In vitro susceptibility testing is NOT useful in the management of aspergillosis in patients with haematological malignancies

Russell Lewis, Associate Professor
Infectious Diseases, S. Orsola-Malpighi Hospital
Dept. of Medical and Surgical Sciences
University of Bologna, Bologna, Italy
Disclosures

Research support
Speaking fees
Advisory boards
Problems of using mould MICs to make clinical decisions

1. Culture-based management of invasive mould disease is becoming less common

2. The MIC test has many methodological limitations

3. We really don’t know the clinical predictive value of an MIC in the management of aspergillosis

4. MIC-based dosing adjustments can be a bad idea
Problems of using mould MICs to make clinical decisions

1. Culture-based management of invasive mould disease is becoming less common

2. The MIC test has many methodological limitations

3. We really don’t know the clinical predictive value of an MIC in the management of aspergillosis

4. MIC-based dosing adjustments can be a bad idea
Culture-based diagnostics in randomized clinical trials of aspergillosis

Seràgnoli Hematology Institute (2010-2016): varies between 18-36% percent

* Includes cytology

Voriconazole 58.3%
AMB-D 48.9%

L-AMB 38%

VOR 21%
VOR+ANID 17.8%

ISA 12%
VOR 13%

© by author
Culture diagnosis of aspergillosis by bronchoscopy is often biomodal

Affected by host immune status; pathogen virulence; antifungal therapy; and diagnostic techniques
Most therapeutic decisions are made before culture

Is your patient at risk?

What is your strategy to address this risk?

- Biomarker screening (GM ± PCR)
- Antifungal prophylaxis

What will trigger a diagnostic workup?

- Positive biomarker(s)
- Persistent fever
- Clinical suspicion for mould (e.g., skin lesions, sinusitis)

24 hrs

- Thoracic CT
  - Infiltrates consistent with mould disease?
  - Yes: Bronchoscopy + BAL, culture, GM ± PCR, Start antifungal therapy
  - No: Search extrathoracic sites (head sinus CT) if GM, PCR positive?

48 hrs

Most therapeutic decisions are made before culture.

48 hrs
Yes
Bronchoscopy + BAL, culture, GM ± PCR, Start antifungal therapy

No
Search extrathoracic sites (head sinus CT) if GM, PCR positive? Start/continue antifungal therapy?

96-168 hrs
Isolate growth

216 hrs
MICs read, reported (often passively)

MIC testing useful only for treatment failure?

Aspergillus isolate surveillance/ Cumulative antibiograms?

- **2017 ESCMID-ECMM-ERS Aspergillus Guidelines**
  - Antifungal susceptibility testing should be performed regularly for epidemiological purposes including \( \geq 100 \) isolates (AIII).
  - In settings with environmental azole resistance, no change to the primary regimen for IA is recommended when resistance rates are <10% (AIII).
  - If azole resistance rates are \( >10\% \), first-line therapy with voriconazole plus echinocandin (BIII) or liposomal amphotericin B (BIII) is recommended.

Isolates from probable/proven disease, colonizing isolates, environmental isolates? Stratify by patient prophylaxis status?

Multiple issues in construction and reporting in antimicrobial cumulative antibiograms (CLSI M39-A4)...what are the standards for moulds?
Problems of using mould MICs to make clinical decisions

1. Culture-based management of invasive mould disease is becoming less common

2. Many methodological concerns with the MIC test and interpretation

3. We don’t know the clinical predictive value of an MIC

4. MIC-based dosing adjustments can be a bad idea
Mould susceptibility testing conditions

- Aerobic, high-glucose liquid medium
- Shape of microdilution well
- Defined high inoculum
- No immune cells
- No fluctuation in drug exposure
- No biofilms
- Drug stability?
Do current MIC methods have sufficient accuracy to detect resistance?

**QC strain: A. fumigatus ATCC 204305**

**Table:**

<table>
<thead>
<tr>
<th>MIC (mg/L)</th>
<th>Oral sol (400 mg x 2)</th>
<th>tablet</th>
<th>iv</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.015</td>
<td>98%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>0.03</td>
<td>88%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>0.06</td>
<td>59%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>0.125</td>
<td>23%</td>
<td>86%</td>
<td>81%</td>
</tr>
<tr>
<td>0.25</td>
<td>5%</td>
<td>19%</td>
<td>20%</td>
</tr>
<tr>
<td>0.5</td>
<td>1%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

**PK/PD breakpoint (tablet, IV)**
Should we believe a single MIC measurement generated with imprecise methods?

Problem could be even worse if the laboratory is using a non-validated testing method.

ECOFF Standpoint

Pharmacologist standpoint
“The problem of extrapolating laboratory results to the clinical situation presents such a minefield of difficulties that microbiologists usually prefer to concentrate on obtaining reproducible estimates of antimicrobial susceptibility in the laboratory, using standardized methods, and leave the problem of clinical relevance to the physician.”
Problems of applying mould MICs in the clinical setting

1. Microbiological culture-based management of invasive mould disease is becoming less common

2. Methodological concerns with the MIC test

3. We really don’t know the clinical predictive value of an MIC

4. MIC-based dosing adjustments may be a bad idea
Has Antifungal Susceptibility Testing Come of Age?

John H. Rex1 and Michael A. Pfaller2

1Division of Infectious Diseases, Department of Internal Medicine, Center for the Study of Emerging and Reemerging Pathogens, University of Texas–Houston Medical School; and 2Molecular Epidemiology and Fungus Testing Laboratory, Departments of Pathology and Epidemiology, University of Iowa College of Medicine and College of Public Health, Iowa City

The in vitro susceptibility of an infecting organism to the antimicrobial agent selected for therapy is one of several factors that influence the likelihood that therapy for an infection will be successful. To appreciate the value of antifungal susceptibility testing, it is helpful to review the overall predictive utility of antibacterial susceptibility testing. After >30 years of study, in vitro susceptibility can be said to predict the response of bacterial infections with an accuracy that is well summarized as the “90-60 rule”: infections due to susceptible isolates respond to therapy ~90% of the time, whereas infections due to resistant isolates respond ~60% of the time. On the basis of a growing body of knowledge, standardized susceptibility testing for selected organism-drug combinations (most notably, Candida species and the azole antifungal agents) has been shown to have similar predictive utility. Antifungal susceptibility testing is now increasingly and appropriately used as a routine adjunct to the treatment of fungal infections.

Susceptible: 90% response
Resistance: 60% response

*Extrapolated from immunocompetent patients with mono-microbial bacterial infections treated with single agent with predictable pharmacokinetics
Does the 90/60 rule really fit for fluconazole in candidemia?

Host factors, such as severity of illness and age, were more predictive of mortality than fluconazole MICs.
All-cause mortality in isavuconazole-treated patients with aspergillosis stratified by neutrophil recovery (Culture positive + GM positive)

What does the MIC beyond neutrophil recovery for aspergillosis?
Overall response at end of therapy in patients with positive baseline cultures (SECURE Trial)

Day 42 all-cause mortality (SECURE Trial)

![Graph showing the percentage of mortality for Isavuconazole and Voriconazole at different MIC levels.]

- Isavuconazole:
  - $\leq 1$ mg/L: 23 patients
  - 2 mg/L: 6 patients
  - 4 mg/L: 4 patients
  - 8 mg/L: 2 patients
  - $> 8$ mg/L: 1 patient

- Voriconazole:
  - $\leq 1$ mg/L: 17 patients
  - 2 mg/L: 6 patients
  - 4 mg/L: 6 patients

Correlation of triazole MICs with outcome in aspergillosis?

No significant relationship (P>0.05) was identified between the AUC/MIC ratio and mortality at day 42, the overall response at EOT, or the clinical response at EOT.

No relationship was observed between MIC values and outcome parameters.
Galactomannan trends are associated with outcome of aspergillosis

- By day 7, GMI increases of >0.25 units from baseline significantly increased the risk of death compared to those with no increase or increases <0.25 (hazard ratio, 9.766; 95% confidence interval [CI], 4.356–21.9; P< .0001).

- For each unit decrease by day 7 from baseline, the odds of successful therapy doubled (odds ratio, 2.154; 95% CI, 1.173–3.955)

No prominent differences were found between drugs, neutropenic status, and GMI over time (P= .1127).
AUC/EC\textsubscript{50} : An \textit{in vivo} MIC for aspergillosis?

Mathematical model

Individual predicted AUC

Observed patient GM response

Modeled GM response

Bayesian prior AUC/IC\textsubscript{50}

Pop. PK

Simulation

GM over time

AUC/EC\textsubscript{50}

Estimated patient-specific EC\textsubscript{50}

A higher EC\textsubscript{50} would be expected in patients with:
A high fungal burden, the presence of antifungal resistance mechanisms, a delay in the initiation of antifungal therapy, infection within sanctuary sites, and profound immunosuppression.
Problems of applying mould MICs in the clinical setting

1. Microbiological culture-based management of invasive mould disease is becoming uncommon.

2. Methodological concerns with the MIC test.

3. We really don’t know the clinical predictive value of an MIC.

4. MIC-based dosing adjustments may be a bad idea.
MIC-based dose adjustment: facts and fables

Johan W. Mouton¹*, Anouk E. Muller¹,², Rafael Canton³, Christian G. Giske⁴, Gunnar Kahlmeter⁵ and John Turnidge⁶

¹Department of Medical Microbiology and Infectious Diseases, Erasmus MC, Rotterdam, The Netherlands; ²Department of Medical Microbiology, Haaglanden Medical Centre, The Hague, The Netherlands; ³Servicio de Microbiología, Hospital Universitario Ramón y Cajal and Instituto Ramón y Cajal de Investigación Sanitaria (IRYs), Madrid, Spain; ⁴Department of Laboratory Medicine, Division of Clinical Microbiology, Karolinska Institute and Karolinska University Hospital, Stockholm, Sweden; ⁵Department of Clinical Microbiology, Central Hospital, 351 85, Växjö, Sweden; ⁶Adelaide Medical School, University of Adelaide, Adelaide, Australia
MICs are not strict minimum but rather **observable** minimum subject to change. Therefore, the MIC does not represent a concentration that can be compared to any **in vivo** concentration found during treatment.

MICs are inaccurate unless performed in multiple replicates. Results are subject to biological and assay-related variation. Therefore...MICs from an infecting strain are not sufficiently accurate for calculation of individual PK:PD targets and could result in underdosing if by chance the reported MIC is on the low end of values observed if MIC test was performed multiple times.

A 4-fold variation in the MIC could result in a 8-fold difference in antifungal dosing.
What should be the dosing target for PK/PD calculations?

**Table 1.** Suggested interpretation of the MIC for target attainment under various conditions

<table>
<thead>
<tr>
<th>MIC found</th>
<th>Interpretation for target attainment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within WT, ≤ECOFF</td>
<td>ECOFF</td>
</tr>
<tr>
<td>&gt;ECOFF</td>
<td>MIC + two 2-fold dilutions(^a)</td>
</tr>
</tbody>
</table>

\(^a\)Number of dilutions could be higher or lower than two depending on the proficiency of the lab and the drug–species distribution.
and yet, MICs sometimes are useful…

65 y/o female with AML, fever, severe respiratory difficulty, H1N1 influenzae, ANC 250

BAL grew *A. terreus*, GM 3.1

<table>
<thead>
<tr>
<th>Antifungal</th>
<th>MIC</th>
<th>EUCAST Interp.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B</td>
<td>4 mg/L</td>
<td>R</td>
</tr>
<tr>
<td>Anidulafungin</td>
<td>&gt;4 mg/L</td>
<td>R</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>&gt;4 mg/L</td>
<td>R</td>
</tr>
<tr>
<td>Micafungin</td>
<td>&gt;4 mg/L</td>
<td>R</td>
</tr>
<tr>
<td>Isavuconazole</td>
<td>2 mg/L</td>
<td>R</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>1 mg/L</td>
<td>S</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>0.06</td>
<td>S</td>
</tr>
</tbody>
</table>
“Medicine is a science of uncertainty, and an art of probability”

Sir William Osler, M.D.
(1849-1919)
Less useful than you think

In vitro susceptibility testing is NOT useful in the management of aspergillosis in patients with haematological malignancies

Russell Lewis, Associate Professor
Infectious Diseases, S. Orsola-Malpighi Hospital
Dept. of Medical and Surgical Sciences
University of Bologna, Bologna, Italy