The race to stop the silent tsunami of antifungal drug resistance

Paul E. Verweij, MD
Centre of Expertise in Mycology Radboudumc/CWZ

Hosted by Paul Webber
paul@webbertraining.com

Disclosures

(potentiële) belangenverstrengeling | Zie hieronder
---|---
Voor bijeenkomst mogelijk relevante relaties met bedrijven | Bedrijfsnamen
- Sponsoring of onderzoeksgeld
- Honorarium of andere (financiële) vergoeding
- Aandeelhouder
- Andere relatie, namelijk ...

Hosted by Paul Webber  paul@webbertraining.com
www.webbertraining.com
The Race to Stop the Silent Tsunami of Antifungal Drug Resistance
Dr. Paul E. Verweij, Centre of Expertise in Mycology, Radboud University Medical Center
A Webber Training Teleclass

Disclosure collaborations

UMCs

WAGENINGEN UR
For quality of life

clm

rivm
Rijksinstituut voor Volksgezondheid en Milieu

Aspergillus fumigatus and its habitat

Hosted by Paul Webber  paul@webbertraining.com
www.webbertraining.com
The Race to Stop the Silent Tsunami of Antifungal Drug Resistance
Dr. Paul E. Verweij, Centre of Expertise in Mycology, Radboud University Medical Center
A Webber Training Teleclass

Human aspergillus disease

Is the host at risk?

Consistent with fungal disease?

Evidence for Aspergillus?

Pathogenesis invasive aspergillosis

Hosted by Paul Webber  paul@webbertraining.com
www.webbertraining.com
Management of invasive aspergillosis

Antifungal therapy

Surgery

Reduce immune suppression

Antifungal therapy

Fungal cell

Human cell

Hosted by Paul Webber  paul@webbertraining.com
www.webbertraining.com
The Race to Stop the Silent Tsunami of Antifungal Drug Resistance
Dr. Paul E. Verweij, Centre of Expertise in Mycology, Radboud University Medical Center
A Webber Training Teleclass

Activity of antifungal agents

Pre-azole era – before 2002

Amphotericin B deoxycholate
Invasive pulmonary aspergillosis – mortality 70%
CNS aspergillosis – mortality 99%

Hosted by Paul Webber paul@webbertraining.com
www.webbertraining.com
The Race to Stop the Silent Tsunami of Antifungal Drug Resistance
Dr. Paul E. Verweij, Centre of Expertise in Mycology, Radboud University Medical Center
A Webber Training Teleclass

Triazole era – after 2002: Change.....“Yes we can”


Invasive pulmonary aspergillosis
– mortality <30%

CNS aspergillosis
– mortality 45% - 60% (VCZ)

Case

15 year old child with X-linked CGD
Had previously survived an infection with A. nidulans
Was on ITZ prophylaxis for 6 years

Hosted by Paul Webber  paul@webbertraining.com
www.webbertraining.com
Case

During ITZ prophylaxis a pulmonary infiltrate developed. Sputum culture (April 4th 2002)

A. fumigatus

ITZ  >16 mg/l
VCZ  4 mg/l
POS  1 mg/l

High dose VCZ (12 mg/kg/day) - survived

Azole R invasive aspergillosis

Table 1. Characteristics of Nine Patients From Whom A. fumigatus Resistant to Multiple Triazoles Was Cultured.

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age of Patient</th>
<th>Underlying Disease</th>
<th>Date of Isolation</th>
<th>Site of Isolation</th>
<th>Disease Classification</th>
<th>Previous Azole Exposure</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>15</td>
<td>X-linked chronic granulomatous disease</td>
<td>April 4, 2002</td>
<td>Sputum</td>
<td>Bronchiolitis obliterans</td>
<td>ITZ 16 mg/l</td>
<td>N/A</td>
<td>Survived</td>
</tr>
<tr>
<td>Male</td>
<td>73</td>
<td>None</td>
<td>Dec. 3, 2003</td>
<td>Ear swab</td>
<td>Invasive aspergillus of middle ear, pneumatocele</td>
<td>N/A</td>
<td>Surgery and topical therapy</td>
<td>Survived</td>
</tr>
<tr>
<td>Male</td>
<td>16</td>
<td>Hypertensive</td>
<td>Nov. 9, 2004</td>
<td>Bronchial alveolar lavage fluid</td>
<td>Bronchiolitis obliterans</td>
<td>ITZ 16 mg/l</td>
<td>N/A</td>
<td>Survived</td>
</tr>
<tr>
<td>Female</td>
<td>76</td>
<td>Pulmonary Aria</td>
<td>June 16, 2005</td>
<td>Sputum</td>
<td>Invasive aspergillosis, possible</td>
<td>None</td>
<td>Voriconazole (high dose)</td>
<td>Survived</td>
</tr>
<tr>
<td>Male</td>
<td>38</td>
<td>Chronic granulomatous disease</td>
<td>Nov. 2, 2005</td>
<td>Lung aspirate</td>
<td>Bronchiolitis obliterans, probable</td>
<td>Prophylaxis with fluconazole</td>
<td>N/A</td>
<td>Died</td>
</tr>
<tr>
<td>Female</td>
<td>63</td>
<td>Chronic obstructive pulmonary disease</td>
<td>Feb. 14, 2006</td>
<td>Bronchial alveolar lavage fluid</td>
<td>Invasive aspergillosis, probable</td>
<td>Voriconazole</td>
<td>Survived</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>19</td>
<td>Chronic granulomatous disease</td>
<td>April 14, 2006</td>
<td>None</td>
<td>None</td>
<td>N/A</td>
<td>Voriconazole</td>
<td>Survived</td>
</tr>
<tr>
<td>Male</td>
<td>45</td>
<td>Aspergillosis in leukemia and allergic fungal sinusitis</td>
<td>May 1, 2006</td>
<td>None</td>
<td>None</td>
<td>Prophylaxis with voriconazole</td>
<td>N/A</td>
<td>Died</td>
</tr>
</tbody>
</table>

Hosted by Paul Webber  paul@webbertraining.com
www.webbertraining.com
The Race to Stop the Silent Tsunami of Antifungal Drug Resistance
Dr. Paul E. Verweij, Centre of Expertise in Mycology, Radboud University Medical Center
A Webber Training Teleclass

Epidemiology of azole resistance in 2002

Antifungal azole drug targets

Hosted by Paul Webber paul@webbertraining.com
www.webbertraining.com
The Race to Stop the Silent Tsunami of Antifungal Drug Resistance
Dr. Paul E. Verweij, Centre of Expertise in Mycology, Radboud University Medical Center
A Webber Training Teleclass

Analysis of the fungal culture collection

250 isolates from the environment
5 azole resistant

32 patients
31 TR34/L98H

Environmental sampling

Hosted by Paul Webber  paul@webbertraining.com
www.webbertraining.com
The Race to Stop the Silent Tsunami of Antifungal Drug Resistance
Dr. Paul E. Verweij, Centre of Expertise in Mycology, Radboud University Medical Center
A Webber Training Teleclass

Environmental sampling

<table>
<thead>
<tr>
<th>Category</th>
<th>Isolate no.</th>
<th>Source of isolate</th>
<th>Year of isolation</th>
<th>MIC (mg/litre)*</th>
<th>tfam substitution*</th>
<th>Codon 98</th>
<th>Other(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIZ</td>
<td>V17-34</td>
<td>Air sample, patient room</td>
<td>2003</td>
<td>&gt;16</td>
<td>1</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>V22-76</td>
<td>Air sample, patient room</td>
<td>2003</td>
<td>16</td>
<td>16</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>TIZ</td>
<td>V31-36</td>
<td>Air sample, patient room</td>
<td>2003</td>
<td>16</td>
<td>16</td>
<td>2</td>
<td>0.5</td>
</tr>
<tr>
<td>V41-38</td>
<td>Water sample</td>
<td>2007</td>
<td>16</td>
<td>4</td>
<td>0.5</td>
<td>0.5</td>
<td>0.29</td>
</tr>
<tr>
<td>V41-37</td>
<td>Water sample</td>
<td>2007</td>
<td>16</td>
<td>4</td>
<td>0.5</td>
<td>0.5</td>
<td>0.036</td>
</tr>
<tr>
<td>V41-36</td>
<td>Soil</td>
<td>2007</td>
<td>16</td>
<td>4</td>
<td>0.5</td>
<td>0.5</td>
<td>0.036</td>
</tr>
<tr>
<td>V41-35</td>
<td>Soil</td>
<td>2007</td>
<td>16</td>
<td>4</td>
<td>0.5</td>
<td>0.5</td>
<td>0.036</td>
</tr>
<tr>
<td>V41-34</td>
<td>Soil</td>
<td>2007</td>
<td>16</td>
<td>4</td>
<td>0.5</td>
<td>0.5</td>
<td>0.29</td>
</tr>
<tr>
<td>V41-33</td>
<td>Soil</td>
<td>2007</td>
<td>16</td>
<td>4</td>
<td>0.5</td>
<td>0.5</td>
<td>0.036</td>
</tr>
</tbody>
</table>

* VCZ, voriconazole; POS, posaconazole; AMB, amphotericin B; TER, terbinfine; CAS, caspofungin.

---

Environmental and patient TR34/L98H isolates typing

- Clinical, azoleR
- Environment, azoleR

---

Hosted by Paul Webber  paul@webbertraining.com
www.webbertraining.com
The Race to Stop the Silent Tsunami of Antifungal Drug Resistance
Dr. Paul E. Verweij, Centre of Expertise in Mycology, Radboud University Medical Center
A Webber Training Teleclass

The evolution of resistance mechanisms involving TR

1998 34 bp
198H

1995 2000 2005 2010

2006 53 bp

2009 46 bp
Y121F/T289A

2012 46^4 bp
Y121F/T289A/G448S

Acquired resistance frequency in A. fumigatus 2013 – 2017; NL

2013 2014 2015 2016 2017

7.6% 7.2% 10.7% 12.9% 14.7%

23.7%

16%

14.6%

12.9%

10.6%

Hosted by Paul Webber  paul@webbertraining.com
www.webbertraining.com
The Race to Stop the Silent Tsunami of Antifungal Drug Resistance
Dr. Paul E. Verweij, Centre of Expertise in Mycology, Radboud University Medical Center
A Webber Training Teleclass

Hosted by Paul Webber  paul@webbertraining.com
www.webbertraining.com
The Race to Stop the Silent Tsunami of Antifungal Drug Resistance
Dr. Paul E. Verweij, Centre of Expertise in Mycology, Radboud University Medical Center
A Webber Training Teleclass

Aspergillus fumigatus on the move...

What are the clinical implications of azole resistance?

How is azole resistance selected in the environment?

Clinical: does resistance result in treatment failure?

WT
M220K
TR34/L98H
G54W

AAC 2010; 54:860-5; AAC 2010; 54:8745-64

Hosted by Paul Webber  paul@webbertraining.com
www.webbertraining.com
The Race to Stop the Silent Tsunami of Antifungal Drug Resistance
Dr. Paul E. Verweij, Centre of Expertise in Mycology, Radboud University Medical Center
A Webber Training Teleclass

Clinical: does resistance result in treatment failure?

<table>
<thead>
<tr>
<th></th>
<th>ITZ</th>
<th>VCZ</th>
<th>POS</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT</td>
<td>0.125</td>
<td>0.25</td>
<td>0.03</td>
</tr>
<tr>
<td>TR_{34L98H}</td>
<td>&gt;16</td>
<td>2</td>
<td>0.5</td>
</tr>
<tr>
<td>G54W</td>
<td>&gt;16</td>
<td>0.125</td>
<td>&gt;16</td>
</tr>
<tr>
<td>M220I</td>
<td>&gt;16</td>
<td>0.25</td>
<td>0.5</td>
</tr>
</tbody>
</table>

In vivo efficacy of posaconazole

14 day survival %

0.0 0.5 1.0 1.5 2.0
10Log mg/kg posaconazole

AAC 2010; 54:860-5.

Hosted by Paul Webber  paul@webbertraining.com
www.webbertraining.com
The Race to Stop the Silent Tsunami of Antifungal Drug Resistance
Dr. Paul E. Verweij, Centre of Expertise in Mycology, Radboud University Medical Center
A Webber Training Teleclass

In vivo efficacy of posaconazole

Does azole resistance contribute to treatment failure?

What was the status of the underlying condition?
Was there sufficient voriconazole exposure?
High mortality of CNS aspergillosis
Was the timing of therapy appropriate?
Did the azoleR isolate cause the disease?

Hosted by Paul Webber  paul@webbertraining.com
www.webbertraining.com
The Race to Stop the Silent Tsunami of Antifungal Drug Resistance
Dr. Paul E. Verweij, Centre of Expertise in Mycology, Radboud University Medical Center
A Webber Training Teleclass

Clinical implications of azole resistance

Prevalence of azole resistant IA in specific host groups?
Mortality of azole resistant IA?

Azole resistance frequency: ICU LUMC

107 patients on antifungal therapy
156 patients treated (suspected of IA)
38 patients positive culture for IA
10 patients with resistant IA
28 patients with susceptible IA
10/38 = 26%
M₉₀ = 100%
M₉₀ = 79%

Hosted by Paul Webber  paul@webbertraining.com
www.webbertraining.com
The Race to Stop the Silent Tsunami of Antifungal Drug Resistance
Dr. Paul E. Verweij, Centre of Expertise in Mycology, Radboud University Medical Center
A Webber Training Teleclass

Overall mortality in vori R versus vori S in non-ICU patients

<table>
<thead>
<tr>
<th>Day 90</th>
<th>VCZ-S</th>
<th>VCZ-R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>18%</td>
<td>47%</td>
</tr>
<tr>
<td>p=0.011</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Lestraide B, et al. EECMID 2018; abst. 00718
Radboudumc

Timing of appropriate antifungal therapy

log-rank test, p=0.0049

appropriate

27%

inappropriate

10 days

Diagnosis IA (154)
VCZ therapy
Culture A. fumigatus
MIC-test
VCZ-S
VCZ-R
continue VCZ (124)
Switch to appropriate AF therapy (30)

Lestraide B, et al. EECMID 2018; abst. 00718
Radboudumc

Hosted by Paul Webber paul@webbertraining.com
www.webbertraining.com
The Race to Stop the Silent Tsunami of Antifungal Drug Resistance
Dr. Paul E. Verweij, Centre of Expertise in Mycology, Radboud University Medical Center
A Webber Training Teleclass

On the move......38 year old female admitted to the ICU

Influenza-associated aspergillosis

Aspergillus tracheobronchitis.......inside the bronchi

Hosted by Paul Webber  paul@webbertraining.com
www.webbertraining.com
Azole resistance

### In vitro susceptibility

<table>
<thead>
<tr>
<th>Patient</th>
<th>Underlying disease</th>
<th>Phenotype</th>
<th>Age (years)</th>
<th>azole resistant (susceptible)</th>
<th>MIC (mg/L) (interpretation)</th>
<th>Resistance mutation</th>
<th>Initial antifungal therapy</th>
<th>Subsequent treatment regimen</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/2/14</td>
<td>59.6</td>
<td>Mixed</td>
<td>1</td>
<td>0.015 (S)</td>
<td>2</td>
<td>TRA2 (TRI2/ TDM)</td>
<td>Voriconazole (S)</td>
<td>Li-Ado (42)</td>
<td>Died (42)</td>
</tr>
<tr>
<td>5/5/202</td>
<td>58.5</td>
<td>Mixed</td>
<td>1</td>
<td>0.015 (S)</td>
<td>2</td>
<td>TRA2 (TRI2/ TDM)</td>
<td>Voriconazole (S)</td>
<td>Li-Ado (42)</td>
<td>Died (42)</td>
</tr>
<tr>
<td>5/5/203</td>
<td>Asthma, eosinosis</td>
<td>Mixed</td>
<td>2</td>
<td>0.015 (S)</td>
<td>2</td>
<td>TRA2 (TRI2/ TDM)</td>
<td>Voriconazole (S)</td>
<td>Li-Ado (42)</td>
<td>Died (42)</td>
</tr>
<tr>
<td>5/5/204</td>
<td>Long course, COPD</td>
<td>Resistant</td>
<td>3</td>
<td>0.015 (S)</td>
<td>2</td>
<td>TRA2 (TRI2/ TDM)</td>
<td>Voriconazole (S)</td>
<td>Li-Ado (42)</td>
<td>Survived</td>
</tr>
<tr>
<td>5/5/205</td>
<td>Long course, COPD</td>
<td>Resistant</td>
<td>4</td>
<td>0.015 (S)</td>
<td>2</td>
<td>TRA2 (TRI2/ TDM)</td>
<td>Voriconazole (S)</td>
<td>Li-Ado (42)</td>
<td>Survived</td>
</tr>
</tbody>
</table>

16 patients – 5 azole R (31%)

- 3 mixed azoleS and azoleR infection
- Environmental mutations
- VCN
- 3 died, 2 survived
The Race to Stop the Silent Tsunami of Antifungal Drug Resistance
Dr. Paul E. Verweij, Centre of Expertise in Mycology, Radboud University Medical Center
A Webber Training Teleclass

Pathogenesis of mixed infection


Environmental route: Screening for azole resistance - VIPcheck™

Hosted by Paul Webber  paul@webbertraining.com
www.webbertraining.com
The Race to Stop the Silent Tsunami of Antifungal Drug Resistance
Dr. Paul E. Verweij, Centre of Expertise in Mycology, Radboud University Medical Center
A Webber Training Teleclass

Post-azole era – after 2015?

Liposomal AmB, combinations

Invasive azoleR pulmonary aspergillosis – mortality 80%

CNS azoleR aspergillosis – mortality >85%

A. fumigatus on the move......

Hosted by Paul Webber  paul@webbertraining.com
www.webbertraining.com
The Race to Stop the Silent Tsunami of Antifungal Drug Resistance
Dr. Paul E. Verweij, Centre of Expertise in Mycology, Radboud University Medical Center
A Webber Training Teleclass

Hosted by Paul Webber  paul@webbertraining.com
www.webbertraining.com
The Race to Stop the Silent Tsunami of Antifungal Drug Resistance
Dr. Paul E. Verweij, Centre of Expertise in Mycology, Radboud University Medical Center
A Webber Training Teleclass

Hosted by Paul Webber  paul@webbertraining.com
www.webbertraining.com

Radboudumc
The Race to Stop the Silent Tsunami of Antifungal Drug Resistance
Dr. Paul E. Verweij, Centre of Expertise in Mycology, Radboud University Medical Center
A Webber Training Teleclass

Environmental azole exposure?

Plant protection

130,000 kg vs 400 kg

Material protection

Survival in azole-containing and azole-free environments

Can compete with WT in azole-free environment

Advantage over WT in azole-containing environment

Hosted by Paul Webber  paul@webbertraining.com
www.webbertraining.com
The Race to Stop the Silent Tsunami of Antifungal Drug Resistance
Dr. Paul E. Verweij, Centre of Expertise in Mycology, Radboud University Medical Center
A Webber Training Teleclass

Survival in azole-containing and azole-free environments

Azole-resistant phenotype
TR34/L98H
TR24/Y121F/T289A

Fitness
Survives in competition with WT

In-host adaptation and triazole resistance

Starting azole therapy
Switching azole therapy
Stopping azole therapy

Hosted by Paul Webber  paul@webbertraining.com
www.webbertraining.com
The Race to Stop the Silent Tsunami of Antifungal Drug Resistance
Dr. Paul E. Verweij, Centre of Expertise in Mycology, Radboud University Medical Center
A Webber Training Teleclass

Sampling of compost heaps in the Netherlands

Understanding resistance selection

Hosted by Paul Webber  paul@webbertraining.com
www.webbertraining.com
The Race to Stop the Silent Tsunami of Antifungal Drug Resistance
Dr. Paul E. Verweij, Centre of Expertise in Mycology, Radboud University Medical Center
A Webber Training Teleclass

Understanding resistance selection

Azole +

9% S

91% R

\( \text{TR}_{46}/Y121F/T289A - 80\% \)

\( \text{TR}_{46}/Y121F/M172I/T289A/G448S - 2\% \)

\( \text{TR}_{46}^3/Y121F/M172I/T289A/G448S - 9\% \)

Understanding resistance selection

2012 – \( \text{TR}_{46}^4 \)

2015

2013

2012

\( \text{TR}_{46}^3 \) in patients

Hosted by Paul Webber  paul@webbertraining.com
www.webbertraining.com
The Race to Stop the Silent Tsunami of Antifungal Drug Resistance
Dr. Paul E. Verweij, Centre of Expertise in Mycology, Radboud University Medical Center
A Webber Training Teleclass

Ultimate aim

Medical problem
Preventive measures

Resistance hot spots
Understanding resistance selection

Conclusions

Hosted by Paul Webber  paul@webbertraining.com
www.webbertraining.com
The Race to Stop the Silent Tsunami of Antifungal Drug Resistance
Dr. Paul E. Verweij, Centre of Expertise in Mycology, Radboud University Medical Center
A Webber Training Teleclass

Conclusions: evacuation is not an option....

Understanding resistance selection is critical to retain the azole class for both medical and non-medical applications

---

www.webbertraining.com/schedulep1.php

<table>
<thead>
<tr>
<th>Date</th>
<th>Title</th>
<th>Speaker</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>September 27, 2018</td>
<td>CHLORHEXIDINE USE AND BACTERIAL RESISTANCE</td>
<td>Prof. Jean Yves Maillard, Cardiff University, Wales</td>
<td></td>
</tr>
<tr>
<td>September 30, 2018</td>
<td>FREE European Teleclass - Broadcast live from the 2018 IPS conference</td>
<td>Cottrell Lecture - SURVEILLANCE BY OBJECTIVES: USING MEASUREMENT IN THE PREVENTION OF HEALTHCARE ASSOCIATED INFECTIONS</td>
<td>Prof. Jennie Wilson, University of West London</td>
</tr>
<tr>
<td>October 2, 2018</td>
<td>FREE European Teleclass - Broadcast live from the 2018 IPS conference</td>
<td>Ayliffe Lecture - THE IMPACT OF DISINFECTANTS ON ANTIMICROBIAL RESISTANCE - AN AYLIFFE PREDICTION</td>
<td>Prof. Shaheen Mehtar, Stellenbosch University, Cape Town, South Africa</td>
</tr>
<tr>
<td>October 11, 2018</td>
<td>FREE CBIC Teleclass</td>
<td>INFECTION CONTROL CHAMPIONS ARE MADE, NOT BORN</td>
<td>To be announced</td>
</tr>
<tr>
<td>October 17, 2018</td>
<td>(South Pacific Teleclass)</td>
<td>BIOFILMS IN THE HOSPITAL ENVIRONMENT - INFECTION CONTROL IMPLICATIONS</td>
<td>Prof. Karen Vickery, Macquarie University, Australia</td>
</tr>
<tr>
<td>October 18, 2018</td>
<td>FREE European Teleclass - Broadcast live from the 2018 IPS conference</td>
<td>INFECTION PREVENTION CORE PRACTICES: RESETTING THE BAR FOR SAFE PATIENT CARE</td>
<td>Prof. Ruth Carrico, University of Louisville</td>
</tr>
</tbody>
</table>

Hosted by Paul Webber  paul@webbertraining.com
www.webbertraining.com
The Race to Stop the Silent Tsunami of Antifungal Drug Resistance
Dr. Paul E. Verweij, Centre of Expertise in Mycology, Radboud University Medical Center
A Webber Training Teleclass

Thanks to Teleclass Education

**Patron Sponsors**

- Diversey
  - www.diversey.com
- Virox
  - www.virox.com
- GOJO
  - www.gojo.com
- World Health Organization
  - Infection Prevention and Control Global Unit
  - www.who.int/gpsc/en

Hosted by Paul Webber  paul@webbertraining.com
www.webbertraining.com