS, Lewis RE, Kontoyia
CID 2018



[a] Primary prophylaxis during initial remission-induction chemotherapy
[b] Prophylaxis during re-induction for relapsed leukemia, prolonged corticosteroid treatment for graft-versus-host disease
[c] CT pulmonary angiography used in some centers to identify angioinvasive process (vessel occlusion sign) inside nodular infiltrates or consolidations; highly suggestive of invasive mold disease and not affected by antifungal prophylaxis
[d] PCR test for *Aspergillus* spp. with or without detection of L98H, tandom repeat 34, T289A, and Y1212F triazole resistance mutations. Not approved in U.S. or available in most centers.
[e] Susceptibility testing not available in many centers and breakpoints not well established for non-*Aspergillus* molds
TDM, therapeutic drug monitoring; PK, pharmacokinetic; CT, computed tomography; PCR, polymerase chain reaction; IV, intravenous; AMB, amphotericin B

Question 2- Best approach: mold active prophylaxis vs biomarker driven IA

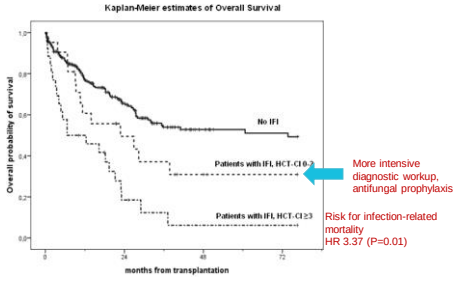
Question 2- Risk stratification& best approach to prophylax, impact of co-morbidities

HSCT CI risk score for prognosis of invasive fungal disease

- **312 patients with HSCT-CI risk score assessment undergoing first allogeneic HSCT**
  - 62% acute leukemia, 58% alternative donor source
- 55% low of intermediate **risk score (0-2),** 45% high HSCT-CI **risk score (≥ 3)**
- Cumulative incidence of probable-proven IFI at 1 year was 8.5% with a significant higher incidence in patients with high HCT-CI (12%) vs. those with low-intermediate HCT-CI (5%; p = 0.006).
- By multivariate analysis, disease status at transplant and high HCT-CI, when combined with acute GVHD, were independently associated with the risk of post-transplant IFI.

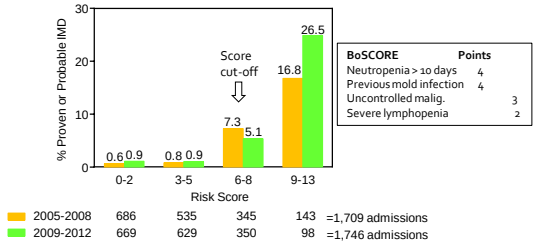
Busca A...Bruno B. BMT 2018

HSCT CI risk sco for prognosis of invasive fung disease



Busca A et al. ASH 2015

BoSCORE: A clinical risk mod for invasive mol disease in hematology pts that separates low (<1%) versu high (> 5%) probability for IMD



Stanzani M et al. *PloS One* 2013

Question 3- Azole antifungals drug interactions, need for TDM, chronic toxicities

Therapeutic drug monitoring of triazoles

- Voriconazole/ posaconazole serum trough concentrations correlate with risk of breakthrough mold infection[1-4]
- TDM recommended in cases of suspected breakthrough infection[1,2]
  - True failure vs. inadequate (dose) exposure?
- Breakthrough mold infection in the setting of voriconazole levels > 1 mcg/mL → higher probability of mucormycosis[5]
- Need with new posaconazole formulations or isavuconazole?

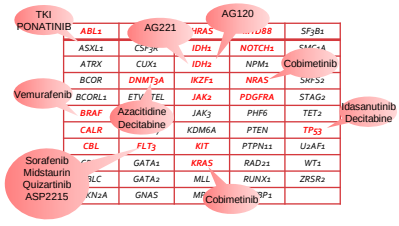
1-Ashbee et al. J Antimicrob Chemother 2014;69:1162-76
2-Andes Pascual & Marchetti. Antimicrob Agent Chemother 2009;53:24-34
3-Park et al. Clin Infect Dis 2012;55:1080-87.
4-Pascual et al. Clin Infect Dis 2008;46:201-11.
5-Trifilio et al. Bone Marrow Transplant 2007;39:425-9.

Azoles: Potential for low levels and drug Interactions

- Polypharmacy
- Underlying renal or hepatic dysfunction
- Drugs with narrow therapeutic index
- Debilitation /malnutrition/ chronic immunosuppression
- Mucositis

Risk is both dynamic and cumulative, therefore the relative impact of each factor at different time points in unknown

A new era for drug toxicity and interactions of azoles with targeted therapies?



58% of new therapies in Phase I-III clinical trials have relative or absolute contraindications for triazole prophylaxis of CYP 3A4, QTc prolongation)

Slide: Cristina Papayannidis, M.D.

Chronic use of VRC can be associated with overlapping toxicities

Visual disturbances 20.6%

Hepatotoxicity 13%

Rash 13%

Peripheral neuropathy 9%

Hallucinations 4.3%, encephalopathy

Nausea and Vomiting, 5-10%

How you Approach Breakthrough IA

Clinical trials NOT have not studied these patients!!

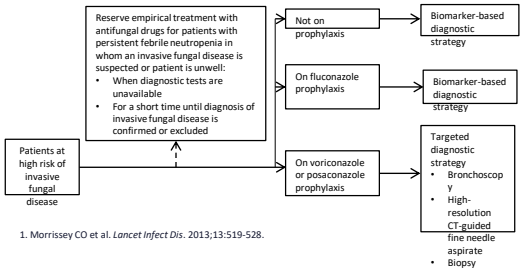
Clinical trial (inclusion/exclusion criteria) EORTC/MSG Definitions

Homogeneous, lower risk population, Most pts were on fluconazole prophylaxis!

Pts with BK IA

Diagnostic uncertainty, comorbidities, prior exposure to mold –active agents, co-infections, **advanced stages of underlying disease**

Integrated Antifungal Strategies for Patients at Risk of IA: no good head to head comparisons



1. Morrissey CO et al. *Lancet Infect Dis*. 2013;13:519-528.

Question 4- Combination therapy

Why are we still using combinatio therapy?

- No quality data of how to manage breakthrough mold infections in 2018 in leukemia/SCT patients
- Most important decisions affecting outcome are made preemptively
- Rational for preemptive combination therapy after breakthrough?
  - Higher risk of resistant, virulent moulds (e.g., mucormycosis)
  - Occult sites of infection
  - Breakthrough on antifungal prophylaxis is a poor prognostic sign (both fungus and host)
  - Groups at high risk of underexposures (e.g., pediatric pts on VRC)
  - Combination therapy is often safer compared to higher dosed triazole or L-AMB monotherapy
- In the optimal scenario, a cautious early preemptive use of combination therapy with early reevaluation seems the most logical and theoretically plausible in real life

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Question 5- Assessing impact on IA on outcomes

How to show any benefit with new drugs (alone or combination ? Declining attributable mortality in IA

From Pagano et al. Haematologia

Year	Attributable mortality
1987-1998	48%
1999-2003	38.5%
2004-2007	27%

Problems with attributable mortality is opportunistic mycoses

Attributable or contributable mortality? (Van de Pepplel RJand DeBoer MG. CID 2018)

Competing risks (e.g., terminal gram negative sepsis- Sipsas NV...Kontoyiannis DP. Cancer 2009)

Low autopsy rates (Lewis RE.. Kontoyiannis DP. Mycoses 2014)

Constant change in qualitative and quantitative immunosuppression

Should lack of "significant" mortality difference from outdated trials be our guiding principle?

- **In the era of improvement in supportive care and decreasing attributable mortality from IMIs, are we having a "myopic" view of when mortality should be assessed? (traditionally d 42 and/or d 84)**
- **Outside the scenario of refractory hem disease, control of an IMI increasingly contributes to outcomes via influencing intensity of subsequent chemo (key outcome not evaluated in clinical trials)**
  - **57% have chemotherapy treatment delay**
  - **28.6% have change in chemotherapy protocol, including switch to palliative care)**
- **Perhaps looking at mortality in later time points (e.g., d180 or d 360) post the diagnosis of IMI could be helpful**

Even C et al. Haematologica 2011. *Impact of invasive fungal disease on the chemotherapy schedule and event-free survival in acute leukemia patients who survived fungal disease: a case-control study*

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Question 6- azole-resistant IA

Triazole resistance in Aspergillus? another element of complexity

White- no data

Shaded areas showing countries that have reported TR_{34}/L98H and TR_{46}/Y121F/T289A resistance mechanism
Verweij, Chowdhary, Melchers & Meis. Clin Infect Dis 2016;62:362-368.

Changes in In Vitro Susceptibility Patterns of Asperg to Triazoles and Correlation With Aspergillosis Outc at MDACC Tertiary Care Cancer Cente 1999-2015:

a complex story

- Tested 290 sequential Aspergillus isolates (respiratory sources) A) during 1999-2002 (before voriconazole and posaconazole) and B): 2003-2015
- Tested for polymorphisms in ergosterol biosynthetic genes (cyp51A, erg3C, erg1) in the *Aspergillus fumigatus* isolates isolated from both periods that had non-wild-type (WT) MICs.
- For the 107 patients with hematologic cancer and/or HSCT with invasive pulmonary aspergillosis, correlation in vitro susceptibility with 42-day mortality.
- Non-WT MICs were found in 37 (13%) isolates and was only low level (MIC <8 mg/L) in all isolates.
- Higher-triazole MICs were more frequent in the second period and were *Aspergillus*-species specific, and only encountered in *A. fumigatus*.
- No polymorphisms in cyp51A, erg3C, erg1 genes were identified.
- There was no correlation between in vitro MICs with 42-day mortality in patients with invasive pulmonary aspergillosis, irrespective of antifungal treatment.
- Asian race (odds ratio [OR], 20.9; 95% confidence interval [CI], 2.5-173.5; P = .005) and azole exposure in the prior 3 months (OR, 9.6; 95% CI, 1.9-48.5; P = .006) were associated with azole non-WT MICs.

Heo ST… Kontoyiannis DP. CID 2017

Question 7- How to test new drugs in a "saturated" field

Emerging new agents (alone or in combination)

- An arylamide (T-2307)
- An inhibitor of fungal glycosylphosphatidylinositol biosynthesis (APX001A)
- A compound with a novel and as-yet-unknown target (ASP 2397)
- An orotomide (F901318)
- A chitin biosynthesis inhibitor (Nikkomycin Z;VFS-1)
- A histone deacetylase inhibitor (MGCD290)
- Calcineurin inhibitors/combinations
- Other (e.g., BDM-1; inhibitor of components of G-protein signalling pathways)
- Novel CYP inhibitors (Viamet; VT1129/1161)
- New generations of echinocandins (CD101, enfumafungin,
- New formulations of amphotericin B (AMB nanoparticles, chochleate AMB)

Osherov N & Kontoyiannis DP. Med Mycol 2016

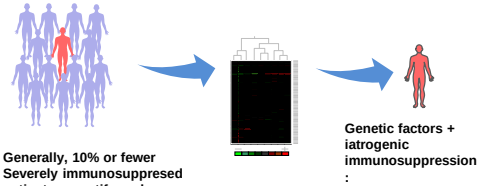
Other Research Questions for IA

- Identify the best biomarkers, or combination of markers and radiology to start pre-emptive therapy
  - Measuring volatile organic compounds in BAL
  - Role for CT angiography for early diagnosis of peripheral lung lesions due to molds
- Roles of FNA vs lavage, VATS, OLB in the diagnostic algorithm
- Co-infections: impact on diagnosis, outcome
- Models of risk by incorporating genomic predictions
- Immunotherapy
- Sequential use of azoles

Ongoing and Future Research Questions for IA

- Define/evaluate "salvage" therapy
- Impact of sequential antifungal therapy (leukemia->SCT) to BT IA epidemiology
- Secondary prophylaxis ? when to stop
- Outpatient exposures and patient education (DP Kontoyiannis. Annals of Intern Medicine 2013)
- Best "Bundle Strategy" for management
- QOL in pts with IA
- Chronic lung aspergillosis syndromes
- ICU aspergillosis (dx, treatment)
- IA in unusual sites
- IA in CF patients
- IA in non classical hosts (e.g., SLE, post influenza)
- IA and new targeted therapies
  - Post ibrutinib or other SKIs, CPIs

Genomics era for risk stratification

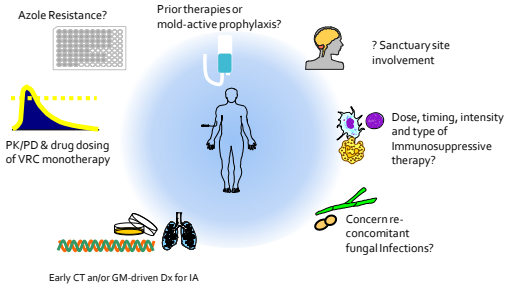


Generally, 10% or fewer Severely immunosuppresed patients on antifungal prophylaxis develop TBT IA

Genetic risk factors (SNPs)?

Genetic factors + iatrogenic immunosuppression : → hypersusceptible population?

Individualized antifungal therapy in IA



Leventakos K… Kontoyiannis DP. CID 2008

Thank you!

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