Treatment of invasive pulmonary aspergillosis

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

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Chronic pulmonary aspergillosis: rationale and clinical guidelines for diagnosis and management

David W. Denning¹, Jacques Cadranet², Catherine Beigelman-Aubry³, Florence Ader⁴, Arunalo Chakrabarti⁵, Stijn Blot⁶, Andrew J. Ullmann⁷, George Dimopoulos⁸ and Christoph Lange⁹ on behalf of the European Society for Clinical Microbiology and Infectious Diseases and European Respiratory Society

FIGURE 1 A schematic to illustrate the different forms of chronic pulmonary aspergillosis, in particular the overlap that is often seen.
Contents of this talk

• Overview of antifungal pharmacology, PK/PD, trivia
• Summary of published studies on efficacy
• Summary of the 2016 IDSA recommendations
• A (very) brief look at the future
POTENTIAL TARGETS FOR ANTIFUNGAL THERAPY

2a

- CYTOPLASMIC MEMBRANE
  - Polycenes → ergosterol membrane integrity
  - Azoles
  - Allylamines
  - Morpholines
  - Tolnaftate

  \{ ergosterol synthesis \}

- CELL WALL
  - Polyoxins → chitin synthesis
  - Papulacandin
  - Echinocandin
  - Aculeacin
  \{ β-Glucan synthesis \}

- METALS
  - metal chelation

- METABOLIC INHIBITORS

- NUCLEIC ACID SYNTHESIS
  - 5-Fluorocytosine → RNA, DNA synthesis

- NUCLEAR DIVISION
  - Griseofulvin → microtubuli

- MITOCHONDRIA

- MACROMOLECULE BIOSYNTHESIS
Fungal cell wall – cell membrane

- Ergosterol
- Polyenes
- (Tri)azoles
- Echinocandins

Hardison and Brown Nature Immunol 2012
Streptomyces nodosus
The antifungal drugs I: polyenes

- Amphotericin B
  - 1955, made by *Streptomyces nodosus* (Orinoco river, Venezuela), ampho A and B
  - Macrolactone structure (macrolide)
  - Amphoteric compound $\rightarrow$ both *acid* and *base*
  - Poorly soluble at pH 7 $\rightarrow$ emulsification with *deoxycholate* (bile acid) (Fungizone® 1958) or *lipid derivatives*

- Spectrum:
    - NB: *Aspergillus terreus* (*flavus*), *Pseudallescheria boydii*, *Fusarium, Candida lusitaniae, C. guilliermondii* intrinsically resistant
  - Protozoa: *Trypanosoma, Schistosoma, Echinococcus, Leishmania, Naegleria* (‘brain eating amoeba’)
Polyene mechanism of action

• Affinity for sterols: ergosterol>>cholesterol
  • Formation of pores → leakage of fungal kations (Na\(^+\), K\(^+\), H\(^+\), Ca\(^{++}\), Mg\(^{++}\))
  • Sterol sequestration → membrane instability
  • Oxidative damage in the cell

• Immunomodulatory effects via binding Toll-like receptors: > pro-inflammatory
  • ↑ NO production, TNF-alpha, IL6, IL 8
  • ↑ Oxidative burst → increased fungal killing by macrophages, PMN

Palacios PNAS 2011
Mesa-Arango Front Microbiol 2012
Polyene toxicity 1:

- Renal toxicity (amphoB, deoxycholate)
  - Renal vasoconstriction $\rightarrow$ decrease in glomerular filtration
  - Distal tubular solute loss: hypoK$,^+\text{, hypoMg}^{++}$, metabolic acidosis
  - $>$reversible, salt-loading prevents $\pm$
  - Determinants: AmphoB dose, pre-existing chronic kidney disease, concomitant nephrotoxic drugs

- Cardiac toxicity
  - Direct cardiac toxicity
  - Hyperkalemia (rapid infusion)

- Neurologic toxicity
  - Confusion, delirium, psychosis
  - Myelin degeneration in plexus, cerebral leukoencephalopathy

$\rightarrow\rightarrow$ Lipid formulations of amphoB

Laniado-Laborin Rev Iberoam Micol 2009
Lipid derivatives: encapsulation in lipid complexes
- Liposomal AmfoB (AmBisome®)
- AmfoB Lipid Complex (ABLC) (Abelcet®)
- Amfo B Colloidal Dispersion (ABCD) (Amphocil/Amphotec®)
Amfotericin B lipid formulations

- Rapid clearing from bloodstream – high tissue concentrations
- Accumulation within reticulo-endothelial system – macrophages/monocytes
  - Lip amphoB: > epithelial lining fluid
  - ABLC/ABCD: lung tissue, pulmonary alveolar macrophages

![Graphs showing pharmacokinetics of amphotericin B deoxycholate (DAmB), liposomal amphotericin (LAmB), and amphotericin B lipid complex (ABLC) in the endovascular fluid (top row), endothelial cells (middle row), and alveolar epithelial cells (bottom row). Data are mean ± standard deviation of three animals.](image)
Amphotericin B lipid formulations

- Rapid clearing from bloodstream – high tissue concentrations
- Accumulation within reticulo-endothelial system – macrophages/monocytes

→ Require/allow higher dose
  3-5mg/kg (0,5-1,5mg/kg amfoB-deoxycholate)

→ Less nephrotoxicity
  - Avoidance of deoxycholate
  - Preferential release amfoB to site of infection<<renal cells
    → fungal cell wall (lip amphoB) or
    → reticulo-endothelial system (lip amfoB, ABLC/ABCD) → release amfoB mediated by macrophages (‘dump truck’ phenomenon)

- ... still risk for nephrotoxicity (concomitant nephrotoxins)
Polyene toxicity 2: infusion-related toxicity

- Local irritative reactions: thrombophlebitis
- Systemic infusion reactions: amphoB-deoxycholate ≠ liposomal amphoB

- **Ampho B – deoxycholate:** fever, chills, rigors, nausea, vomiting, headache ('shake and bake')
  - 1-3h after initiation of infusion
  - Slowing rate of infusion

→ ampho B, immunologic mechanism (cytokine production from innate immune cells)
→ less frequent with ABLC, even less with Lip amphoB
Polyene toxicity 2: infusion-related toxicity

- **Lip amphoB**: distinct infusion-related syndrome:

  3 clusters
  - Chest pain, hypoxia, dyspnea
  - Severe abdomen, flank or leg pain
  - Flushing and urticaria

- Within 5 minutes of infusion
  \( \leftarrow \text{R}/: \text{diphenhydramine}~1mg/kg, \text{infusion interruption, rechallenge without problem} \)

  → liposome, complement activation
  → variability of time and centers? production variability?
The antifungal drugs II: azoles

- **Imidazoles** \((C_3H_4N_2)\)
  - Ketoconazole (1976°), miconazole, clotrimazole

- **Triazoles** \((C_2H_3N_3)\)
  - 2nd generation: voriconazole, posaconazole, isavuconazole, ravuconazole

- **Antifungal spectrum**
  - Candida spp.
    - intrinsically resistance in C. krusei, glabrata,…
  - Aspergillus: itraconazole<2nd generation triazoles
  - Mucorales, zygomycetes: posaconazole, isavuconazole, ravuconazole
Triazole mechanism of action

- **Inhibition of cytochrome P450 dependent fungal lanosterol 14alpha-demethylase**
  - → inhibition of ergosterol synthesis
  - → depletion of ergosterol + accumulation of toxic sterol intermediate metabolites
  - → increased fungal cell membrane permeability

- **Inhibition of mammalian cytochrome P450 - 3A4/2C9/2C19**
  - → X oxidation, reduction, hydrolysis drugs

- **Inhibition of P-glycoprotein membrane transporter**

- **Itraconazole**: anti-angiogenesis
Triazole toxicity: all

• Interactions
  • CYP3A4: itra, posa > fluco, vorico
  • CYP2C9/CYP2C19: fluco, vorico

  Ciclosporin, tacrolimus, sirolimus, phenytoin,…

• Hepatoxicity:
  • mild elevation transaminases (2-12%) → fulminant hepatitis
  • idiosynchatic
  • cytolysis, cholestasis
  • >reversible, <<fatal
Triazole toxicity: **voriconazole**

- **Vision changes:** abnormal vision, light flashes, colour changes,
  - Up to 20%
  - Usually transient
  - Direct block of signal transduction in retinal cells (Wei-Hong Invest Ophtalmol Vis Sci 2015)

- **Neurological symptoms**
  - Concentration disturbances, ‘feeling strange’
  - Confusion, agitation, psychosis

- **Skin rash**
  - 7%
  - i.a. phototoxicity
  - Increased risk of skin carcinoma?

- **Periostitis**
  - >##months
  - increased fluoride concentrations

- **Alopecia and nail changes**
  - >##months
  - Up to 87% (alopecia) and 70% (nail) (Malani Clin Infect Dis 2012)
Triazole toxicity: *cyclohextrin*

- Sulfobutylether-beta-cyclodextrin (SBEC) added as solubilizing agent for lipophilic drugs (voriconazole, itraconazole, posaconazole, amiodarone)

- **Animal models:**
  - vacuolization in renal tubular cells
  - foamy macrophages in liver and lung
  - mild toxicity in doses 50x human dose

- **Human volunteers (including renal dysfunction):**
  - accumulation of SBEC in renal dysfunction,
  - but no deterioration

- **Retrospective studies** → systematic review in Brigg-Turner Int J Antimicrob Ag 2015
  - 7 studies
  - No differences in renal toxicity IV vorico vs. other antifungals
  - No differences in renal toxicity IV vorico vs. PO vorico
Triazole PK/PD 1

• Voriconazole
  • IV, oral 90% bioavailability (30% reduced if intake with fat)
  • Large volume of distribution, good tissue penetration, including CNS/abscesses
  • > hepatic metabolisation (CYP 450 2C19, 2C9, 3A4), <5% urinary excretion

• Unpredictable PK (dose-concentration) relationship
  • Nonlinear pharmakokinetics
  • Substrate and inhibitor of CYP2C19, 2C9, 3A4
  • Genetic polymorphism → poor (5%, 20% Asians) vs. extensive metabolizers (CYP2C9/CYP2C19)

• Predictable PD (concentration-effect) relationship
  • Treatment succes ~ >1mg/L
  • Toxicity ~ >5,5mg/L
  → therapeutic drug monitoring
Table 3. Voriconazole-Related Adverse Events in Therapeutic Drug Monitoring (TDM) vs Non-TDM Groups

<table>
<thead>
<tr>
<th></th>
<th>TDM (n = 55)</th>
<th>Non-TDM (n = 53)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Possible or stronger relationship</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All events</td>
<td>23 (42)</td>
<td>22 (42)</td>
<td>97a</td>
</tr>
<tr>
<td>Elevation of hepatic enzymes</td>
<td>15 (27)</td>
<td>14 (26)</td>
<td>92a</td>
</tr>
<tr>
<td>Encephalopathyb</td>
<td>8 (15)</td>
<td>7 (13)</td>
<td>84a</td>
</tr>
<tr>
<td>Othersc</td>
<td>5 (9)</td>
<td>8 (15)</td>
<td>34a</td>
</tr>
<tr>
<td>Severe events</td>
<td>7 (13)</td>
<td>5 (9)</td>
<td>586a</td>
</tr>
<tr>
<td>Elevation of hepatic enzymes</td>
<td>4 (7)</td>
<td>3 (6)</td>
<td>&gt; .99d</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>2 (4)</td>
<td>0</td>
<td>.49d</td>
</tr>
<tr>
<td>Others</td>
<td>2 (4)</td>
<td>2 (4)</td>
<td>&gt; .99d</td>
</tr>
<tr>
<td><strong>Probable or likely relationship</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All events</td>
<td>12 (22)</td>
<td>9 (17)</td>
<td>53a</td>
</tr>
<tr>
<td>Elevation of hepatic enzymes</td>
<td>3 (6)</td>
<td>4 (8)</td>
<td>71d</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>6 (11)</td>
<td>5 (9)</td>
<td>.80a</td>
</tr>
<tr>
<td>Others</td>
<td>3 (6)</td>
<td>2 (4)</td>
<td>&gt; .99d</td>
</tr>
<tr>
<td>Severe events</td>
<td>2 (4)</td>
<td>2 (4)</td>
<td>&gt; .99d</td>
</tr>
<tr>
<td>Elevation of hepatic enzymes</td>
<td>0</td>
<td>1 (2)</td>
<td>.49d</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>1 (2)</td>
<td>0</td>
<td>&gt; .99d</td>
</tr>
<tr>
<td>Others</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>&gt; .99d</td>
</tr>
<tr>
<td><strong>Drug discontinuation due to adverse events</strong></td>
<td>2 (4)</td>
<td>9 (17)</td>
<td>92a</td>
</tr>
</tbody>
</table>

The Effect of Therapeutic Drug Monitoring on Safety and Efficacy of Voriconazole in Invasive Fungal Infections: A Randomized Controlled Trial

Table 4. Treatment Response in Therapeutic Drug Monitoring (TDM) vs Non-TDM Groups

<table>
<thead>
<tr>
<th></th>
<th>TDM (n = 37)</th>
<th>Non-TDM (n = 34)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment success</td>
<td>30 (81)</td>
<td>20 (59)</td>
<td>.04</td>
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<tr>
<td>Complete response</td>
<td>21 (57)</td>
<td>13 (38)</td>
<td>.12</td>
</tr>
<tr>
<td>Partial response</td>
<td>9 (24)</td>
<td>7 (21)</td>
<td>.71</td>
</tr>
<tr>
<td>Stable response</td>
<td>1 (3)</td>
<td>2 (6)</td>
<td>.60</td>
</tr>
<tr>
<td>Treatment failure</td>
<td>6 (16)</td>
<td>12 (35)</td>
<td>.07</td>
</tr>
</tbody>
</table>

Abbreviation: TDM, therapeutic drug monitoring.
Triazole PK/PD 2

• Posaconazole
  • Oral bioavailability delayed-release tablets better and more predictable than oral suspension (requires fatty food), saturation at 800mg daily dose, IV recently available
  • Large volume of distribution, less CNS penetration
  • 15% hepatic metabolisation (non CYP 450), 77% unchanged secretion faeces, <5% urine

  • Therapeutic drug monitoring
    • Variable oral bioavailability (Gvhd, mucositis, PPI)
    • Association clinical success/failure and concentrations (>1mcg/ml)

• Isuvaconazole?
  • Oral (no interaction with food) and IV (filter required)
  • Long half life (5d), loading dose
  • Hepatic metabolisation, CYP 3A4 substrate and inhibitor

  • Therapeutic drug monitoring?
The antifungal drugs III: echinocandins

• Lipopeptides
  • Antibacterial: daptomycin (\(\leftrightarrow\)Streptomyces roseosporus)
  • Antifungal: semi-synthetic echinocandins
    • Caspofungin \(\leftarrow\)Pneumocandin B\(_0\) (Glarea lozoyensis) (Ascomycota, Fungi)
    • Anidulafungin \(\leftarrow\)echinocandin B0 (Aspergillus nidulans)
    • Micafungin \(\leftarrow\)FR901370 (Coleophoma empetri)

• Antifungal spectrum
  • Candida spp.
  • Aspergillus spp.
  • Not active against mucorales, Fusarium, Rhizopus...
Echinocandins mechanism of action

- Non-competitive inhibition of (1,3) beta D glucan synthase
  - decreased beta glucan cell wall osmotic integrity
  - osmotic lysis

Cfr. Beta-lactam and peptidoglycan cross-linking: « penicillin against fungi »

- Enhancing host response by exposing highly antigenic beta-glucan epitopes (Pathogen Associated Molecular Patterns (PAMPs) to antigen-presenting cells
  - ‘unmasking’ ←→ buried beneath mannoprotein layer

Wheeler PLOSpathogens 2006
Echinocandin PK

- IV
- >10h half life
- Large distribution volume – poor penetration in ‘difficult’ compartments (pleura, eye, CNS)
- Linear dose-response
- No renal excretion, no renal dose adjustment
- Clearance↗ with body weight (caspofungin: >70-80kg→dose increase 70mg/kg)

Metabolization

- Anidulafungin: spontaneous degradation, excreted through bile
- Caspofungin: spontaneous degradation + hepatic metabolism
  - Some interaction:
    - C decreases tacrolimus (20%), ciclosporin increases C (35%)
    - Drug inducers (phenytoin, carbamazepine, rifampicin, dexamethazone) decrease C concentrations
  - Increased concentrations with hepatic insufficiency
- Micafungin: catechol-O-methyltransferase metabolism
Echinocandin PD

- **Candida**
  - Concentration-dependent fungicidal
  - AUC/MIC, breakpoint MIC 2mg/L
  - post-antifungal effect
- **Aspergillus**
  - Concentration-dependent fungistatic
  - Cmax/Minimum effective concentration, ‘breakpoint’ MEC 1mg/L
  - No or short (<0,5h) post-antifungal effect
- ‘Eagle effect’: paradoxal increase in fungal growth with exceeding echinocandin concentrations (Candida, Aspergillus)
  - ?Changing morphology
  - ?Increasing chitin content instead of beta-1,3-glucan
  - In vitro, clinical relevance?

Pound J Antimicrob Chemother 2010
Echinocandin toxicity

• Few and rare
  • Hypersensitivity (histamin release)
  • Hepatotoxicity
  • Cardiac toxicity?
    • Rat model: decreased cardiac contractility
    • Case reports: cardiac failure following echinocandin infusion
    • Mechanism: mitochondrial toxicity?

Stover J Clin Pharm Ther 2014
Treatment of invasive aspergillosis: 6 options

- Amphotericin B deoxycholate
- Lipid derivatives amphotericin B
- Voriconazole
- Posaconazole
- Isuvaconazole
- Echinocandins
Treatment of invasive aspergillosis: 6 options

- Amphotericin B deoxycholate
- Lipid derivatives amphotericin B
- Voriconazole
- Posaconazole
- Isuvaconazole
- Echinocandins

- Vorico vs. amphoB-deoxycholate
- amphoB-lipid vs. amphoB-deoxychol
- isuvaconazole vs. posaconazole
- vorico+anidula vs. vorico
- amphoB-lipid, vorico, posa, caspofungin, micafungin (salvage, breakthrough...)
- vorico vs. lipid amphoB?
- echinocandin vs. azole?
- echinocandin vs. lipid amphoB?

RCT
Observational, uncontrolled
No data
P: 277 patients with probable IA (>hematological malignancy)

I: voriconazole 6mg/kg/12h d1, 4mg/kg/12h d2 →

C: amphotericin B deoxy 1-1,5mg/kg

O1: complete/partial response 52,8% vs. 31,6% (absolute risk diff 21,2% (10,4 to 32,9))

O2: 12 week survival 70,8% vs. 57,8% (HR 0,59 (0,40-0,80))

O3: adverse events 343 vs. 421 (p=0,02)
Liposomal Amphotericin B as Initial Therapy for Invasive Mold Infection: A Randomized Trial Comparing a High–Loading Dose Regimen with Standard Dosing (AmBiLoad Trial)

Oliver A. Cornely, Johan Maertens, Mark Bresnik, Ramin Ebrahimi, Andrew J. Ullmann, Emilio Bouza, Claus Peter Heussel, Olivier Lorlholary, Christina Rieger, Angelika Boehme, Michael Asse, Heinz-August Horst, Anne Thielbeut, Markus Rehkle, Dietmar Reichert, Nicola Vianello, Stefan W. Krause, Eduardo Olivarría, and Ruedi Herbrecht, for the AmBiLoad Trial Study Group

P: 201 patients with possible IA (>hematological malignancy)

I: Lip amphiB 10mg/kg/d (14d:→3mg/kg/d)

C: Lip amphiB 3mg/kg

O1: complete/partial response 46% vs. 50% (absolute risk diff 4% (-10 to +18))

O2: EOT survival 59% vs. 70% (diff 13%, -2 to +26)

O3: adverse events: ↗ increase serum creatinine, hypokalemia in high dose group(p<0.05)
### Analysis 1.1. Comparison of Lipid-based amphotericin B versus standard amphotericin B, Outcome 1: Death.

#### Study or subgroup

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Lipid-based</th>
<th>Standard</th>
<th>Risk Ratio (M-H fixed-effects)</th>
<th>Weight</th>
<th>Risk Ratio (M-H fixed-effects)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid-based</td>
<td>aN</td>
<td>nN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fat-free</td>
<td>645</td>
<td>200</td>
<td>3.1</td>
<td></td>
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<td>Lipid-based</td>
<td>553</td>
<td>655</td>
<td>6.7</td>
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<td>20.6</td>
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<td>Lipid-based</td>
<td>3/43</td>
<td>34/34</td>
<td>40.7</td>
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<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>677</td>
<td>521</td>
<td>71.1%</td>
<td>0.77 (0.54, 1.10)</td>
<td></td>
</tr>
</tbody>
</table>

#### Total events (lipid-based, 57)

- Heterogeneity: CHI² = 0.72, df = 3 (P = 0.87), I² = 0%
- Test for overall effect: Z = 1.45 (P = 0.15)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Lipid-based</th>
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<th>Weight</th>
<th>Risk Ratio (M-H fixed-effects)</th>
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<tbody>
<tr>
<td>Lipid-based</td>
<td>aN</td>
<td>nN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fat-free</td>
<td>1/21</td>
<td>2/21</td>
<td>2.3</td>
<td>0.50 (0.05, 5.10)</td>
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</tr>
<tr>
<td>Lipid-based</td>
<td>1/04</td>
<td>11/78</td>
<td>3.7</td>
<td>0.09 (0.06, 1.59)</td>
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</tr>
<tr>
<td>Lipid-based</td>
<td>4/21</td>
<td>6/24</td>
<td>5.2</td>
<td>0.59 (0.19, 1.85)</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>132</td>
<td>123</td>
<td>10.6%</td>
<td>0.61 (0.23, 1.59)</td>
<td></td>
</tr>
</tbody>
</table>

#### Total events (57)

- Heterogeneity: CHI² = 0.12, df = 2 (P = 0.94), I² = 0%
- Test for overall effect: Z = 1.01 (P = 0.31)

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<th>Standard</th>
<th>Risk Ratio (M-H fixed-effects)</th>
<th>Weight</th>
<th>Risk Ratio (M-H fixed-effects)</th>
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<td>aN</td>
<td>nN</td>
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<tr>
<td>Fat-free</td>
<td>1/99</td>
<td>13/95</td>
<td>1.5</td>
<td>1.19 (0.64, 2.24)</td>
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<tr>
<td>Lipid-based</td>
<td>9/16</td>
<td>95</td>
<td>15.0%</td>
<td>1.19 (0.61, 2.34)</td>
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<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>98</td>
<td>95</td>
<td>15.0%</td>
<td>1.19 (0.61, 2.34)</td>
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#### Total events (95)

- Heterogeneity: not applicable
- Test for overall effect: Z = 0.51 (P = 0.64)

<table>
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<th>Standard</th>
<th>Risk Ratio (M-H fixed-effects)</th>
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<tbody>
<tr>
<td>Lipid-based</td>
<td>aN</td>
<td>nN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fat-free</td>
<td>5/46</td>
<td>3/50</td>
<td>3.3</td>
<td>1.81 (0.46, 7.16)</td>
<td></td>
</tr>
<tr>
<td>Lipid-based</td>
<td>46</td>
<td>50</td>
<td>3.3%</td>
<td>1.81 (0.46, 7.16)</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>953</td>
<td>789</td>
<td>100.0%</td>
<td>0.85 (0.64, 1.14)</td>
<td></td>
</tr>
</tbody>
</table>

#### Total events (97)

- Heterogeneity: CHI² = 0.37, df = 2 (P = 0.88), I² = 0%
- Test for overall effect: Z = 1.10 (P = 0.27)
- Test for subgroup differences: CHI² = 0.09, df = 1 (P = 0.41), I² = 0%

---

13 trials, 1960 patients, >empirical therapy (febrile neutropenia)

Lipid-based amphotericin B not more effective than amphotericin B–deoxycholate on mortality (RR 0.5, CI 0.64-1.14)

...but decreased invasive fungal infection (RR 0.65, CI 0.44-0.97)
Lipid-based amphoB decreased renal toxicity (RR 0.45, CI 0.37-0.54) and number of dropouts (RR 0.78, CI 0.62-0.97)
P: 454 patients with possible/probable/proven IA (hematological malignancy, hematopoietic cell transplantation)

I: voriconazole 6mg/kg/12h d1, 4mg/kg/12h d2 → + anidulafungin 200mg d1, 100mg d2 →

C: voriconazole 6mg/kg/12h d1, 4mg/kg/12h d2 → + placebo

O1: 6 week mortality 19,3% vs. 27,5% (absolute risk diff -8,2% (-19 to +1,5))

O2: 12 week mortality 29,3% vs. 39,4% (absolute risk diff -10% (-21,4 to +1,1))

O3: adverse events similar in both groups

Marr Ann Intern Med 2015
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


P: 527 patients with possible/probable/proven IA (>80% hematological malignancy, 20% hematopoietic cell transplantation)

I: isavuconazole 200mg/8h d1, 200mg/d d3→

C: voriconazole 6mg/kg/12h d1, 4mg/kg/12h d2→

O1: 6 week mortality 19% vs. 20% (absolute risk diff -1% (-7.8 to +5.7))

O2: drug-related adverse events 42% vs. 60%, lower rate of hepatobiliary, eye, skin disorders in isavuconazole group

<10% (non-inferiority margin)
Efficacy of Caspofungin against Invasive Candida or Aspergillus Infections in Neutropenic Patients

Robert Belts, et al.

Caspofungin is an inhibitor of yeast growth in patients with invasive fungal infections. All available clinical trials demonstrated the efficacy of caspofungin in neutropenic patients with documented invasive aspergillosis (> refractory or intolerant of conventional antifungal therapy).

I: Lipid amphotericin B, caspofungin, miconazole, itraconazole, voriconazole, posaconazole

C: (>) none, (<) other salvage

O: Complete or partial response in 40%-60% (20-40% if refractory disease, complete< partial response)

« (...) (fill in your drug) proved may be effective and safe therapy in invasive aspergillosis in patients with high risk/previous failure/... »
Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America

Thomas F. Patterson, George R. Thompson III, David W. Denning, Jay A. Fishman, Susan Hadley, Raoul Herbrecht, Dimitrios P. Kontoyiannis, Kieren A. Marr, Vicki A. Morrison, M. Hong Nguyen, Brahmi Segal, William J. Steinbach, David A. Stevens, Thomas J. Walsh, John R. Wingard, Jo-Anne H. Young, and John E. Bennett

1University of Texas Health Science Center at San Antonio and South Texas Veterans Health Care System; 2University of California, Davis; 3National Aspergillosis Centre, University Hospital of South Manchester, University of Manchester, United Kingdom; 4Massachusetts General Hospital and Harvard Medical School, and Tufts Medical Center, Boston, Massachusetts; 5University of Strasbourg, France; 6University of Texas MD Anderson Cancer Center, Houston; 7Duke University School of Medicine and the Sidney Kimmel Comprehensive Cancer Center, Baltimore, Maryland; 8Hennepin County Medical Center and University of Minnesota, Minneapolis; 9University of Pittsburgh, Pennsylvania; 10University at Buffalo Jacobs School of Medicine and Biomedical Sciences, and Roswell Park Cancer Institute, New York; 11Duke University Medical Center, Durham, North Carolina; 12California Institute for Medical Research, San Jose; 13New York–Presbyterian Hospital/Weill Cornell Medical Center, New York; 14University of Florida, Gainesville; 15University of Minnesota, Minneapolis; 16Laboratory of Clinical Infectious Diseases, National Institute of Allergy and Infectious Disease, National Institutes of Health, Bethesda, Maryland
Rating the quality of evidence

1. Establish initial level of confidence

<table>
<thead>
<tr>
<th>Study design</th>
<th>Initial confidence in an estimate of effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized trials</td>
<td>High confidence</td>
</tr>
<tr>
<td>Observational studies</td>
<td>Low confidence</td>
</tr>
</tbody>
</table>

2. Consider lowering or raising level of confidence

<table>
<thead>
<tr>
<th>Lower if</th>
<th>Higher if</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of bias</td>
<td>Large effect</td>
</tr>
<tr>
<td>Inconsistency</td>
<td>Dose response</td>
</tr>
<tr>
<td>Indirectness</td>
<td>All plausible confounding &amp; bias</td>
</tr>
<tr>
<td>Imprecision</td>
<td>- would reduce a demonstrated effect or - would suggest a spurious effect if no effect was observed</td>
</tr>
<tr>
<td>Publication bias</td>
<td></td>
</tr>
</tbody>
</table>

3. Final level of confidence rating

<table>
<thead>
<tr>
<th>Confidence in an estimate of effect across those considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
</tr>
<tr>
<td>🟢🟢🟢🟢</td>
</tr>
</tbody>
</table>
Determining the strength of the recommendation

<table>
<thead>
<tr>
<th>Strength of Recommendation</th>
<th>Strong</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population: Most people in this situation would want the recommended course of action and only a small proportion would not</td>
<td></td>
</tr>
<tr>
<td>Healthcare workers: Most people should receive the recommended course of action</td>
<td></td>
</tr>
<tr>
<td>Policy makers: The recommendation can be adapted as a policy in most situations</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Weak</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population: The majority of people in this situation would want the recommended course of action, but many would not</td>
</tr>
<tr>
<td>Healthcare workers: Be prepared to help people to make a decision that is consistent with their own values/decision aids and shared decision making</td>
</tr>
<tr>
<td>Policy makers: There is a need for substantial debate and involvement of stakeholders</td>
</tr>
</tbody>
</table>
Quality of evidence – strength of recommendation

- **Strong recommendation**
  - High-quality evidence
  - Moderate-quality evidence
  - Low-quality evidence

- **Weak recommendation**
  - High-quality evidence
  - Moderate-quality evidence
  - Low-quality evidence

Patterson CID 2016
Triazoles

- Triazoles are preferred agents for treatment and prevention of IA in most patients (20)

- We recommend primary treatment with voriconazole for IPA (25)

- Alternative therapies for IPA include (...) isuvaconazole (27)
Amphotericin B

- Lipid formulations of amphiB should be considered in settings in which azoles are contra-indicated or not tolerated (17)
- AmphiB deoxycholate should be reserved for use in resource-limited settings in which no alternatives are available (17)

- Alternative therapies for IPA include (...) liposomal amphiB (27)
- Alternative therapies for IPA include (...) other lipid formulations of amphiB (27)
Echinocandins

- Echinocandins are effective in salvage therapy, but are *not* recommended as routine monotherapy of IA (19)

- Primary therapy with an echinocandin is not recommended (29)

- Echinocandins can be used in settings in which azole and polyene antifungals are contraindicated (29)
Combination therapy

- Combinations of polyenes or azoles with echinocandins suggest additive or synergistic effects in some preclinical studies (23)

- Combination antifungal therapy with voriconazole and an echinocandin may be considered in select patients with documented IPA (28)

Patterson CID 2016
Triazole therapeutic drug monitoring

- TDM recommended once steady state has been reached
  - To enhance therapeutic efficacy
  - To minimize toxicity

- Trough levels for azoles and interacting drugs* should be obtained
  - *ciclosporin, sirolimus, tacrolimus...
Duration of therapy

- We recommend that treatment of IPA be continued for a minimum of 6-12 weeks, largely dependent on degree and duration of immunosuppression, site of disease and evidence of disease improvement (30).

- Serial monitoring of serum galactomannan can be used in appropriate patient subpopulations (hematology, HSCT) who have elevated GM at baseline to monitor disease progression and therapeutic response and predict outcome (43).
Adjunctive therapy

• Reducing doses or eliminating immunosuppressive agents when feasible, is advised (32)

• Surgery should be considered for localized disease that is easily accessible to debridement (e.g. sinusitis, cutaneous disease) (36)

• Colony-stimulating factors may be considered in neutropenic patients with IA (33)

• Granulocyte transfusions can be considered for neutropenic patients with IA that is refractory or unlikely to respond to standard therapy, for anticipated duration for more than one week (34)
Refractory disease

• We recommend an individualized approach that takes into consideration
  • Rapidity, severity, extent of infection
  • Patient comorbidities
  • Exclusion of emergence of a new pathogen (39)

• Additional antifungal may be added to current therapy, or combination therapy from different classes other than those in the initial regimen may be used (41)

• Agents include amphotericin B lipid, micafungin, caspofungin, posaconazole, itraconazole (42); triazole should take consideration of prior antifungal therapy, host factors, PK, antifungal resistance
• Incidence 0.8-9.4% in Netherlands,
• reports in Belgium, France, Danmark, Italy, Austria, China, India → incidence Europe 3.2%
• Cross-resistance itra-vorico-posa
• Associated with therapeutic failure: mortality 7/8 patients (<12 weeks)
• (point) mutation Cyp51A + second point mutation promotor-region: TR/L98H (>90%)
• → ↓ permeability of azole channels in fungal cell membrane
• Cfr.mutation phytopathogenic fungi
• 5 agricultural fungicides (propi-, bromu-, tebu-, epoxi-, difenoconazol) are triazoles
The antifungal pipeline

No new antifungal drug classes...
The antifungal pipeline

- 4 compounds in clinical development for systemic disease (+ 2 entering clinical development)

- 2 recent failures:
  - HeatShockProtein 90 antibodies (Efungumab (Mycograb®))
  - oral histone-deacetylase inhibitor MGCD290

Denning and Bromley Science 2015