Prevention and management of antifungal-resistant infections in the ICU

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My prerequisites to participate in these activities are the autonomy of scientific thought, independence of opinion and freedom of expression, aspects that this company respects.
Scope of the presentation

- Introduction
- The need for limiting indications for prophylaxis of invasive candidiasis
- The need for a paradigm shift in the diagnostic and therapeutic approach to AF therapy: “Early” therapeutic start-stop approach
- The need for audit of multi-component AFS measures as a AFS “bundle”
- The need for multi-disciplinary engagement
- Conclusions
Introduction
• Candida species are by far the predominant agent of fungal sepsis accounting for 10% to 15% of all HAIs, and 5% of all cases of severe sepsis and septic shock

• Notably, 1/3 of all episodes of candidemia occur in the ICU and invasive candidiasis (IC) is a serious complication in ICU, with high morbidity and mortality of up to 90% in patients with septic shock. Among patients with IC in the ICU, 2/3 will have candidaemia, and 80% of non-candidaemic patients will have intra-abdominal candidiasis.

• The epidemiology of Candida infections is continuously changing, with the emergence of new MDR species in SA such as Candida auris, of particular concern

• The high prevalence of azole-resistant C. parapsilosis causing bloodstream infections in the private sector in SA were recently highlighted, including amino acid substitutions in the FKS genes responsible for echinocandin resistance in C. glabrata.

Colombo et al. Lancet Infect Dis 2017; 17: e344–56
Naicker et al. Medical Mycology Case Reports 2016;11: 24–26
Need for limiting indications for prophylaxis of invasive candidiasis
Indications for prophylaxis of IC

• AF prophylaxis in non-neutropenic critically ill patients remains controversial including surgical patients with severe acute pancreatitis

• Whilst fluconazole prophylaxis in ICU patients (adults and neonates) may reduce the incidence of IC, collateral damage with regards to epidemiological changes and emergence of resistance in non-Candida albicans spp., prohibit universal prophylaxis in these high-risk populations

• Previous exposure to antifungals is clearly associated with a shift in species distribution and MIC “creep” of antifungal agents (e.g. C. parapsilosis), in addition to the subsequent threat of emergence of cross-resistance to both triazoles and echinocandins, described in C. glabrata, a species notorious to sequentially acquire and express multiple resistance genes

Montravers et al. Critical Care 2013,17:137
Indications for prophylaxis of IC

• The dominance of triazole-resistant non-C. albicans pathogens causing bloodstream infections (BSIs) in SA was recently confirmed (*C. parapsilosis*), particularly in ICU patients in the private sector.

• Overuse of triazoles for prophylaxis and treatment of candidaemia and other fungal infections may have led to the emergence and subsequent nosocomial transmission of these triazole-resistant strains.

• Similar confounding variables appear to apply to *C. auris* in SA (van Schalkwyk et al).

Indications for prophylaxis of IC

- Therefore, the approach to prophylaxis should not be universal but rather selective, in which only the following specific high-risk patient groups are targeted:
  - **Surgical patients**
    - Presenting with anastomotic leakage after abdominal surgery
    - Re-operation of the digestive tract during the same hospitalization
  - **Neonates**
    - Extremely low birth weight (ELBW) infants (BW < 1000 g) in neonatal ICUs with a baseline rate of IC of 5-10%

- The unique epidemiology of IC in SA, underscored by the predominance of *C. albicans* and *C. parapsilosis*, in the public and private sector, respectively necessitates multi-disciplinary AFS teams to choose prophylactic agents based on local surveillance data.

Bassetti et al. *Intensive Care Med* 2015; 41:1336–1339
Manzoni et al. *Arch Dis Child* 2009; 94:983
Need for a paradigm shift in the diagnostic and therapeutic approach to AF therapy

“Early” therapeutic start-stop approach
Need for a paradigm shift in the approach to AF therapy

• From a clinical point of view, early and appropriate diagnosis and treatment of IC is the key for a significant reduction in mortality.

• To minimize the negative impact of this infection, several management strategies had previously been proposed and utilized: prophylaxis, empirical therapy, pre-emptive therapy, and culture-based treatment (directed).

• Both prophylaxis—based on universal AF treatment—and empirical therapy—based on the persistence of fever non-responsive to antibacterials and a combination of risk factors—may overexpose the patients to treatment, potentially increasing the rates of resistance to AFs.

• Notably, up to 70% of critically ill patients receive systemic AF therapy although they have no documented invasive fungal infection, suggesting the need for a paradigm shift in the approach to AF therapy and alternative strategies contained within the implementation of novel AFS programs.
Need for a paradigm shift in the approach to AF therapy

- Three fundamental principles to prevent and manage anti-fungal resistant infections in the ICU may pertain
  - **Tenet 1.** Substitute the concepts of pre-emptive or empiric therapy by “early” AF treatment, in which both modalities would be present.
  - **Tenet 2.** Use non-culture-based assays concurrent to risk factors for IC to identify patients for initiation of “early” AF therapy
  - **Tenet 3.** Use non-culture-based assays concurrent to risk factors for IC to identify patients for discontinuation of “early” AF therapy
Tenet 1. Substitute the concepts of pre-emptive or empiric therapy by “early” AF treatment, in which both modalities would be present.
Substitute the concepts of pre-emptive or empiric therapy by “early” AF treatment

• Given the advent of biomarkers such as (1,3)-β-D-glucan (BDG) for practical purposes and to simplify auditing of AFS process measures, the concepts of pre-emptive or empiric therapy should be substituted by “early” AF treatment, in which both modalities would be present.

• The possible and ‘ideal” interdependence of:
  • Microbiologic findings
  • Clinical symptoms and signs
  • Serologic and molecular biomarkers

• May help clinicians in the stratification of patients and to select more accurately from an AFS point of view, those ICU candidates for an “early” antifungal treatment, without compromising outcome

Bassetti et al. Intensive Care Med 2015; 41:1336–1339
Tenet 2. Use non-culture-based assays concurrent to risk factors for IC to identify patients for initiation of “early” AF therapy
## ‘Early’ AF therapy based on predictive rules

<table>
<thead>
<tr>
<th>Derivation setting</th>
<th>Model parameters</th>
</tr>
</thead>
</table>
| **Colonisation index**<sup>51</sup> | Single Swiss ICU (n=29)  
Colonisation index = number of positive sites/number of cultured sites (threshold 0.5); corrected colonisation index = number of sites with heavy growth (graded as 0, 1+, 2+, 3+) / number of positive sites (threshold 0.4) |
| **Clinical prediction rule**<sup>52</sup> | 12 US/Brazilian ICUs (n=2890); underlying IC 3.0%  
Either systemic antibiotics (days 1 to 3) or central venous catheter (days 1 to 3), plus two other risk factors: total parenteral nutrition (days 1 to 3), dialysis (days 1 to 3), major surgery (days -7 to 0), pancreatitis (days -7 to 0), steroids (days -7 to 3), other immunosuppressive agents (days -7 to 0)* |
| **Clinical prediction rule**<sup>53</sup> | Six US ICUs (n=557); underlying IC 3.7%  
All of ventilation (days 1 to 3), broad spectrum antibiotics (days 1 to 3), and central venous catheter (days 1 to 3), plus one other risk factor: total parenteral nutrition (days 1 to 3), dialysis (days 1 to 3), major surgery (days -7 to 0), pancreatitis (days -7 to 0), steroids (days -7 to 3), other immunosuppressive agents (days -7 to 0)* |
| **Candida score**<sup>54</sup> | 73 Spanish ICUs (n=1669); underlying IC 5.7%  
Sepsis (2 points), surgery (1 point), total parenteral nutrition (1 point), multifocal candida colonisation (1 point); threshold 2.5 points |
| **UK FIRE study risk predictive model (end day 3 in ICU)**<sup>55</sup> | 96 UK ICUs (n=60778); underlying IC 0.6%  
Pancreatitis, central venous catheter(s), surgical drains in situ, highest heart rate ≥100 min (first 24 h), one or more sites colonised with *Candida* spp |
| **Three-tiered risk predictive model, Australia**<sup>56</sup> | Seven Australian mixed medical-surgical ICUs (n=6685); underlying IC 1.4%  
Summation score of ten independent variables: emergency gastrointestinal or hepatobiliary surgery, non-coated central venous catheter, total parenteral nutrition, admitted from operating theatre, emergency department, or other hospital, steroids ≥50 mg/day, blood transfusion, use of carbapenem or tigecycline, use of third or fourth generation cephalosporin, positive urine culture, positive throat culture |

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Identifying patients at-risk for IC include recognition of a combination of risk factors such as multiple organ failure, sepsis of unknown origin, multisite colonization with Candida spp, mechanical ventilation for >than 7 days, receipt of broad-spectrum antibiotics and prior surgery etc.

In this regard, predictive scores such as the Candida Score (CS) could assist clinicians and AFS teams with distinguishing between Candida spp. colonization versus IC. Such rules permit the stratification and selection of IC high-risk patients who may benefit from early AF therapy.

However, from an AFS point of view, given the very low positive predictive values, many AF treatments have been shown to be unnecessary (~70%).

In contrast, the predictive scores have far better negative predictive values (NPV)

Bassetti et al. *Intensive Care Med* 2015; 41:1336–1339
What’s new in the clinical and diagnostic management of invasive candidiasis in critically ill patients
Table 2 Comparison of invasive candidiasis prediction rules

<table>
<thead>
<tr>
<th>Score, year</th>
<th>Patients (n) type of study</th>
<th>ICUs</th>
<th>Sensitivity (95 % CI)</th>
<th>Specificity (95 % CI)</th>
<th>PPV (95 % CI)</th>
<th>NPV (95 % CI)</th>
<th>Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colonization index, 1994 [46]</td>
<td>29 prospective</td>
<td>1</td>
<td>100</td>
<td>66.6 (43–83)</td>
<td>64.7 (41–83)</td>
<td>100</td>
<td>≥0.5</td>
</tr>
<tr>
<td>Dupont score, 2003 [54]a</td>
<td>57 prospective</td>
<td>1</td>
<td>84</td>
<td>50</td>
<td>67</td>
<td>72</td>
<td>≥3</td>
</tr>
<tr>
<td><em>Candida</em> score, 2006 [39]</td>
<td>1,699 retrospective</td>
<td>73</td>
<td>81 (69–89)</td>
<td>74 (70–77)</td>
<td>24.6 (19–31)</td>
<td>97.4 (95–98)</td>
<td>≥3</td>
</tr>
<tr>
<td><em>Candida</em> score, 2009 [55]</td>
<td>1,107 prospective</td>
<td>36</td>
<td>77.6 (65–86)</td>
<td>66.2 (63–69)</td>
<td>13.8 (10–17)</td>
<td>97.7 (96–98)</td>
<td>≥3</td>
</tr>
<tr>
<td>Ostronsky rule, 2011 [56]</td>
<td>597 retrospective</td>
<td>6</td>
<td>90 (72–97)</td>
<td>48 (44–52)</td>
<td>6 (4–9)</td>
<td>99 (97–99)</td>
<td>MV + BSA + CVC + other</td>
</tr>
</tbody>
</table>

*ICU* intensive care unit, *MV* mechanical ventilation, *BSA* broad-spectrum antibiotics, *CVC* central venous catheter

*a* Grade C
‘Early’ AF therapy based on non-culture based assays

- Culture-based diagnosis is problematic because it is slow (1–7 days) and has poor sensitivity.
  - Only about 50% of cases of IC are candidaemic; bacteraemia coexists in approximately 20% of cases.
  - In intra-abdominal candidiasis, the sensitivity of intra-abdominal fluid or cultures from infected sites is less than 50%, and only 4–20% of cases will be candidaemic. Concurrent bacterial infection is common (roughly 70% of cases).

- MALDI-TOF enables rapid speciation once fungal growth is evident, and has also been used for direct ID of yeasts in blood cultures applying protein extraction protocols.

- Serology-based diagnostics for IC include mannan, antimannan and BDG assays.

- Rapid diagnostic methods (eg, PCR) are not more sensitive than culture (both have a limit of detection of 1-5 CFU/ml, depending on the quantity of blood sampled), but accelerate diagnosis.
‘Early’ AF therapy based on non-culture based assays

- A whole blood assay combining PCR technology and nanoparticle-based hybridization (T2 magnetic resonance) was recently shown to rapidly (<5 h), accurately, and reproducibly detect 1–3 CFU of *C. albicans*, *C. tropicalis*, *C. glabrata*, *C. krusei*, and *C. parapsilosis* per ml of spiked blood or in patients with a low incidence of IC.
- Also recently, findings from the RADICAL study that used PCR/electrospray ionization–mass spectrometry (PCR/ESI) technology, showed 81% sensitivity, 69% specificity, and 97% negative predictive value with PCR/ESI when compared with conventional cultures.

‘Early’ AF therapy based on non-culture based assays

Table 3 Comparison of BDG test findings in non-neutropenic critically ill adult patients (ICU)

<table>
<thead>
<tr>
<th>References</th>
<th>Patient type</th>
<th>Number patients/samples (mean)</th>
<th>IC type (cases)</th>
<th>Cutoff(b)</th>
<th>Sensitivity (95 % CI)</th>
<th>Specificity (95 % CI)</th>
<th>PPV (95 % CI)</th>
<th>NPV (95 % CI)</th>
<th>Proven IC BG(b) (median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissot et al. [38]</td>
<td>Surgical (abdominal) pancreatitis</td>
<td>89/921 [9]</td>
<td>IAC (29)</td>
<td>≥80</td>
<td>65 (46–82)(^a)</td>
<td>78 (63–90)(^a)</td>
<td>68 (48–84)(^a)</td>
<td>77 (61–88)(^a)</td>
<td>223</td>
</tr>
<tr>
<td>León et al. [65]</td>
<td>SAC</td>
<td>176/766 (4.3)</td>
<td>C, IAC (31)</td>
<td>≥80</td>
<td>51.6 (34–69)</td>
<td>86.9 (78–92)</td>
<td>59.3 (44–75)</td>
<td>83.0 (73–89)</td>
<td>259</td>
</tr>
<tr>
<td>Del Bono et al. [64]</td>
<td>Surgical</td>
<td>152/152 (1)</td>
<td>C (53)</td>
<td>≥80</td>
<td>62</td>
<td>98</td>
<td>98.4</td>
<td>57.3</td>
<td>324</td>
</tr>
<tr>
<td>Posteraro et al. [63]</td>
<td>Medical/surgical</td>
<td>95/130 (1.3)</td>
<td>C (13 + 1 M)</td>
<td>≥80</td>
<td>92.9 (66–99)</td>
<td>93.7 (85–90)</td>
<td>72.2 (46–90)</td>
<td>98.7 (92–99)</td>
<td>900</td>
</tr>
<tr>
<td>Mohr et al. [62]</td>
<td>Surgical</td>
<td>57/239 (4)</td>
<td>C [3]</td>
<td>≥80</td>
<td>100(^a)</td>
<td>59(^a)</td>
<td>NDA</td>
<td>NDA</td>
<td>171</td>
</tr>
</tbody>
</table>

\(CI\) confidence intervals, \(IC\) invasive candidiasis, \(C\) candidemia, \(IAC\) intra-abdominal candidiasis, \(SAC\) severe abdominal conditions, \(HC\) hepatic candidiasis, \(M\) mediastinitis, \(NDA\) no data available

\(^a\) Two consecutive BG determinations: maximal BG to time of the IC diagnosis

\(^b\) pg/mL
Early diagnosis of candidemia in intensive care unit patients with sepsis: a prospective comparison of (1→3)-β-D-glucan assay, Candida score, and colonization index

Brunella Posteraro¹, Gennaro De Pascale², Mario Tumbarello³*, Riccardo Torelli¹, Mariano Alberto Pennisi², Giuseppe Bello², Riccardo Maviglia², Giovanni Fadda¹, Maurizio Sanguinetti¹ and Massimo Antonelli²
‘Early’ AF therapy based on predictive rules and biomarkers

• The combination of a positive BDG result and a CS value ≥3 increased the:
  • Sensitivity [100% (95% CI, 76.8% to 100%)]
  • NPV [100% (95% CI, 94.6% to 100%)]
• For diagnosis of IC compared to 92.9% and 97.2% for the BG test alone, respectively.

• “A single-point BDG assay based on a blood sample drawn at the sepsis onset, alone or but preferably in combination with CS, may guide the decision to start AF therapy early in patients at risk for Candida infection”.
Need for a paradigm shift in the approach to AF therapy

Tenet 3. Use non-culture-based assays concurrent to risk factors for IC to identify patients for discontinuation of “early” AF therapy
More recent studies using non-culture-based assays, particularly BDG concurrent to a CS, have aided in establishing whether an "early" therapeutic start-stop approach (i.e. initiation of AF therapy in at-risk patients followed by close follow-up and discontinuation of AF therapy when IC is excluded), has an impact on the outcomes of ICU patients.

Adult patients (n=198) admitted to the ICU were included if they exhibited sepsis at the time of BDG testing and they met Candida score components ≥3.

Of 63 BDG-positive patients, 47 with candidaemia and 16 with probable Candida infection, all [31.8% (63/198)] received antifungal therapy.

Of 135 BDG-negative patients, 110 [55.5% (110/198)] did not receive antifungal therapy, whereas 25 [12.6% (25/198)] were initially treated, then stopped.

Using this approach, antifungal therapy was avoided in 73% of potentially treatable patients and it was shortened in another 20%, without impacting on outcomes such as mortality whilst saving 3500 Euros/patient.
Discontinuation of empirical antifungal therapy in ICU patients using 1,3-β-D-glucan

Marcio Nucci1*, Simone A. Noué1, Patricia Esteves2, Thais Guimarães3, Giovanni Breda4, Bianca Grassi de Miranda3, Flavio Queiroz-Telles4 and Arnaldo L. Colombo2

- Results: All 21 patients with baseline negative BDG discontinued anidulafungin on D4. None developed candidaemia by D30

- Early discontinuation of empirical echinocandin therapy in high-risk ICU patients based on consecutive neg BDG tests may be a reasonable strategy, with great potential to reduce the overuse of echinocandins in ICU patients
Aim of this study was to determine the impact of a biomarker-based strategy on early discontinuation of AF treatment.

Methods: Prospective randomized controlled single-center unblinded study, performed in a mixed ICU. 110 patients were randomly assigned to a strategy in which empirical AF treatment duration was determined by BDG, mannan, and anti-mannan serum assays, performed on D 0&4; or to a routine care strategy, based on international guidelines, which recommend 14 D of treatment. In the biomarker group, early stop recommendation was determined using an algorithm based on the results of biomarkers.

Results:

- Empirical AF treatment was discontinued early in 29/54 patients in the biomarker strategy group, compared with 1/55 in the routine strategy group (54% vs 2%, p < 0.001, OR (95% CI) 62.6 (8.1–486)).
- Total duration of AF treatment was significantly shorter in the biomarker strategy compared with routine strategy [median (IQR) 6 (4–13) vs 13 (12–14) days, p < 0.0001).
- No significant difference was found in the % of patients with subsequent proven invasive Candida infection, mechanical ventilation-free days, length of ICU stay, cost, and ICU mortality between the 2 groups.

Combined use of BDG and PCT

A recent study also aimed to assess the combined performance of BDG and procalcitonin (PCT) for the differential diagnosis between IC and bacteraemia. When both markers indicated IC (BDG ≥80 pg/ml and PCT <2 ng/ml), they showed higher positive predictive value (PPV) (96%) compared to 79% and 66% for BDG or PCT alone, respectively. When both markers indicated bacteraemia (BDG <80 pg/ml and PCT ≥2 ng/ml), their NPV for IC was similar to that of BDG used alone (95% vs. 93%).

The combined use of PCT and BDG could therefore be helpful in the diagnostic workflow for critically ill patients with suspected candidaemia.
The aim of this study was to evaluate the sensitivity and the levels of BDG among patients with candidaemia due to different Candida species. Retrospective study of all patients who had a single-species candidaemia and BDG testing performed within 48 h from the onset of candidaemia 2009-2015.

107 patients with the following Candida distribution were included: 46 (43%) Candida albicans, 37 (35%) Candida parapsilosis, and 24 (22%) other species.

BDG sensitivity and levels were the highest in C. albicans candidaemia and lowest for C. parapsilosis; respectively, 72% and 410 pg/mL for C. albicans vs 41% and 39 pg/mL for C. parapsilosis, p< 0.015 and p< 0.003)

Therefore, the results of this study showed that the performance of BDG is significantly influenced by Candida species, and may result in poor diagnostic performance in settings where C. parapsilosis is frequent.
Need for audit of multi-component AFS measures as a AFS “bundle”
Besides identifying high-risk patients & “early” therapeutic start-stop approach there are several other AFS process measures that impact on outcomes:

• Timeous administration (“hang-time”)
• “Get it right first time”
• Importance of adequate therapy & source control
• De-escalation & step-down therapy
• Duration
Timeous administration ("hang-time")

Hospital mortality (%)

Delay in start of antifungal treatment (hours)

“Get it right the first time”

Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America


Echinocandins are the preferred 1ˢᵗ-line therapy for proven IC

In patients with susceptible Candida spp, triazoles might be initiated after clinical improvement and negative blood cultures (de-escalation)

Lipid amphotericin B formulations should be considered in patients with CNS involvement, endocarditis, or intolerance or resistance to echinocandins
Better efficacy profiles and decreased toxicity of newer AF agents have most likely contributed to increased use of these agents for empirical treatment. Accordingly, the use of echinocandins has increased from 4.6% to 48.5% in some settings. These newer agents inevitably result in increased cost of care and raise concern about the potential of AF resistance.

In this regard, recent studies showed that echinocandins exposure in ICU patients was low compared with healthy volunteers and other (non-critically ill patients), most likely as a result of a larger VD. This suggests that a weight-based dose regimen should probably be more suitable for patients with substantially altered drug distribution. There are also emerging data linking suboptimal dosing to the emergence of AF resistance and a poor outcome. Dosing of AF agents in patients with ECMO need more studies to define the therapeutic schemes that avoid subtherapeutic levels. In this context, the impact on outcome of TDM warrants further investigations.

Ultimately, like other preventative interventions, future studies will need to weigh the risks and potential benefits of empirical echinocandin therapy for critically ill, immune-competent patients in the ICU.
A multicenter study of septic shock due to candidemia: outcomes and predictors of mortality
Importance of adequate therapy & source control

216 candidaemia with septic shock from Italy – Spain

A multicenter multinational study of abdominal candidiasis: epidemiology, outcomes and predictors of mortality
n=481 patients with intra-abdominal candididias from 13 hospitals in Italy, Spain, Brazil, and Greece over a 3-year period including patients from ICU, medical, and surgical wards.

Multivariate logistic regression showed that:

- Age (OR 1.05, 95% CI 1.03–1.07, P<0.001)
- Increments in 1-point APACHE II scores (OR 1.05, 95% CI 1.01–1.08, P=0.028)
- Secondary peritonitis (OR 1.72, 95% CI 1.02–2.89, P=0.019)
- Septic shock (OR 3.29, 95% CI 1.88–5.86, P<0.001)
- Absence of adequate abdominal source control (OR 3.35, 95% CI 2.01–5.63, P<0.001)

In patients with septic shock, absence of source control correlated with mortality rates above 60% irrespective of administration of an adequate antifungal therapy.
De-escalation & step-down therapy

If:
- the species is susceptible
- the patient is clinically stable
- the patient is able to take oral drug
- the patient has neg bloodcultures following initiation*

But when?

- Candidaemia (IDSA 2016): 3–5 days
- Candidaemia (ESCMID 2012) 10 days
- Intra-abdominal candidiasis (SITI/ISC 2013): 5–7 days
- Candidaemia (ITALIC 2014): 3-4 days

SITI/ISC – Italian Society of Intensive Care /International Society of Chemotherapy
ITALIC – Italian Concencus for Invasive Candidiasis Management

• 14 days from the first negative blood culture in proven cases without
  – abscesses or
  – dissemination

❖The end of candidaemia should be determined by at least one blood culture per day until negativity.

Impact of an AFS “bundle”

Management bundles for candidaemia: the impact of compliance on clinical outcomes

Yoshio Takesue¹,²*, Takashi Ueda², Hiroshige Mikamo¹, Shigeto Oda¹, Shunji Takakura¹, Yuko Kitagawa¹ and Shigeru Kohno¹ on behalf of the ACTIONs Project†

6. Assessment of clinical efficacy on the third to fifth day to consider necessity of alternative therapy
7. Appropriate choice of alternative antifungals
8. At least 2 weeks of therapy after documented clearance of Candida from bloodstream and resolution of attributable symptoms (prolonged therapy for candidaemia with organ involvement)
9. Step-down oral therapy for patients with favourable clinical course
The aim of this study was to investigate nationwide (Japan) compliance with an AFS bundle and their impact on clinical outcomes; n=608 patients were analysed.

Results: The composite compliance rate was only 6.9%, and it increased to 21.4% when compliance was analysed excluding step-down oral therapy.

- There was a significant difference in clinical success between patients with and without compliance [92.9% versus 75.8% P=0.011].
- When step-down oral therapy was excluded, compliance with the bundle was an independent predictor of clinical success (OR 4.42, 95% CI 2.05–9.52) and mortality (OR 0.27, 95% CI 0.13–0.57).
- Independent individual measures contributing to clinical success were:
  - Removal of central venous catheters within 24 h
  - Assessment of clinical efficacy on the third to the fifth day
  - At least 2 weeks of therapy after clearance of candidaemia

Compliance with the bundles for candidaemia had a beneficial effect on clinical outcomes & promotion of the bundle approach may have the potential to narrow the gap between clinical evidence and bedside practice.

Takesue et al. *JAC* 2015;70:587–593
Impact of Education and an Antifungal Stewardship Program for Candidiasis at a Thai Tertiary Care Center

Anucha Apisarnthanarak, MD; Apiwat Yatrasert, MD; Linda M. Mundy, MD, PhD; Thammasat University Antimicrobial Stewardship Team

• The ITS (pre-post) study design, not only resulted in improved overall utilization but also a decrease in fluconazole consumption [from 242 to 117 DDDs per 1000 patient-days (P<0.0001)]

• This was correlated to a reduction in the incidence of non-albicans Candida spp. such as *C. glabrata* (*r*=0.69, *P*<.001) and *C. krusei* (*r*=0.71; *P*<.001)

• This is the only study to date that demonstrated that an AFSP can “restore” or positively effect fungal epidemiology

• Apisarnthanarak et al *Infect Ctrl Hosp Epidem* 2010;31:722-727
Need for multi-disciplinary engagement
Need for multi-disciplinary engagement

- The diagnostic challenges and poor outcomes associated with IC have resulted in excessive empirical use of AFs in various hospital settings, exposing many patients without IC to potential drug toxicities as well as causing spiralling antifungal drug costs and leading to drug-resistant Candida spp.

- To address the complexity of patients at-risk for IC, overcome diagnostic, treatment challenges, and to ensure optimal management of IC, specialist knowledge and experience from a range of health care backgrounds (pharmacy, microbiology, infectious diseases, internal medicine, surgery, anaesthesiology and infection control) is required, thus necessitating multidisciplinary teams, which is not the norm in SA.

- Multidisciplinary teams encompassing the necessary expertise is a pivotal core international recommendation for the approach to antifungal stewardship (AFS).

- Given the lack of ID resources in most SA hospitals, utilizing existing multidisciplinary resources in routine practices, e.g., pharmacists and/or ICU nurses, may enable AFS programs to be initiated and imbedded in routine practices which is required for sustainability of any proposed intervention.

Conclusions
Echinocandins and triazoles have been validated extensively for prophylaxis, empirical therapy, and targeted therapy, but an increase in intrinsically resistant fungi and emergence of secondary resistance as a result of drug-induced selection pressure are of major concern. Also the rapid spread of non- *Candida* species causing ICs and associated antifungal resistance incl MDR is worrisome given the frequency with which the Candida family cause infections and the high mortality reported with infections due to such pathogens.

Whilst at least three compounds are under development [a long-acting echinocandin (CD101, Cidara) and two entirely new AF classes (SCY078, Scynexis, and APX001, Amplyx], the need for an AFS programme’s is recognized, however, the logistics of implementing, training of HCWs and evaluating such a programme is far from clear.

Given the lack of ID resources in most SA hospitals, utilizing existing multidisciplinary resources in a collaborative manner and auditing process measures in a AFS bundle, may enable AFSPs to be initiated and imbedded in routine practice.

Conclusions
AFS programs should perhaps conceptually focus initially on fundamental tenets:

- The unique epidemiology of IC in SA necessitates choice of AF for prophylaxis and “early” AF therapy to be based on local surveillance data
- AF prophylaxis should not be universal in ICU but restricted to specific high-risk patient groups
- To minimize negative outcomes and to simplify audit in AFSP, the term “early” AF therapy should be used rather than pre-emptive or empiric therapy
- To reduce redundant AF consumption an “early’ therapeutic start-stop approach should be based on risk factors (predictive rules or scores) concurrent to biomarkers
- To assess AF utilization and to monitor the impact of interventions, utilizing an AFS audit “bundle” is probably the best strategy for hospitals who have not started AFS yet
- To address the diagnostic and therapeutic complexity of patients at-risk for IC, multidisciplinary teams are necessitated.
Future research needs and considerations

- Fundamental research needs regarding IFI include:
  - A global sentinel network to collect data on emerging pathogens, changing susceptibility patterns, and IFI-attributable mortality in real time.
  - Accelerated molecular diagnosis that would allow earlier targeted treatment
  - Randomized comparison of conceptual treatment strategies integrating clinical stratification and old and new biomarkers vs current treatment standards
  - Confirmatory biomarker studies to guide clinical decision-making on the fundamental issues of when to start and when to stop AF treatment
  - Robust data on attributable mortality that is essential for the design of clinical studies with mortality endpoints
  - The optimal diagnostic and therapeutic strategies for patients with IFIs other than IC
  - Studies on antifungal PK, tissue penetration, and optimal dosing schedules to elucidate the role of TDM (which is a pivotal issue to temper the impact on resistance selection and high mortality associated with IFI)
  - The impact of screening and treatment strategies for polymorphisms of TLR interferon-α host defense pathway (that render ICU patients up to 20 times more likely to acquire candidemia than other ICU patients

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