Uso appropriato degli antifungini

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- Gilead
- Janssen
- MSD
- Mundipharma
- Pfizer

Uso appropriato degli antifungini
The need for antifungal stewarship

- High morbidity
- High mortality, particularly in immunocompromised patients
- Increasing incidence

-increase in at risk populations (age, devices)

-outbreaks of fluco-R *C. parapsilosis, C. auris*

- Substantial economic burden on the health system
- High rates of adverse drug reactions
- Significant drug–drug interactions
- Emergence of antifungal resistance

Uso appropriato degli antifungini

Correct indication	Indication for prophylaxis Indication for treatment (and type of treatment: empirical, targeted) Evaluation of patient's risk and correct diagnosis
Correct antifungal	Drug with the best efficacy and lowest toxicity Drug recommended and licenced for this indication (off label?) Consider the risk of DDIs and cumulative toxicities
Correct dose	BMI, renal clearance, site of infection Challenges in the ICU (RRT, ECMO)
Correct lenght of treatment	Early discontinuation if empirical Step down oral therapy if possible Criteria for ending treatment

Uso appropriato

- Six studies have evaluated the appropriateness of antifungal prescribing, either solely or predominantly in the cancer setting
  - Overall rate of appropriate antifungal prescribing **29.4% - 56.5%**

- Key areas for improvement identified
  - **prolonged duration of antifungal prescribing for both prophylactic and empiric therapy**
  - inappropriate choice of antifungal agent
  - incorrect loading and maintenance dosing
  - suboptimal management of drug–drug interactions
  - poor utilisation of antifungal therapeutic monitoring (TDM)

Table 1 – A scoring system for the evaluation of antifungal prescription adequacy.

Parameter	Question	Points
Indication	Does the patient need an antifungal?	Yes (2); No (0)
Selection	Is the agent active against the disease and is the first choice?	Yes (1) No (0)
Dosage	Correct dosage for indication, weight, renal function, hepatic function, drug interactions?	Yes (1) No (0)
Microbiologic adjustment	Has prescription been adjusted according to laboratory results?	Yes (2) No (0)
Route	If started with IV, changed to oral if possible?	Yes (1) No (0)
Duration	Correct duration?	Yes (2) No (0)

IV = intravenous

Khanina et al. Internal Medicine Journal (2021) 51(Suppl. 7) 18–36

Valerio M et al J Antimicrob Chemother. 2014 Jul;69(7):1993-9

Evaluation of appropriate use
Patient's risk and correct diagnosis

- Diagnosis
  - Availability of diagnostic methods
  - Correct application to specific settings
    - Pre-test probability for evaluation of PPV and NPV
  - Correct interpretation of the results

Open Forum Infectious Diseases

REVIEW ARTICLE

The Role of Diagnostics-Driven Antifungal Stewardship in the Management of Invasive Fungal Infections: A Systematic Literature Review

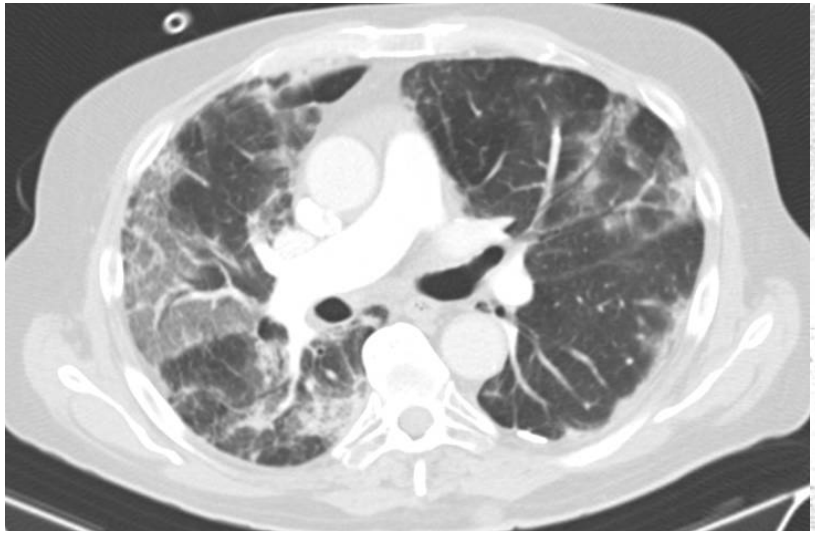
Arunaloke Chakrabarti,[1] Naglaa Mohamed,[2] Maria Rita Capparella,[3] Andy Townsend,[4] Anita H. Sung,[2] Renee Yura,[5] and Patricia Muñoz[6,7,8,9]

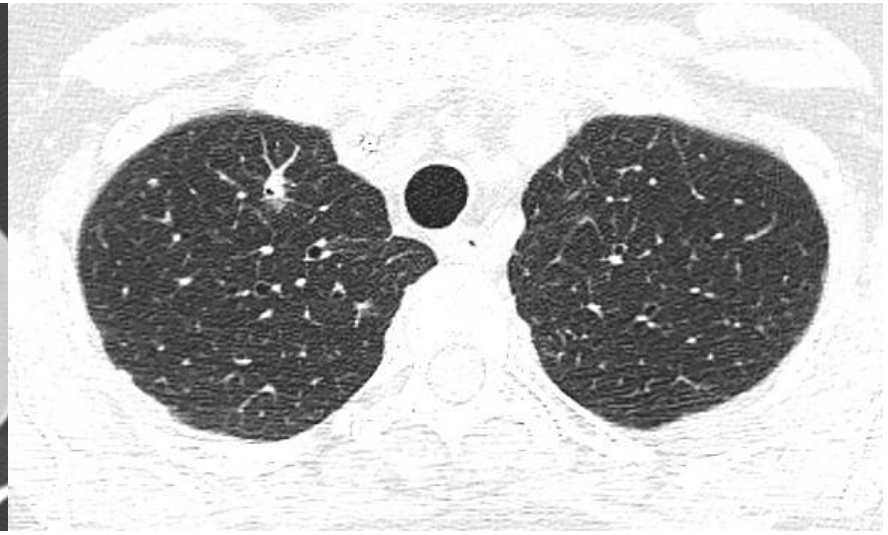
- Systematic literature review evaluated the impact of diagnostics in AFS programs
- Diagnostic approaches included
  - serum β-1–3-D-glucan test (7/17), galactomannan test (4/17), computed tomography scan (3/17), magnetic resonance (2/17), matrix-assisted laser desorption and ionization time-of-flight mass spectrometry (MALDI-TOFMS; 2/17), polymerase chain reaction (1/17), peptide nucleic acid fluorescent in situ hybridization (PNA-FISH) assay (1/17), and other routine methods (9/17)

Decreased

- Time to species identification with using MALDI-TOF and PNA-FISH (n =2)
- Time to targeted therapy and **length of empiric therapy (n=3)**
- **Antifungal consumption by 11.6%–59.0%** (7/13)
- **Cost-savings ranged from 13.5% to 50.6% (5/10)**
- Mortality rate (13/16) and length of stay (6/7)

Diagnosi nel setting giusto:
Beta-D-glucano sierico





Patient in ICU?

Used to start antifugnal?

Used to stop antifugnal?

PCP in immunocomrpomised
Very high PPV
Positive BDG confirms diagnosis if clinically suspected PCP

IA in hematology
Low PPV 50%
Negative result does not exclude IA

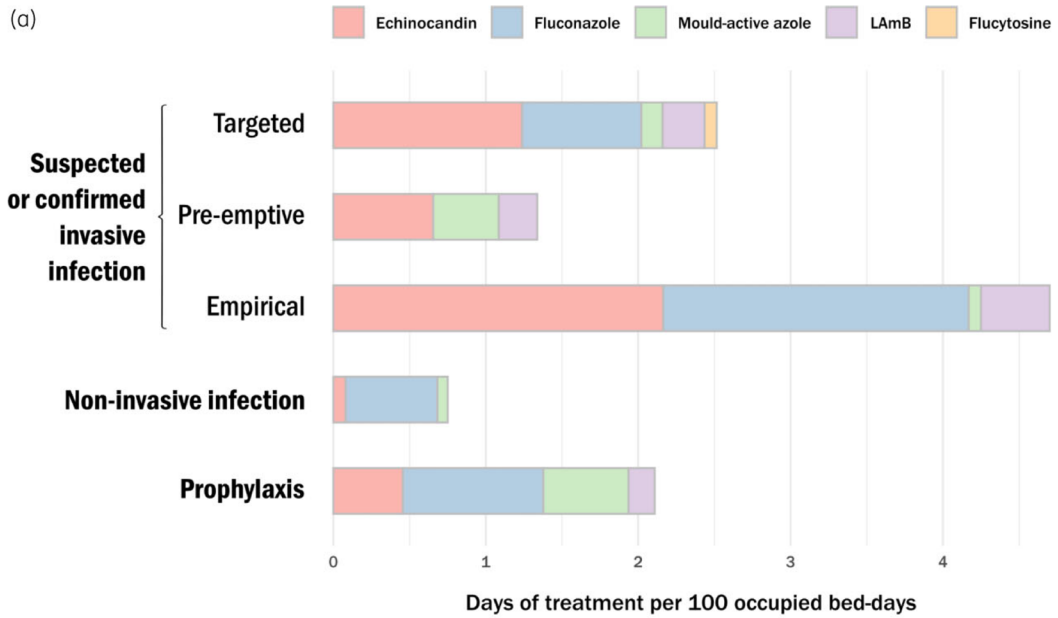
Candidemia in ICU
Hihger sensitivity than blood cultures
High NPV ….

1. Onishi A, et al. *J Clin Microbiol* 2012;50(1):7–15. **2.** Karageorgopoulos DE, et al. *Clin Microbiol Infect* 2013;19(1):39–49.

Target the most prevalent antifungal use

Prophylaxis was most frequently prescribed in oncology and haematology units (40%)

Logan *et al*.



Valerio M et al J Antimicrob Chemother. 2014 Jul;69(7):1993-9
Logan et al. JAC Antimicrob Resist 2022 https://doi.org/10.1093/jacamr/dlac055.

BDG to start treatment (to improve early diagnosis and reduce the mortality)

Intensive Care Med (2022) 48:865–875
https://doi.org/10.1007/s00134-022-06733-x

ORIGINAL

(1 → 3)-β-D-Glucan-guided antifungal therapy in adults with sepsis: the CandiSep randomized clinical trial

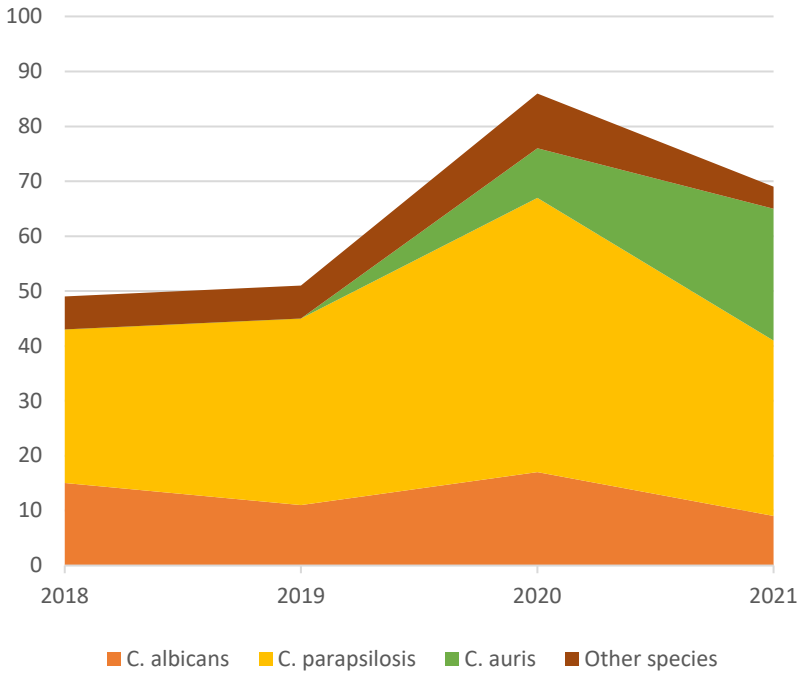
Frank Bloos[1,2*], Jürgen Held[3], Stefan Kluge[4], Philipp Simon[5,12], Klaus Kogelmann[6], Geraldine de Heer[4],

- **Aim** : investigate whether BDG-guidance shortens time to antifungal therapy and thereby reduces mortality of sepsis patients with high risk of invasive Candida infection (ICI).
- **Methods:** **Multicenter, randomized, 2016 – 2019 in 18 ICUs enrolling adult sepsis patients at high risk for ICI**.
- Patients in the control group received targeted antifungal therapy driven by culture results.
- In addition to targeted therapy, **patients in the BDG group received antifungals if at least one of two consecutive BDG samples taken during the first two study days was ≥ 80 pg/mL.**
- Empirical antifungal therapy was discouraged in both groups. Primary endpoint - 28-day-mortality.
- **Results:** 339 patients; ICI was diagnosed in 48 patients (**14.2%**) within the first 96 h after enrollment.
- In the BDG-group, **48.8% (84/172)** patients received antifungals during the first 96 h after enrollment and 6% (10/167) patients in the control group.
- Death until day 28 occurred in 58 of 172 patients (33.7%) in the BDG group and 51 of 167 patients (30.5%) in the control group (relative risk 1.10; 95% confidence interval, 0.80–1.51; $p = 0.53$).
- Median time to antifungal therapy: 1.1 (IQR 1-2.2) in BDG group and 4.4 (IQR 2.0–9.1, $p < 0.01$) days in the control group.

Conclusions: Serum BDG guided antifungal treatment did not improve 28-day mortality among sepsis patients with
risk factors for but unexpected low rate of IC was observed.
This study cannot comment on the potential benefit of BDG-guidance in a more selected at-risk population.

BDG to stop antifungals in ICU? Not everywhere

- Retrospective study: ICU 2018–2021
- Aim - investigate the sensitivity of serum BDG for the diagnosis of candidemia stratified according to causative Candida species in ICU patients.
- All 146 episodes of candidemia with a determination of BDG available within 3 days before or after positive blood culture were recorded



Candida Species (Total Number of Episodes = 146; Total Number of BDG Samples = 187) §	Sensitivity (95% CI)
For all samples (*n* = 187)	51.3% (44.1–58.5%)
For all episodes (*n* = 146)	47.3% (39.0–55.0%)
For *C. albicans* (*n* = 40) samples	65.0% (48.7–78.4%)
For *C. albicans* (*n* = 29) episodes	62.1% (42.8–78.2%)
For *C. parapsilosis* (*n* = 105) samples	48.6% (39.1–58.2%)
For *C. parapsilosis* (*n* = 84) episodes	44.0% (33.7–54.9%)
For *C. auris* (*n* = 26) samples	42.3% (24.5–62.4%)
For *C. auris* (*n* = 21) episodes	42.9% (23.0–65.3%)
For other species (*n* = 16) samples *	50.0% (25.6–74.4%)
For other species (*n* = 12) episodes **	41.7% (16.4–72.2%)

Mikulska M, Magnasco L, Signori A, et al. J Fungi 2022

Journal of *Fungi*

Article

Intensive Care Antifungal Stewardship Programme Based on T2Candida PCR and *Candida* Mannan Antigen: A Prospective Study

Kirsten Møller [5,6], Birthe Riis Olesen [7], Mathias Søderlund [1] and Maiken Cavling Arendrup [6,8,9]

- 219 patients with 504 T2Candida/MAg samples
- IC proven in 29 (13.2%), likely in 7 (3.2%) and possible in 10 (5.5%) patients
- Sensitivity/specificity/PPV/NPV values, for proven/likely versus unlikely IC
- 47%/100%/94%/90% for BC alone
- 50%/97%/75%/90% for T2Candida alone
- 39%/96%/67%/88% for MAg alone
- 70%/90%/63%/93% for the combination of T2Candida/Mag taken 3 days after AFT initiation

- **No reduction in overall use of AFT during the study period compared with the previous year was observed.**
- **An AFSP based on T2Candida and MAg screening contributed to a reduction of unnecessary treatment, but not overall AFT use.**
- The diagnostic performance of T2Candida was lower than previously reported, but increased if T2Candida was combined with MAg.

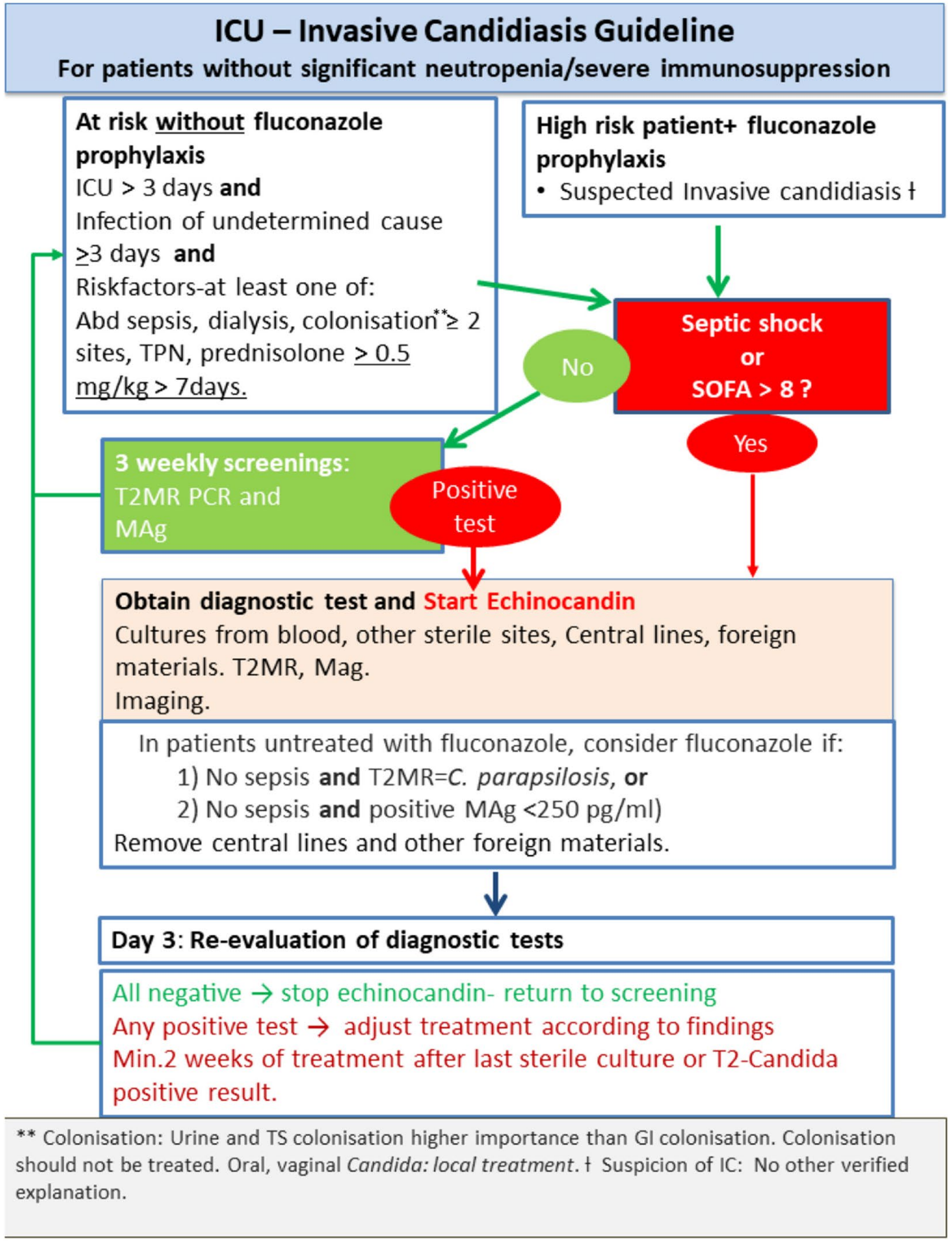
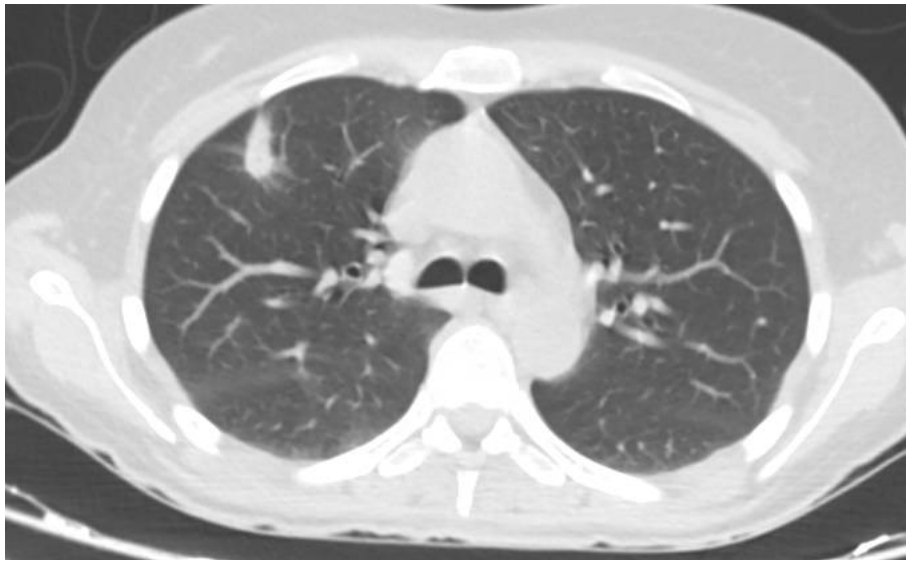

ICU – Invasive Candidiasis Guideline
For patients without significant neutropenia/severe immunosuppression
At risk without fluconazole prophylaxis
ICU > 3 days and
Infection of undetermined cause
>3 days and
Riskfactors-at least one of:
Abd sepsis, dialysis, colonisation** ≥ 2 sites, TPN, prednisolone > 0.5 mg/kg > 7days.
High risk patient+ fluconazole prophylaxis
• Suspected Invasive candidiasis ƚ
Septic shock or SOFA > 8 ?
No
Yes
3 weekly screenings: T2MR PCR and MAg
Positive test
Obtain diagnostic test and Start Echinocandin
Cultures from blood, other sterile sites, Central lines, foreign materials. T2MR, Mag.
Imaging.
In patients untreated with fluconazole, consider fluconazole if:
1) No sepsis and T2MR=C. parapsilosis, or
2) No sepsis and positive MAg <250 pg/ml)
Remove central lines and other foreign materials.
Day 3: Re-evaluation of diagnostic tests
All negative → stop echinocandin- return to screening
Any positive test → adjust treatment according to findings
Min.2 weeks of treatment after last sterile culture or T2-Candida positive result.
** Colonisation: Urine and TS colonisation higher importance than GI colonisation. Colonisation should not be treated. Oral, vaginal Candida: local treatment. ƚ Suspicion of IC: No other verified explanation.

Figure 1. Antifungal Stewardship Programme flowchart algorithm.

Uso appropriato = Diagnosi
Essere motivati

- Ottobre 2022
- Paziente di 47 anni con LLA, inviata al nostro centro per eseguire allo-HSCT
- Asintomatica, PCR neg
- TC pre-HSCT: nodulo spiculato



Anamnesi:

- Profilassi con posaconazolo **soluzione orale** durante la chemioterapia iniziale (no TDM)
- Due episodi di neutropenia febbrile durante le chemioterapie successive, trattati con successo con la terapia antibiotica e anche la terapia empirica con L-AmB

Quel profilassi durante allo-HSCT?

BAL: negativo, incluso GM e colturale aspergilli

Biopsia polmonare:
-GM positivo > terapia antifungina
-colturale aspergilli negativo
-esame istologico ……..
-chemioterapia di condizionamento
…… ife > indicazione alla profilassi secondaria

Lenght of therapy

Received: 2 January 2020 | Revised: 24 January 2020 | Accepted: 28 January 2020
DOI: 10.1111/myc.13056

ORIGINAL ARTICLE

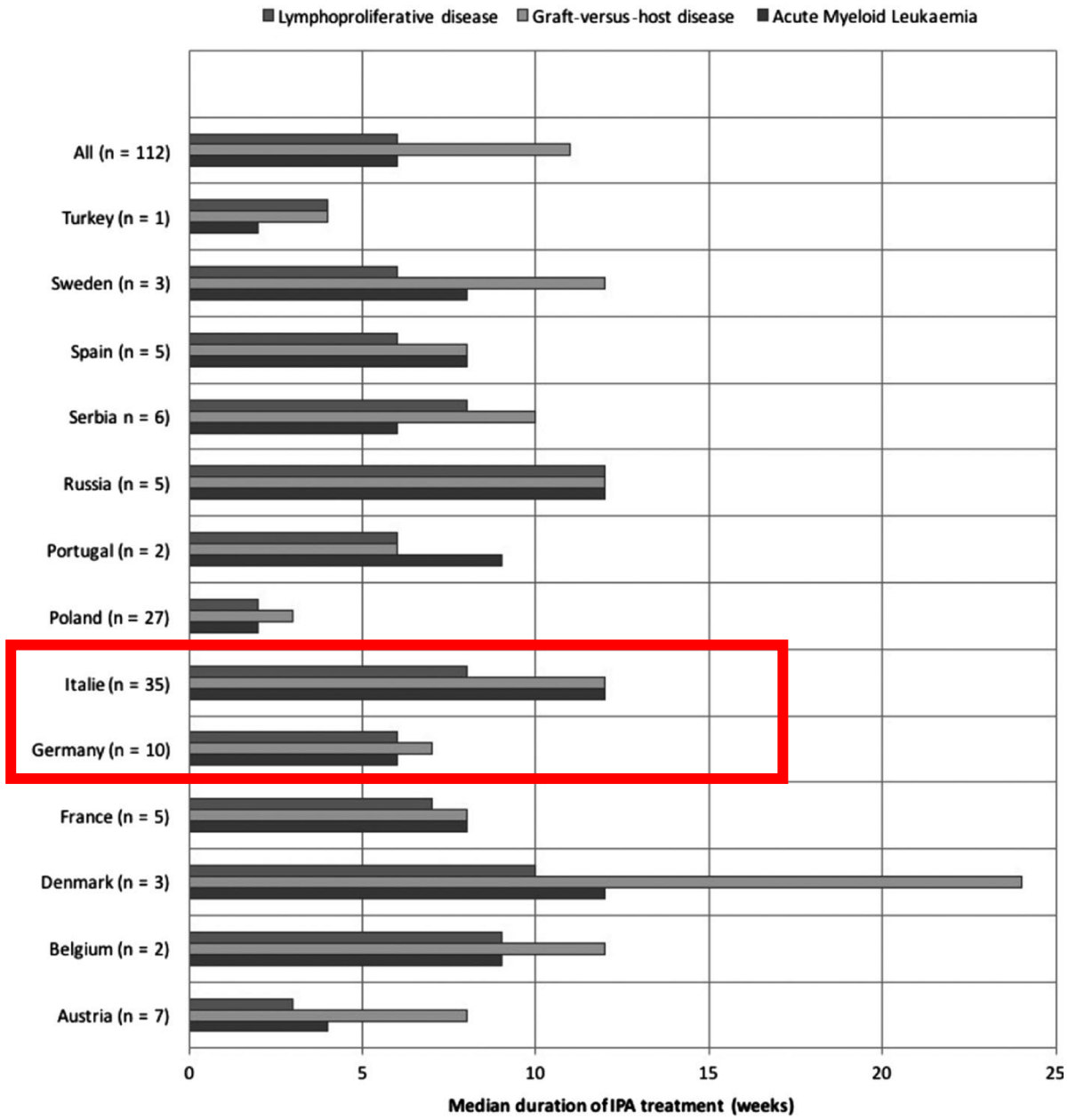
mycoses WILEY

Invasive pulmonary aspergillosis treatment duration in haematology patients in Europe: An EFISG, IDWP-EBMT, EORTC-IDG and SEIFEM survey

Fanny Lanternier[1,2] | Danila Seidel[3,4] | Livio Pagano[5,6,7] | Jan Styczynski[8] | Malgorzata Mikulska[9] | Celine Pulcini[10] | Johan Maertens[11,12] | Patricia Munoz[13] |

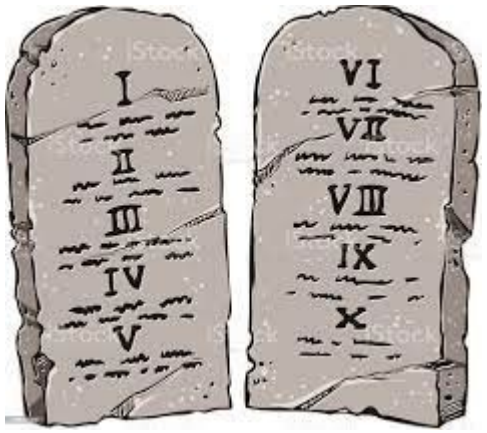
- **Optimal duration of antifungal treatment for IA unknown, no guidelines**
- In 2017 112 physicians from 14/16 countries answered

- Treatment duration differed between haematological malignancies, with a median duration of
  - 6 weeks [IQR 3-12] for patients with AML,
  - 11 weeks [4-12] for patients with alloHSCT and GvHD
  - 6 weeks [3-12] for patients with lymphoproliferative disease
- Treatment duration significantly differed according to country



Uso **appropriato?**

What in case of discordant guidelines or recommendations based on very old studies?



Example: The lenght of treatment in candidemia

- All consecutive adult patients with **uncomplicated** *Candida* BSI 1/09/18-31/08/20
- Included if:
  - treated with an antifungal
  - follow-up blood cultures performed q48h
  - alive at the end of treatment
- 114/420 patients
- Prolonged course 14 d (IQR 14-16) was not associated with lower rate of recurrence or lower 1 year mortality vs. short course 9d (IQR 7-11)

RCT?

Vena et al. submitted

Conclusioni

- Uso appropriato degli antifugnini non è un compito facile (è non è cosi frequente come ci piace pensare)

- Programmi di antifungal stewardship sono fondamenti, e devono includere
  - Pre-authorization (line guida interne),
  - **Postprescription review and feedback (PPRF)**
  - Prescriber education

- Disponibilità delle metodiche diagnostiche e loro corretto utilizzo sono fondamentali

- Durata della terapia antifungina rimane un argomento da studiare

- Sono necessari metodi automatizzati per il monitoraggio delle terapie antifungina

(rate di infezione, rate di test diagnostici eseguiti, prescrizioni, dosi e durate)