

ANTIFUNGAL STEWARDSHIP



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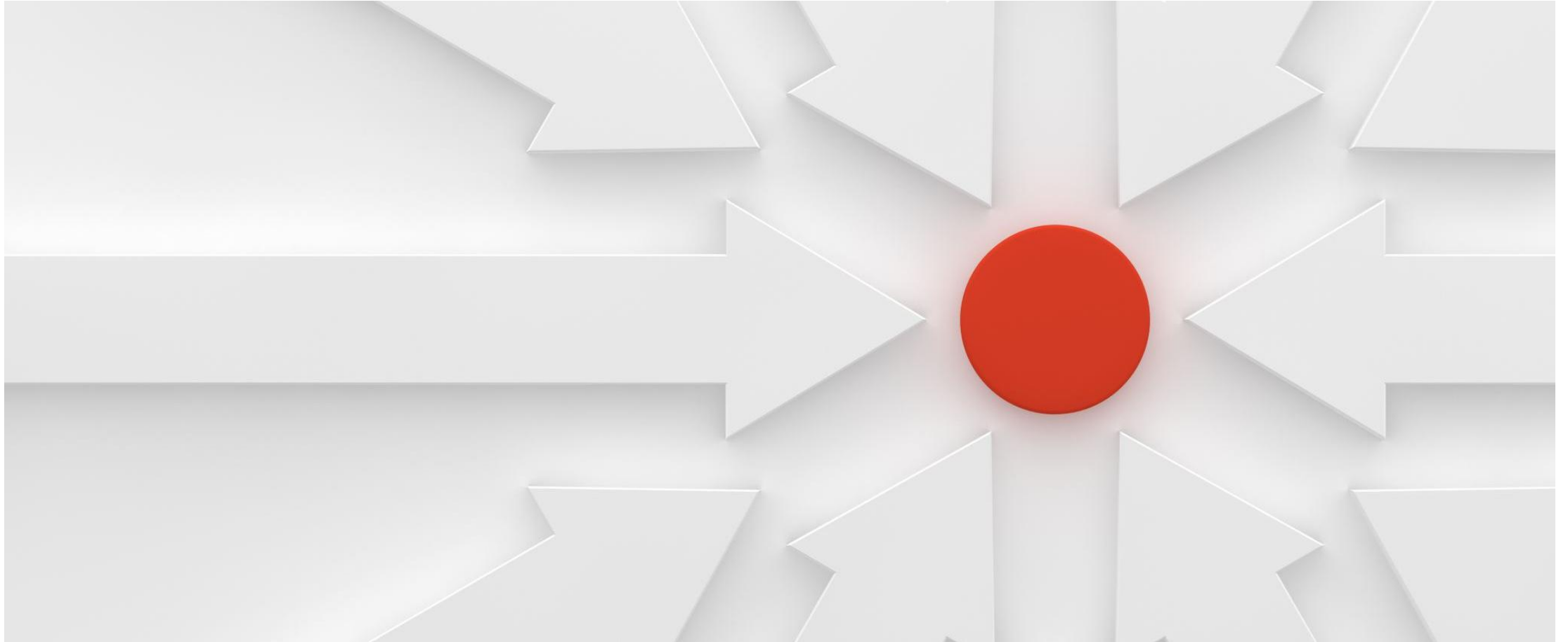
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Medical College Hospital

No Conflict of Interest



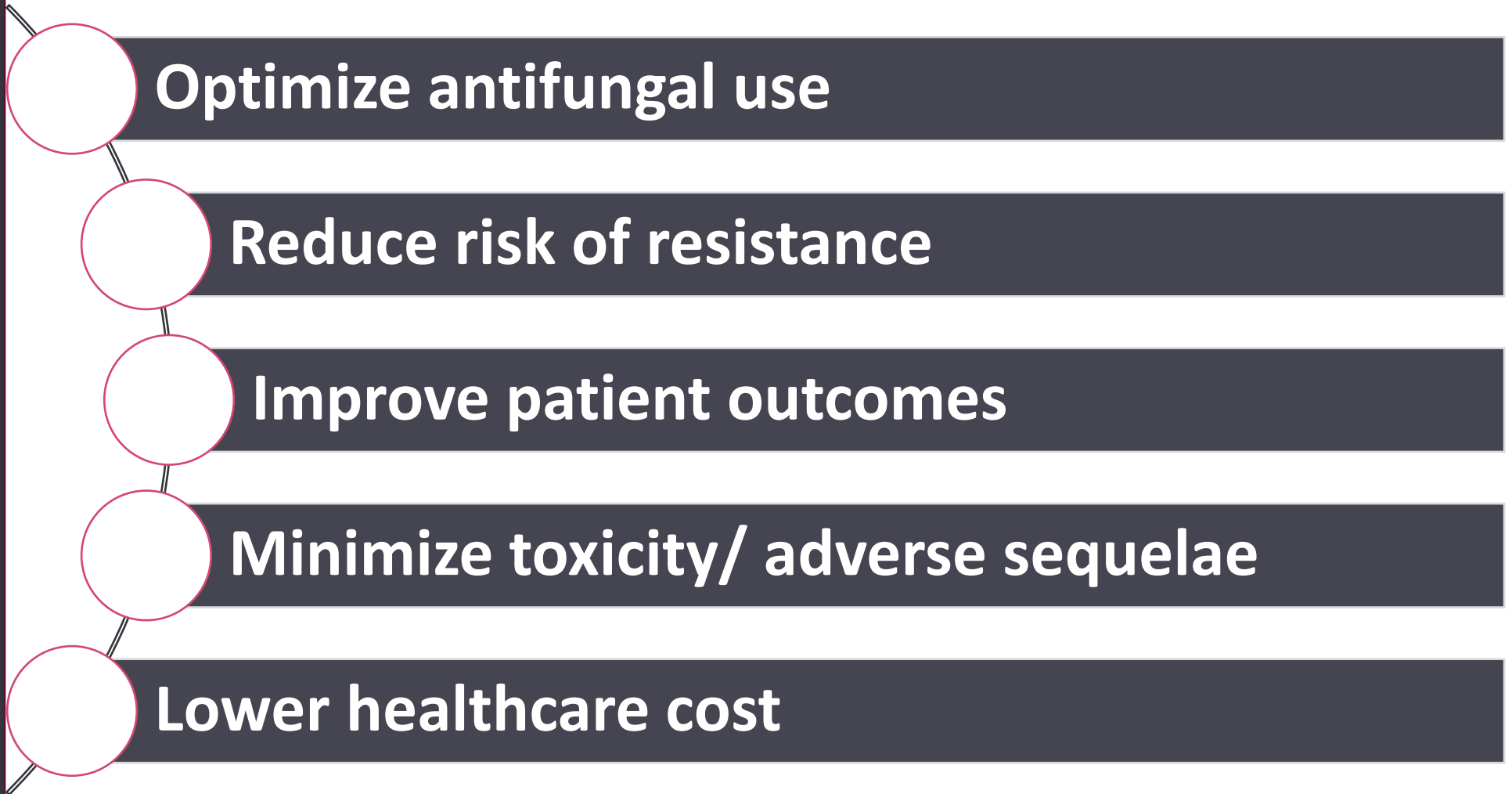
Outline



- Need for Antifungal Stewardship
- Core Principles of Antifungal Stewardship
- Role of Pharmacist in Antifungal Stewardship
- AFS - Diagnostic stewardship
- AFS - ICU, Transplant setting
- Introduction to Antifungal TDM
- Role of Pharmacist in Antifungal TDM



Antifungal stewardship



Antimicrobial stewardship

		Antibiotic stewardship	Antifungal stewardship
Patient Population		All specialties	Mainly immunocompromised patients
Indications		Treatment both empirically and targeted. Short term prophylaxis like surgical prophylaxis	Long term Prophylaxis (risk periods) and Treatment
Duration		Shorter	Prolonged period
Antimicrobial Agents		Lots of antimicrobials Relatively less complex Pk Prescribers more familiar Low cost Toxicity +	Fewer agents Complex Pk Prescribers less familiar High Cost Toxicity +++++

ANTIFUNGALS FOR SYSTEMIC USE

POLYENES

AMPHOTERICIN

ECHINOCANDINS

MICAFUNGIN

CASPOFUNGIN

ANIDULAFUNGIN

TRIAZOLES

FLUCONAZOLE

ITRACONAZOLE

VORICONAZOLE

POSACONAZOLE

ISAVUCONAZOLE



Antifungal Activity Spectra

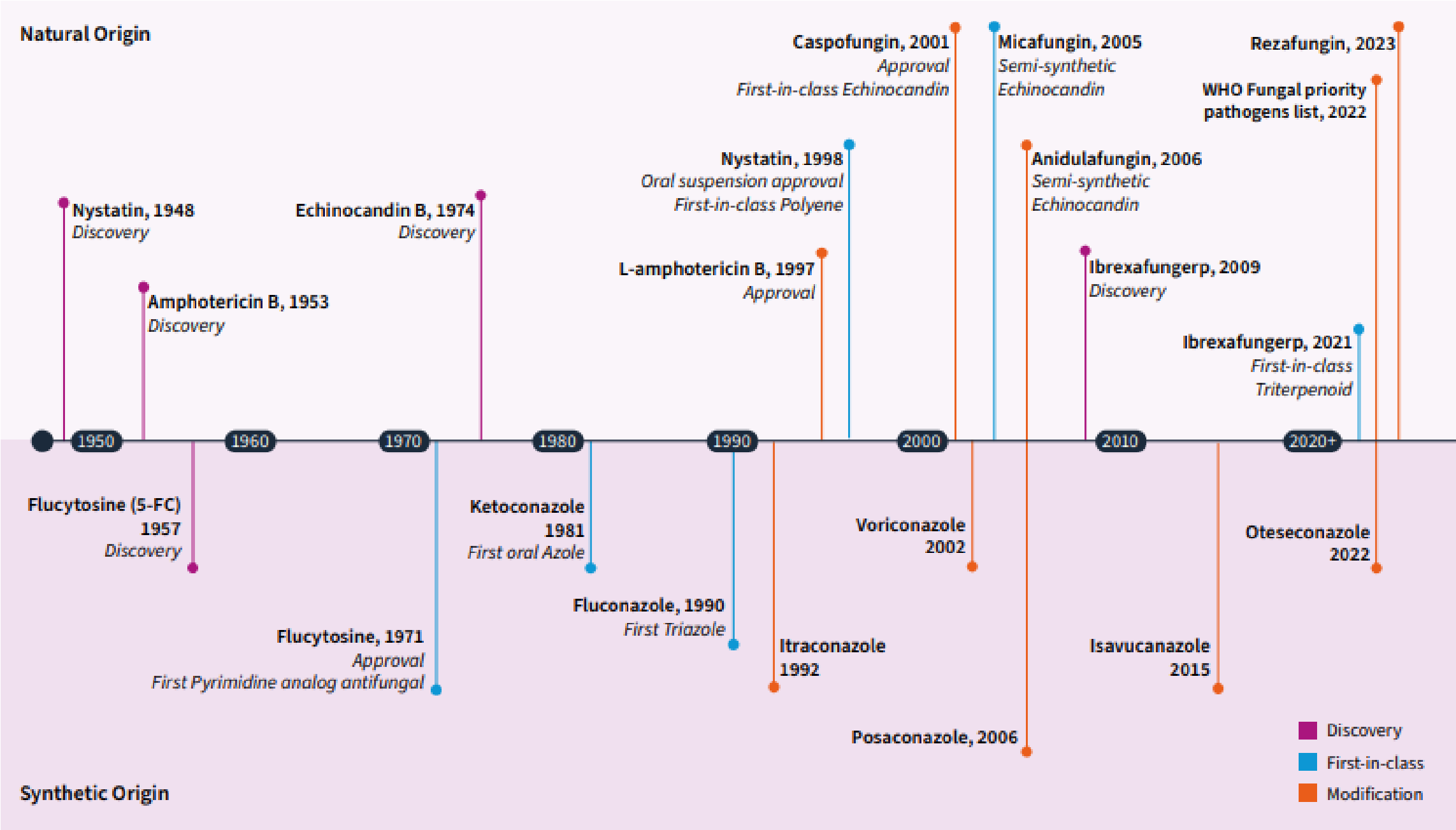
ADD ALL ADD FUNGUS/DRUG PIVOT AXES SEE LEGEND	Antifungal Drugs						
	Fluconazole	Itraconazole	Voriconazole	Posaconazole	Isav-sulf	Micafungin	Amphotericin B
Fungi							
Aspergillus fumigatus	0	±	++	++	++	±	+
Candida albicans	++	+	+	+	+	++	+
Candida auris	0	±	±	±	±	++	±
Candida glabrata	±	±	±	±	±	++	++
Candida krusei	0	0	+	+	+	++	++
Candida parapsilosis	++	+	+	+	+	+	++
Candida tropicalis	++	+	+	+	+	++	++
Cryptococcus sp.	++	+	+	+	+	0	++
Fusarium sp.	0	±	±	±	±	0	±
Mucormycosis	0	0	0	+	+	0	++
Dimorphic Fungi							
Blastomyces	±	++	+	+	+	0	++
Coccidioides	++	++	+	+	+	0	++
Histoplasma	±	++	+	+	+	0	++

Antifungal treatment strategies for invasive fungal infections

Cortegiani, A., Russotto, V., Raineri, S. M., Gregoretti, C., De Rosa, F. G., & Giarratano, A. (2017). *Untargeted Antifungal Treatment Strategies for Invasive Candidiasis in Non-neutropenic Critically Ill Patients: Current Evidence and Insights*. *Current Fungal Infection Reports*, 11(3), 84–91. doi:10.1007/s12281-017-0288-3

Prophylaxis	Administration of antifungal drugs to patients without signs or symptoms of IC but with risk factors for its development	Strategy frequently applied in specific subgroups of patients at risk Low specificity since it covers a population at risk, it does not require the use of complementary diagnostic methods at the beginning
Preemptive	Treatment triggered by evidence of fungal infection, basing on “surrogate marker” or non-culture diagnostic tests, without definitive microbiological identification of fungal pathogen (e.g., positive biomarkers 1-3 beta-D-glucan, mannan-antimannan antibodies, polymerase chain reaction assays)	This strategy aims to narrow the large target population of prophylaxis and to reduce the time of initiation of empiric treatment Intermediate specificity
Empiric therapy	The administration of antifungal drugs to patients presenting signs and symptoms of infection potentially due to fungi and at risk of IC development	Febrile neutropenic patients despite broad-spectrum antibiotics, septic patients with potential intra-abdominal focus of infection
Targeted therapy	Targeted treatment for identified pathogen	High specificity

Fig. 2. Historical overview of systemic antifungal drugs and their marketing authorization



Note: The above timeline does not include antifungal agents approved for topical use, or any agent found on a discontinued drug product list.

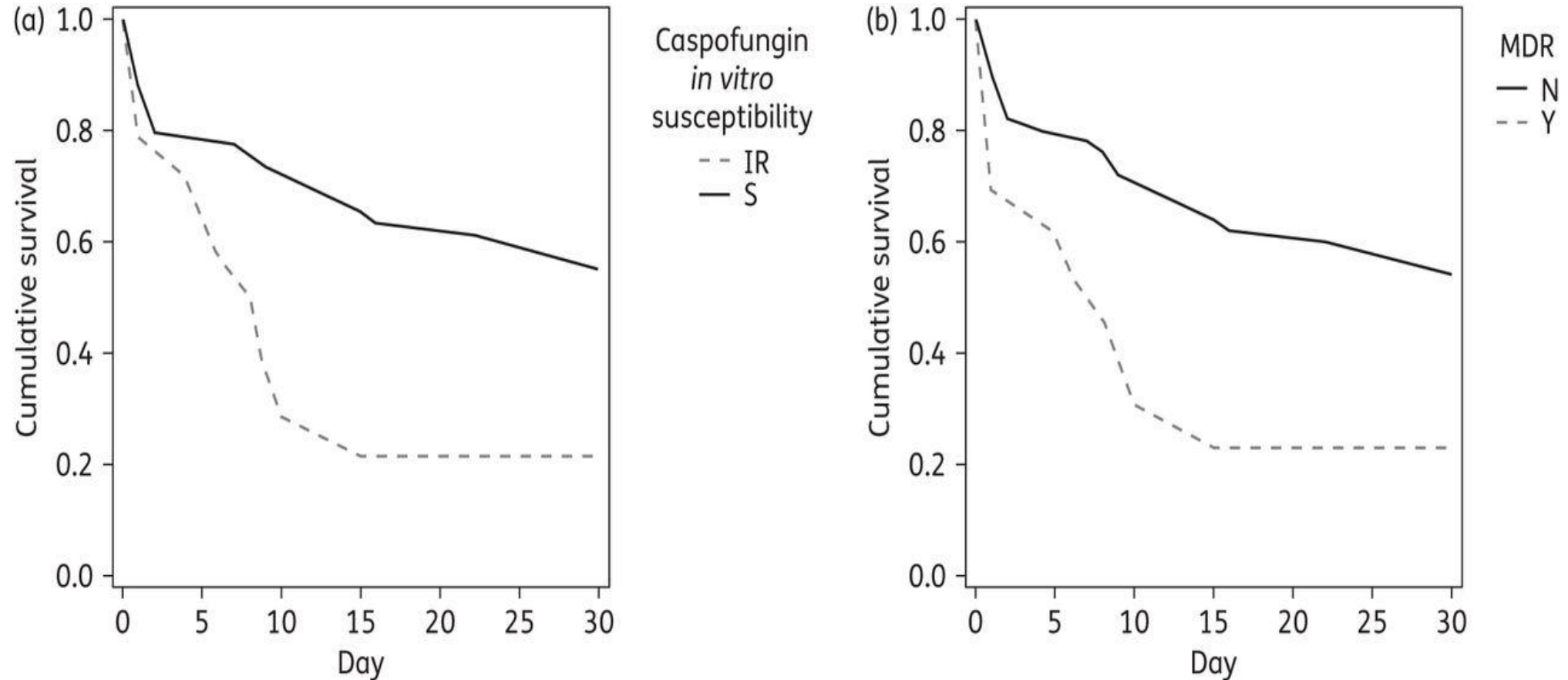
**Only 4 new
antifungal
drugs have
been approved
in the last
10 years.**

WHO fungal priority pathogens list

- WHO recently published the first fungal priority pathogens list (WHO FPPL).
- Aims to focus and drive further research and policy interventions
- To strengthen the global response to fungal infections and antifungal resistance.



MDR Fungal infection and Mortality



Thirty day survival Kaplan–Meier curves in patients with acute leukaemia and candidaemia.
a) Casposungin non-susceptibility
b) MDR

Core Recommendations for Antifungal Stewardship: A Statement of the Mycoses Study Group Education and Research Consortium

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In recent years, the global public health community has increasingly recognized the importance of antimicrobial stewardship (AMS) in the fight to improve outcomes, decrease costs, and curb increases in antimicrobial resistance around the world. However, the subject of antifungal stewardship (AFS) has received less attention. While the principles of AMS guidelines likely apply to stewarding of antifungal agents, there are additional considerations unique to AFS and the complex field of fungal infections that require specific recommendations. In this article, we review the literature on AMS best practices and discuss AFS through the lens of the global core elements of AMS. We offer recommendations for best practices in AFS based on a synthesis of this evidence by an interdisciplinary expert panel of members of the Mycoses Study Group Education and Research Consortium. We also discuss research directions in this rapidly evolving field. AFS is an emerging and important component of AMS, yet requires special considerations in certain areas such as expertise, education, interventions to optimize utilization, therapeutic drug monitoring, and data analysis and reporting.

Keywords. stewardship; antifungal; candidiasis; aspergillosis; guidelines; diagnostics.

3% of all hospital admissions and 7.7% of ICU admissions in US - associated with the prescription of systemic antifungals

30%–50% of antifungal prescriptions could be optimized or are inappropriate

Relatively few hospitals have formal AFS programs – European survey

Application of core elements for AFS depends on the resources and expertise available



Antifungal Stewardship Core Elements

Engagement of Senior Leadership

- Integrate AFS program goals into institutional strategic plans.
- Engage senior leadership members to ensure accountability and dedicated resources.

Accountability & Responsibility

- Core members should include ID MD and ID-trained PharmD
- Team members should provide expertise in the diagnosis and management of IFD.
- Key stakeholders who frequently manage patients with IFD and/or have high rates of antifungal prescribing should be members of the AFS program.

Expertise on Infection Management

- Access to timely diagnostic testing for *Candida* and *Aspergillus* species.

Education & Training

- Target AFS educational programs

Reporting & Feedback

- Track and benchmark antifungal use.
- Assess patient-level outcomes
- Feedback prescribing data

Monitoring & Surveillance

- Establish Local surveillance systems for fungal infections.
- Timely antifungal susceptibility testing.
- Communicate results of fungal diagnostics in real-time
- Review of antifungal drug interactions.
- Timely therapeutic drug monitoring of triazole antifungals.

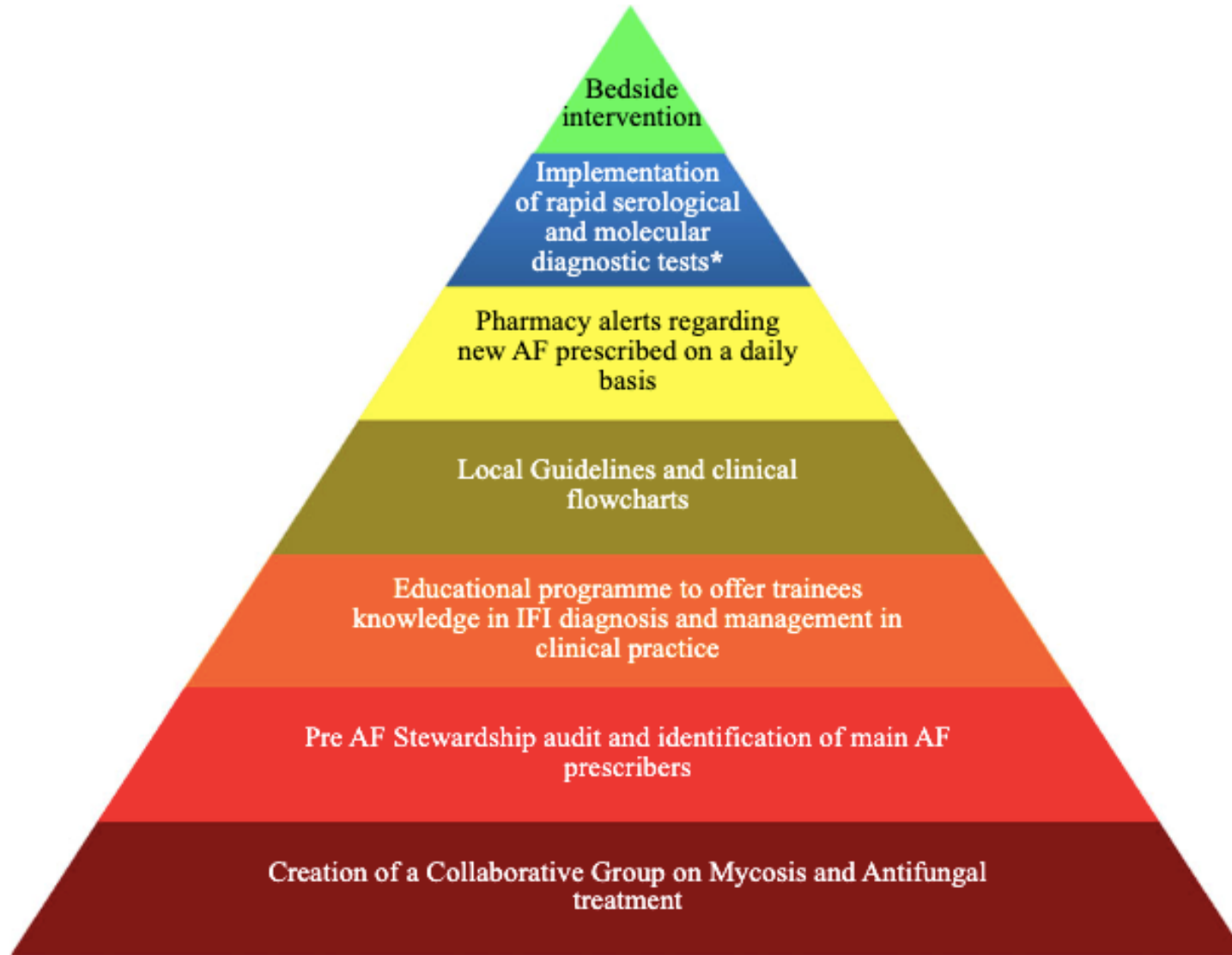
Responsible Antimicrobial Use

- Consult ID for patients with IFD.
- Develop institutional treatment bundles and guidelines for IFD.
- Handshake stewardship rounds and/or post prescription review.
- Evaluate antifungal prescribing regularly and use data-driven strategies to optimize AFS interventions.



Effectiveness of the interventions should be measured using predefined indicators

Share the information and every success of your intervention with all members of the team



AFS metrics

Intervention

Rapid Diagnostics

Oversight

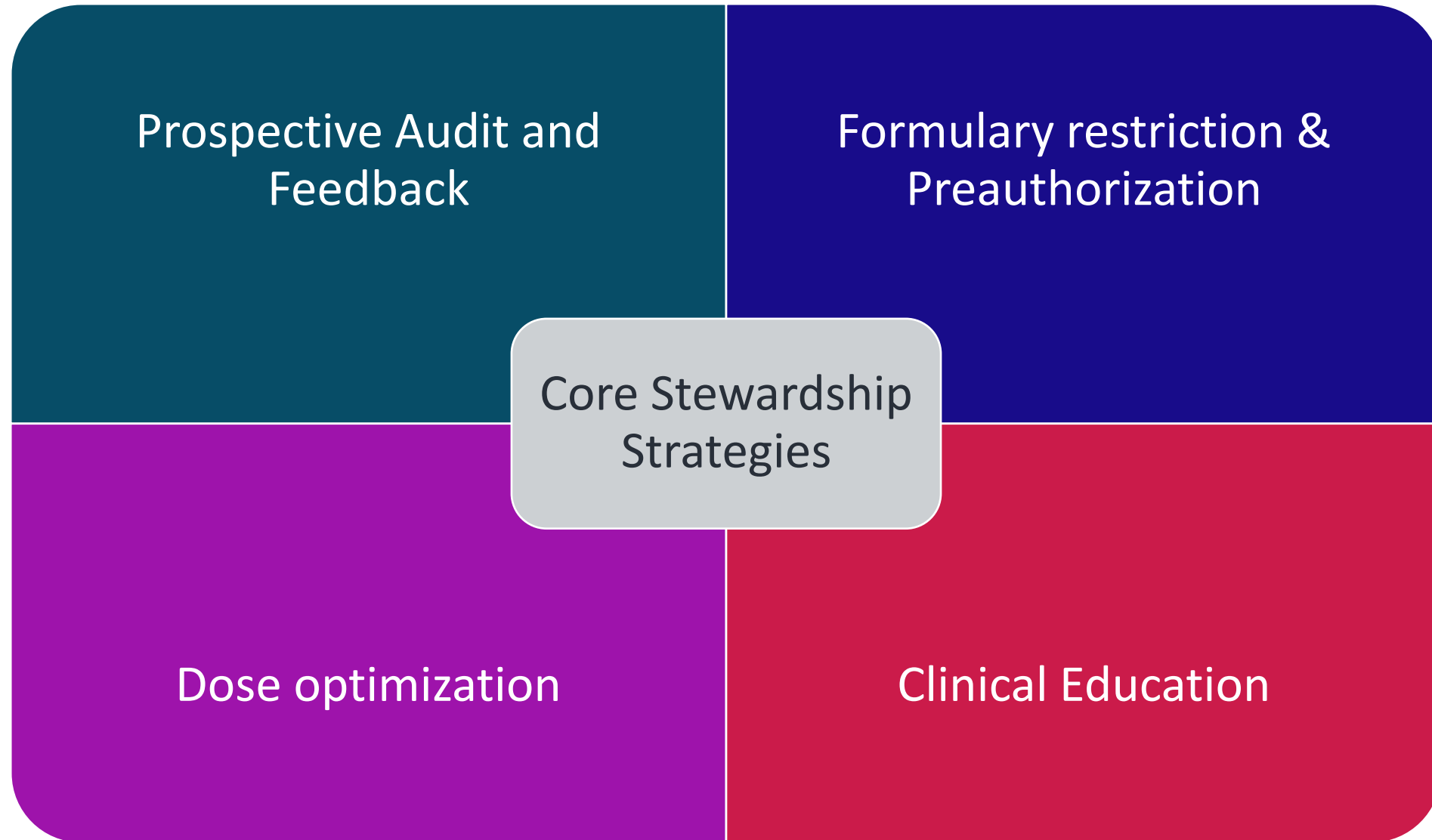
Guidelines

Education

AF use baseline data

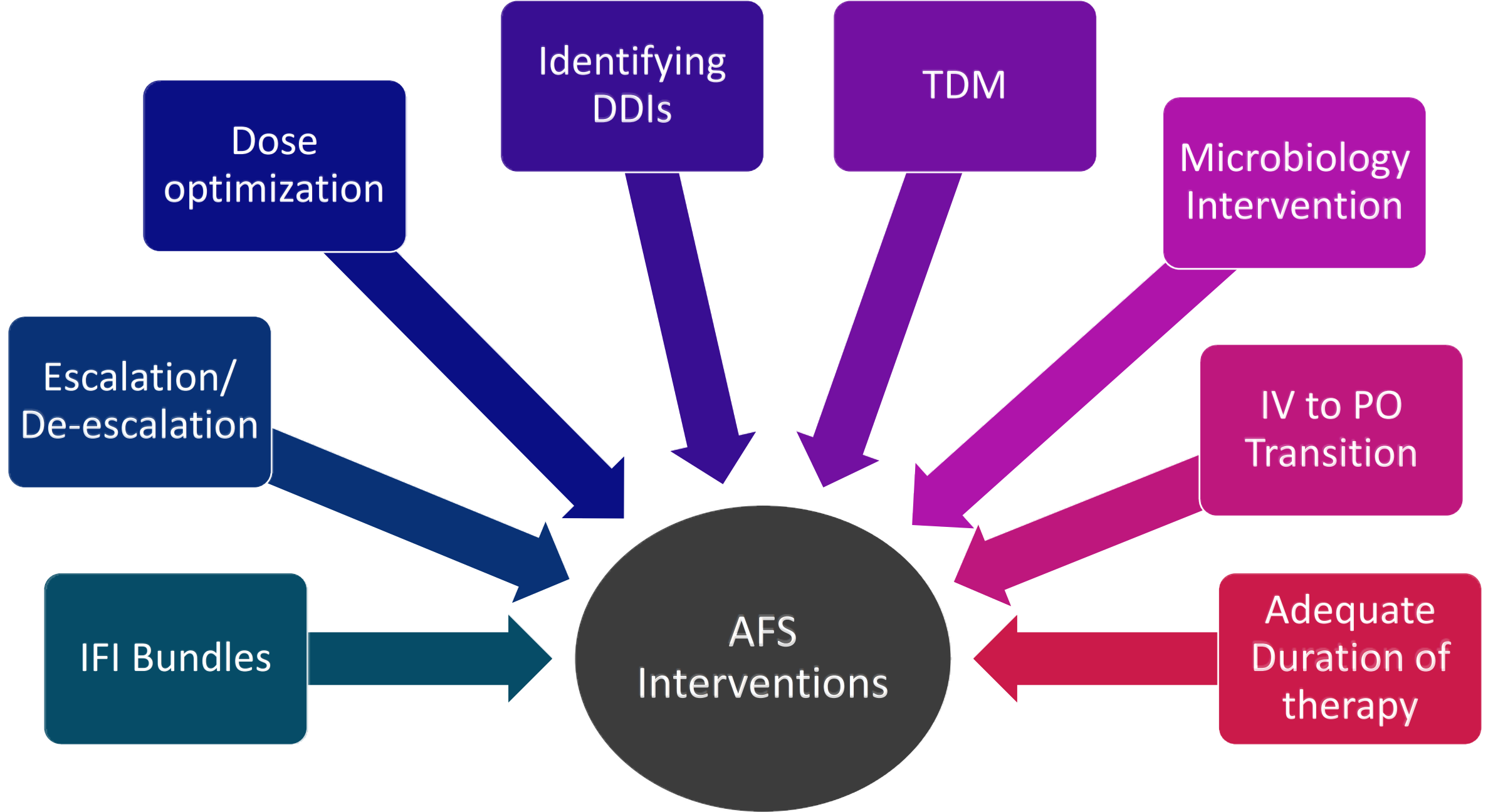
AFS team



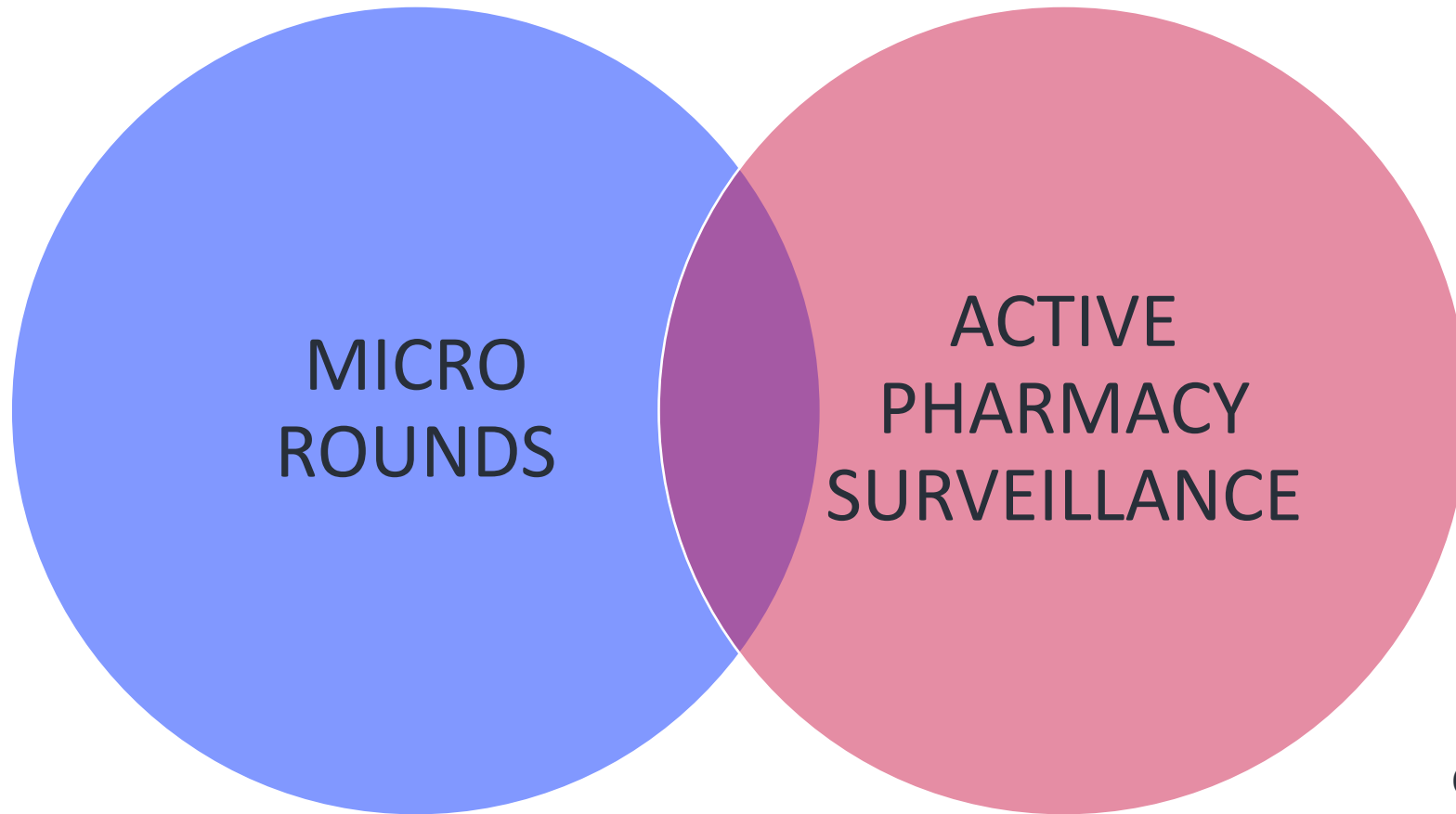


ROLE OF PHARMACIST IN ANTIFUNGAL STEWARDSHIP





AFS AT BCMCH



Combined with AMS



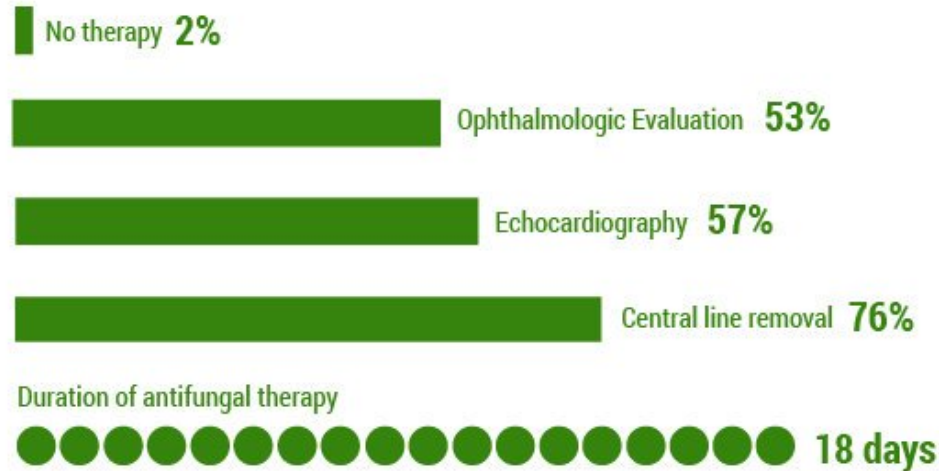
Impact of Infectious Diseases Consultation on Mortality in Candidemia

by Mejia-Chew et al.
Lancet Infectious Diseases, In press, 2019

Consult (N = 776)



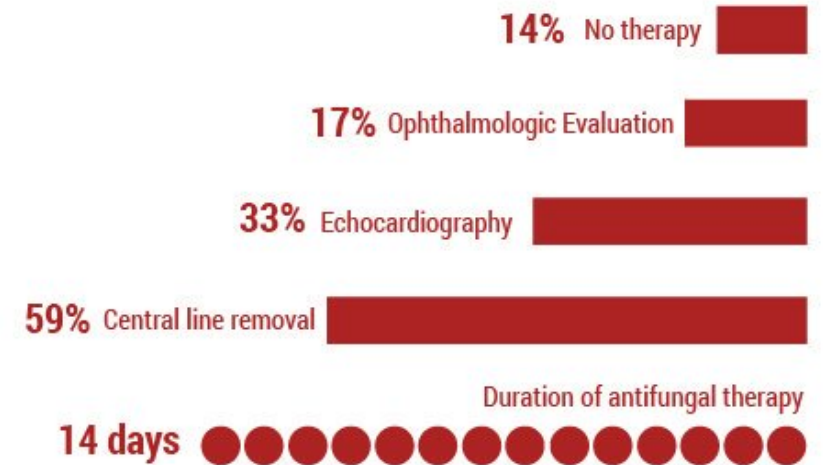
Proportion of evidence-based practices



No consult (N = 915)



Proportion of evidence-based practices



ID consult had a 19% survival benefit*

*Inverse propensity-score weighted Cox model, HR of 0.81 (95% CI: 0.73, 0.91, $p < 0.0001$)



Invasive candidiasis bundle

At the time therapy is being started

- Perform 2 high-volume **blood cultures** (40 mL) prior to starting therapy
- **Removal of existing CVCs** within 24 h of diagnosis
- **Initial appropriate selection and dosing** of antifungals considering local epidemiology started within 12 h of culture
- **Ophthalmological exam** within the first week of diagnosis

After starting therapy

- Follow-up blood cultures daily until **clearance of candidemia** is documented
- **Echocardiography** in patients with persistent fungemia, fever, or new cardiac symptoms
- **Assessment of clinical efficacy** 3–5 d after starting therapy and evaluating the need for alternative therapy based on culture identification and susceptibility results are available
- Administration of **at least 2 wk of therapy after clearance of blood cultures** (longer with organ involvement)
- **Step-down** to oral fluconazole therapy in patients with a favorable clinical course and an isolate with documented susceptibility



Invasive aspergillosis management bundle

At the time therapy is being started

- **Serum galactomannan** test repeated twice in patients not on mold-active azole prophylaxis
- **CT imaging** of chest and/or sinus/brain in patients with symptoms localized at these signs
- **Early bronchoscopy** (within 48 h) with cytology examination and culture of BAL fluid, measurement of galactomannan antigen titer in BAL
- **Initial appropriate selection and dosing** of antifungal agents considering previous antifungal exposure and local epidemiology
- Systematic screening for **drug interactions** using a computerized drug interactions database for any patient starting or stopping a triazole antifungal agent

After starting therapy

- **Periodic (eg, weekly) testing** of serum **galactomannan** (if aspergillosis) as an adjunct criterion to assess treatment response
- **TDM of voriconazole and posaconazole** and possibly isavuconazole serum levels to document adequate drug exposures
- Assessment of therapy **appropriateness** based on **microbiological**, culture, or histological results
- **Repeat chest CT** imaging after 3–4 wk and periodically based on response, to assess infection status and/or progression
- **Step-down** to oral triazole therapy in patients with a favorable clinical course



ROLE OF PHARMACIST IN ANTIFUNGAL TDM



Pre analytical phase

Clinical question

Test selected

Test ordered

Specimen collected

Analytical phase

Sample prepared

Analysis performed

Results verified

Post analytical phase

Results reported

Clinical answer

Action taken

Effect on patient care



OP Voriconazole TDM Workflow

Step 1: TDM Planning & Coordination

ID clinician identifies need for TDM
(new or ongoing Voriconazole therapy)

ID clinician informs ID Clinical
Pharmacist (ID CP)

ID CP contacts TDM Clinical
Pharmacist (TDM CP) with:

- Patient details
- Start date of Voriconazole
- Current dose and frequency

TDM CP:

- Calculates ideal sampling date (typically Day 5)
- Recommends morning trough sample (30 mins before dose)
 - Informs central lab:
- Sampling date & time
- Tube type (EDTA - purple top)
- Plasma separation instructions

Step 2: Sample Collection & Processing

Patient reports to central lab at
informed date/time

Lab technician:

- Collects blood in EDTA tube
- Centrifuges to separate plasma
- Labels and sends plasma to Analytical Chemistry Lab

Step 3: Sample Analysis & Reporting

Analytical Chemistry Lab:

- Performs LC-MS/MS analysis
- Validates and reports:
- Patient/sample ID
- Trough level (mg/L)
- Sampling time
- Therapeutic range reference (e.g., 1–4 mg/L)

Report shared with ID CP, TDM CP,
and ID clinician

Patient's demographic details,
sampling details and report
documented by TDM CP



OP Voriconazole TDM Workflow

Step 4: Interpretation & Action

TDM CP + ID CP interpret level in clinical context (hepatic function, albumin, drug interactions, response)

Recommend:
Continue current dose
Adjust dose
Change route or frequency
Repeat TDM if needed

ID clinician:
Finalizes plan
Documents decision
Communicates with patient

Step 5: Follow-Up

Schedule repeat TDM if:
Dose adjusted
Clinical deterioration
Suspected toxicity or subtherapeutic level
Monitor LFTs and adverse effects regularly





Ashwin Nair TDM CS

Daycare patient
Blood samples for MPA TDM
Patient in dialysis ward

Sampling date - 10/04/2025

Sampling times:

Trough - 7:45 am
0.5 hr - 8:30 am
1 hr. - 9:00 am
1.5 hrs - 9:30 am
2 hrs. - 10:30 am
2.5 hrs - 11:00 am
3 hrs. - 11:30 am
4 hrs. - 12:30 pm
5 hrs. - 1:30 pm
6 hrs. - 2:30 pm
7 hrs. - 3:30 pm
8 hrs. - 4:30 pm

Please collect the samples in purple EDTA tubes, send to central lab, centrifuge and separate the plasma and send to ACL as soon as possible.

23:54

OP patient
Blood sample for Fluconazole TDM
Sampling date - 11/04/2025
Sampling time - 8:30am

Please collect the samples in purple EDTA tubes, send to central lab, centrifuge and separate the plasma and send to ACL as soon as possible.

23:56



ANTIFUNGAL DIAGNOSTIC STEWARDSHIP






Case scenario

67-year-old female admitted in the ICU with Stroke.
Poorly controlled diabetes. She has urethral catheter.
Urine routine shows Yeast in urine
Urine C/s – Candida albicans sensitive to Fluconazole



Overtreatment of Asymptomatic Candiduria among Hospitalized Patients: a Multi-institutional Study

David M. Jacobs ^a, Thomas J. Dilworth^{b,*}, Nicholas D. Beyda^c, Anthony M. Casapao^d, Dana R. Bowers^e

High Prevalence

80% patients with candiduria were asymptomatic.

Guideline Non-Adherence

47% not managed per IDSA guidelines; 43% asymptomatic, 61% symptomatic (P = 0.01).

Overtreatment in Asymptomatic

93% of guideline-discordant asymptomatic cases received antifungals unnecessarily.

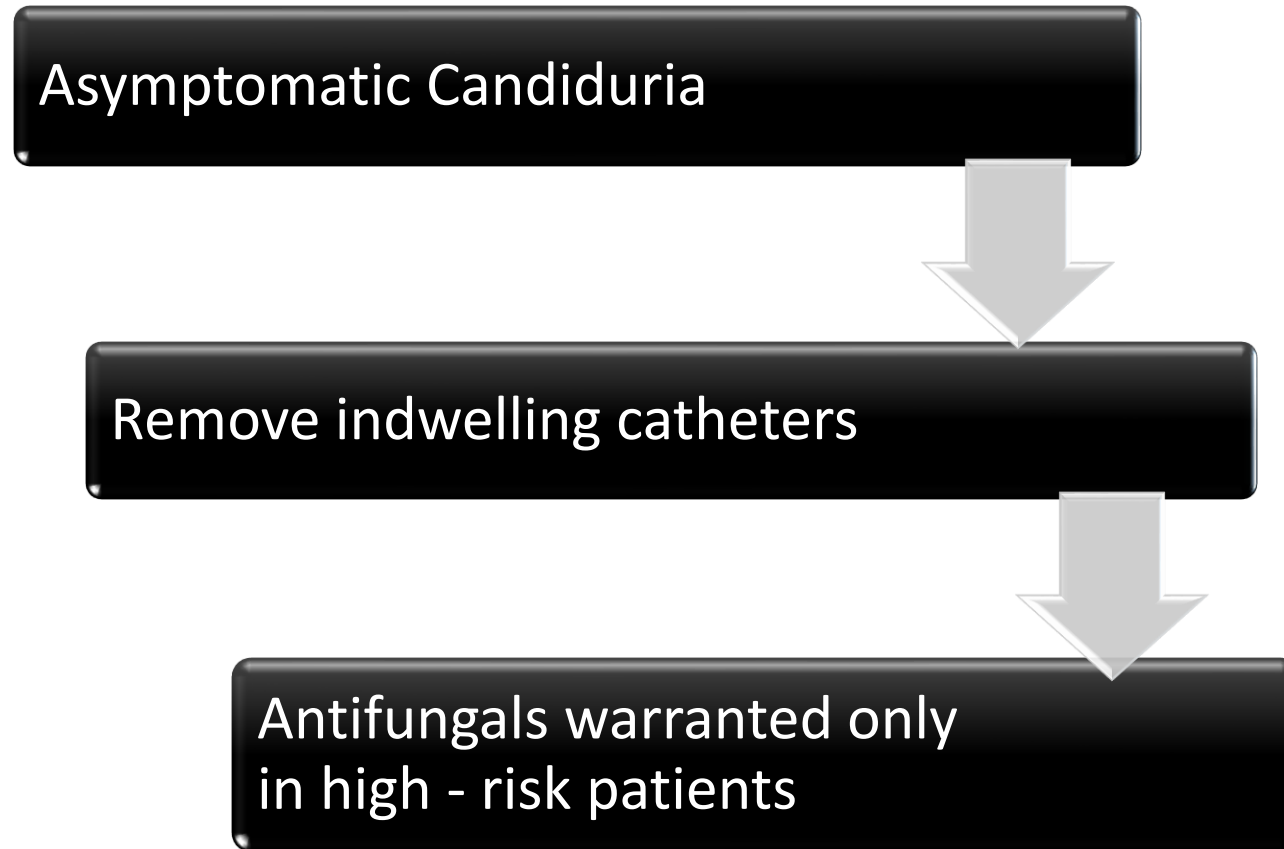
Treatment Duration

33% of non-guideline asymptomatic cases treated >7 days, 5% >14 days.

Antifungal Choice

Fluconazole (96%) most common in asymptomatic cases, followed by micafungin (4%).

2016 IDSA CPG for the Management of Candidiasis



Who is at the risk of Invasive Candidiasis from Candiduria

Neutropenic patients

Patients with renal allografts

Patient who will undergo urological manipulation

Patients with significant urinary obstruction

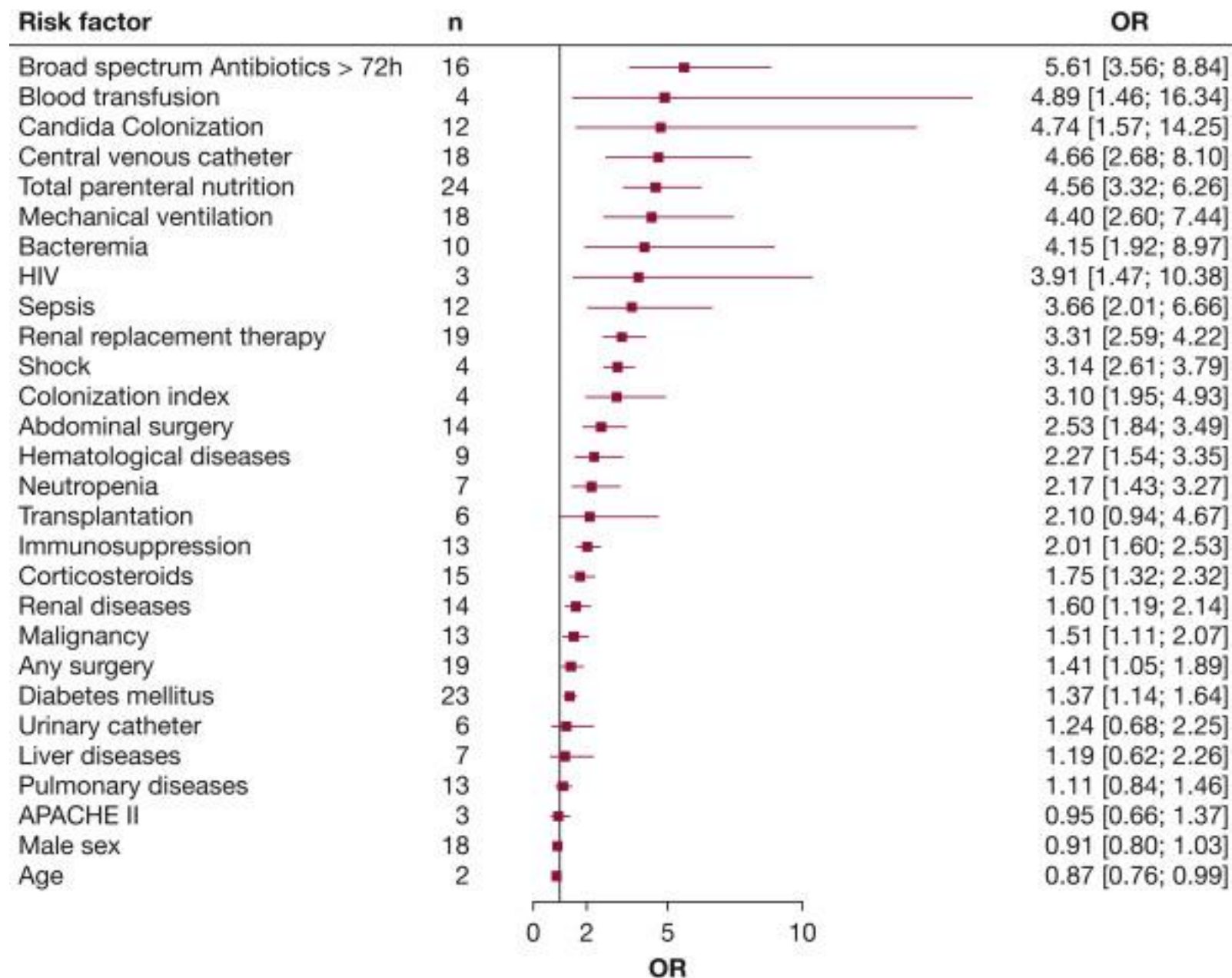
Infants with Low birth weight

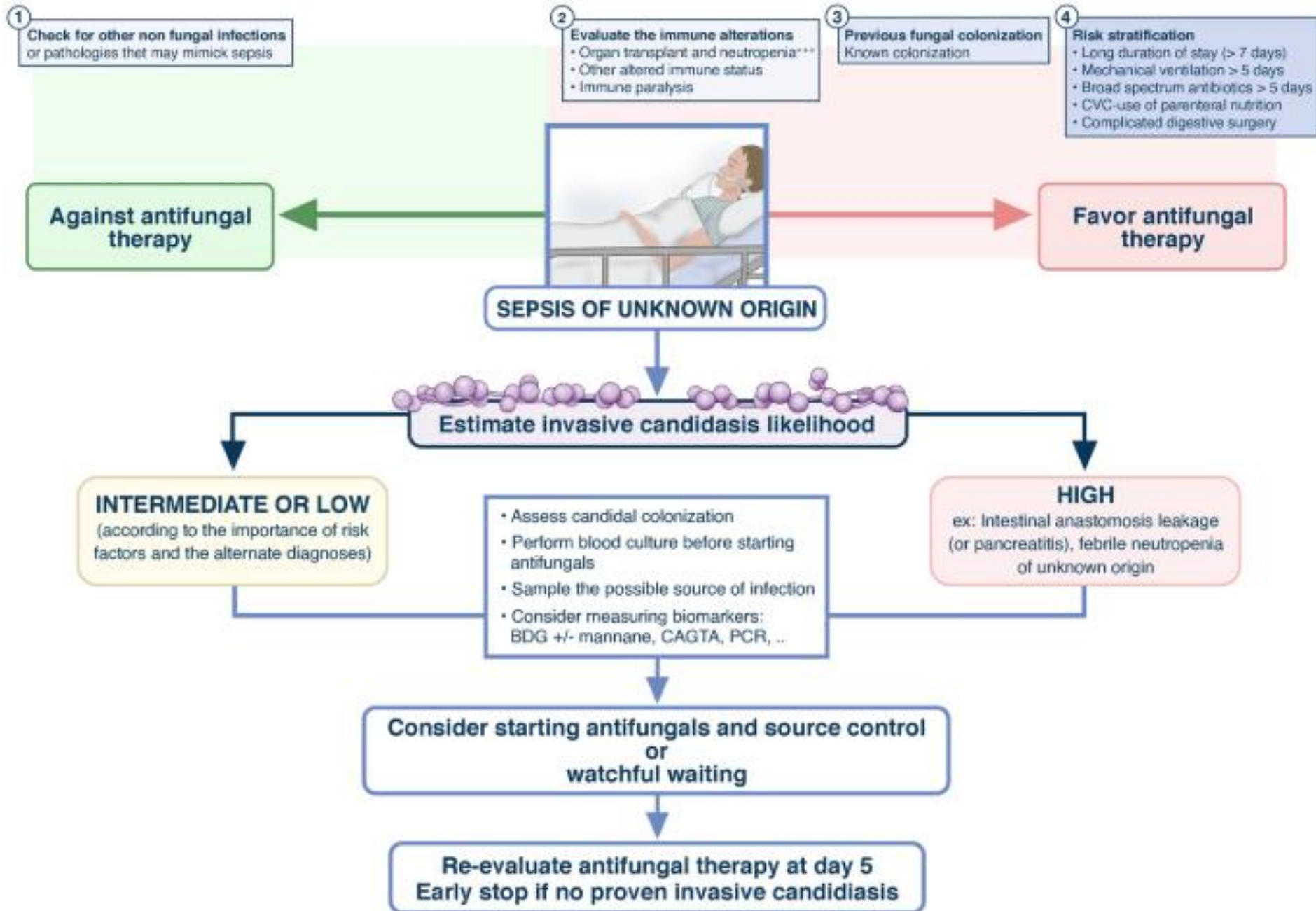


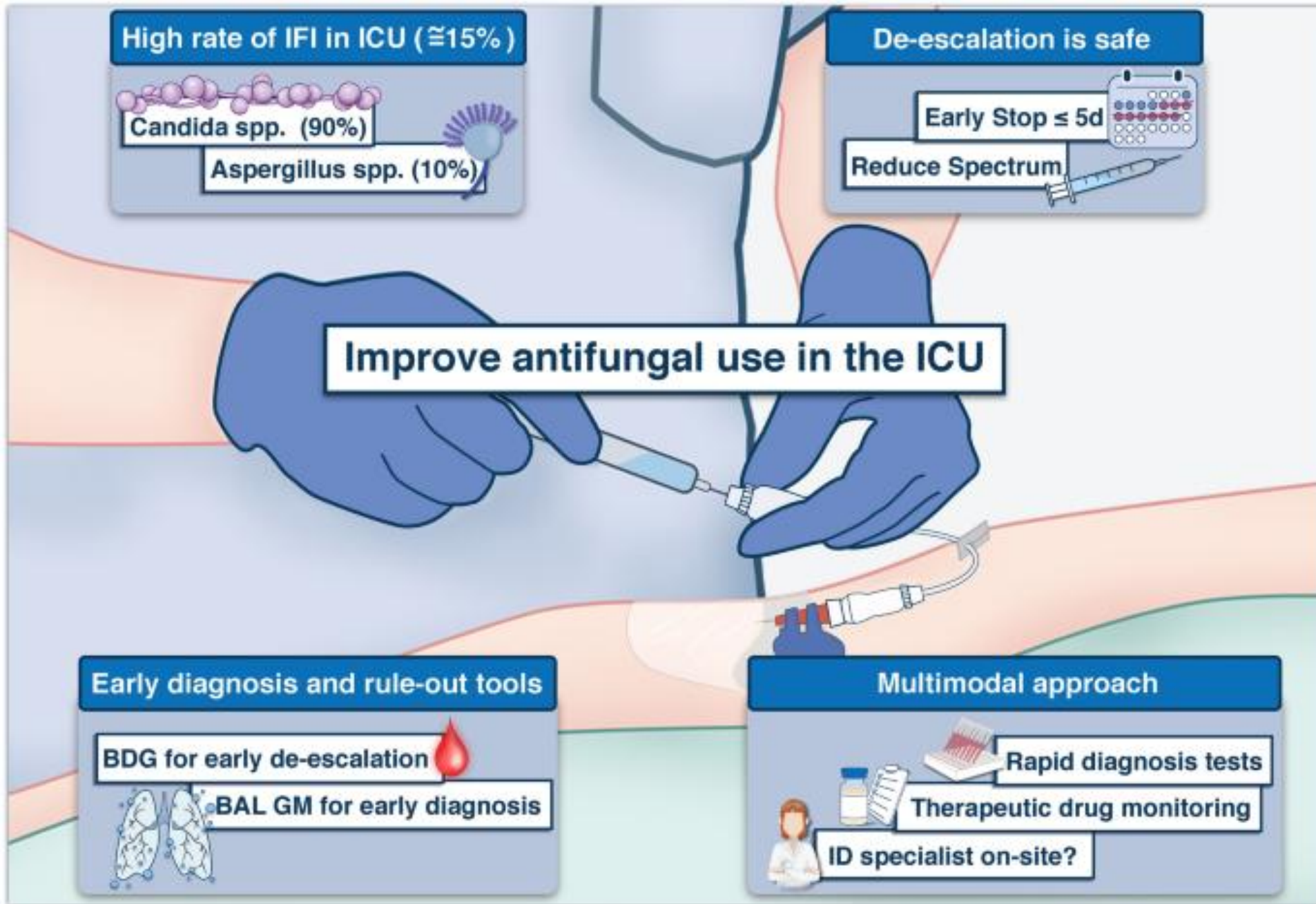
ANTIFUNGAL STEWARDSHIP IN ICU



Risk Factors for Invasive *Candida* Infection in Critically Ill Patients A Systematic Review and Meta-analysis





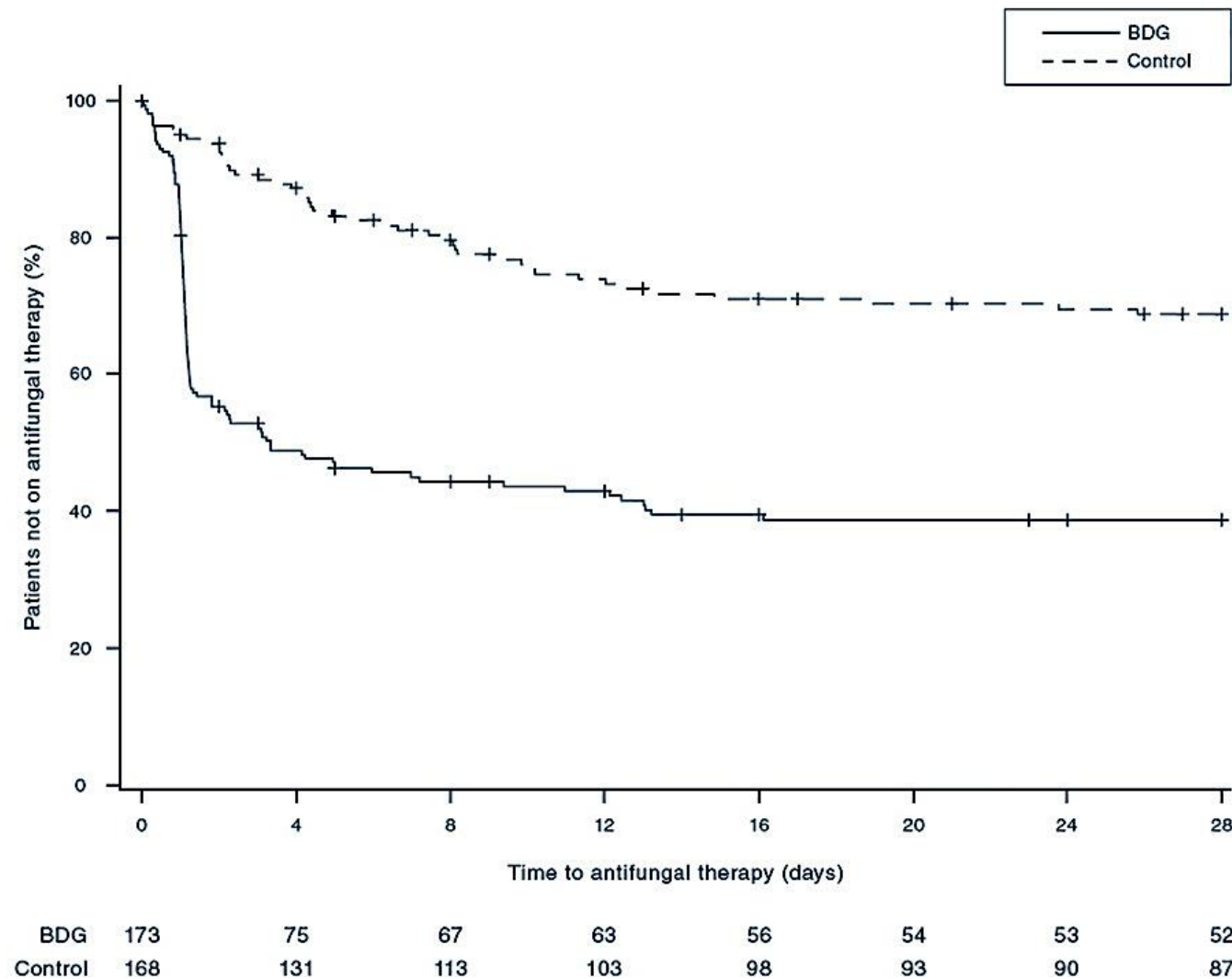


CandiSep RCT

Bloos F et al., Intensive Care Medicine 2022;
48:865–875

(1 → 3)- β -D-Glucan-guided antifungal therapy
in adults with sepsis

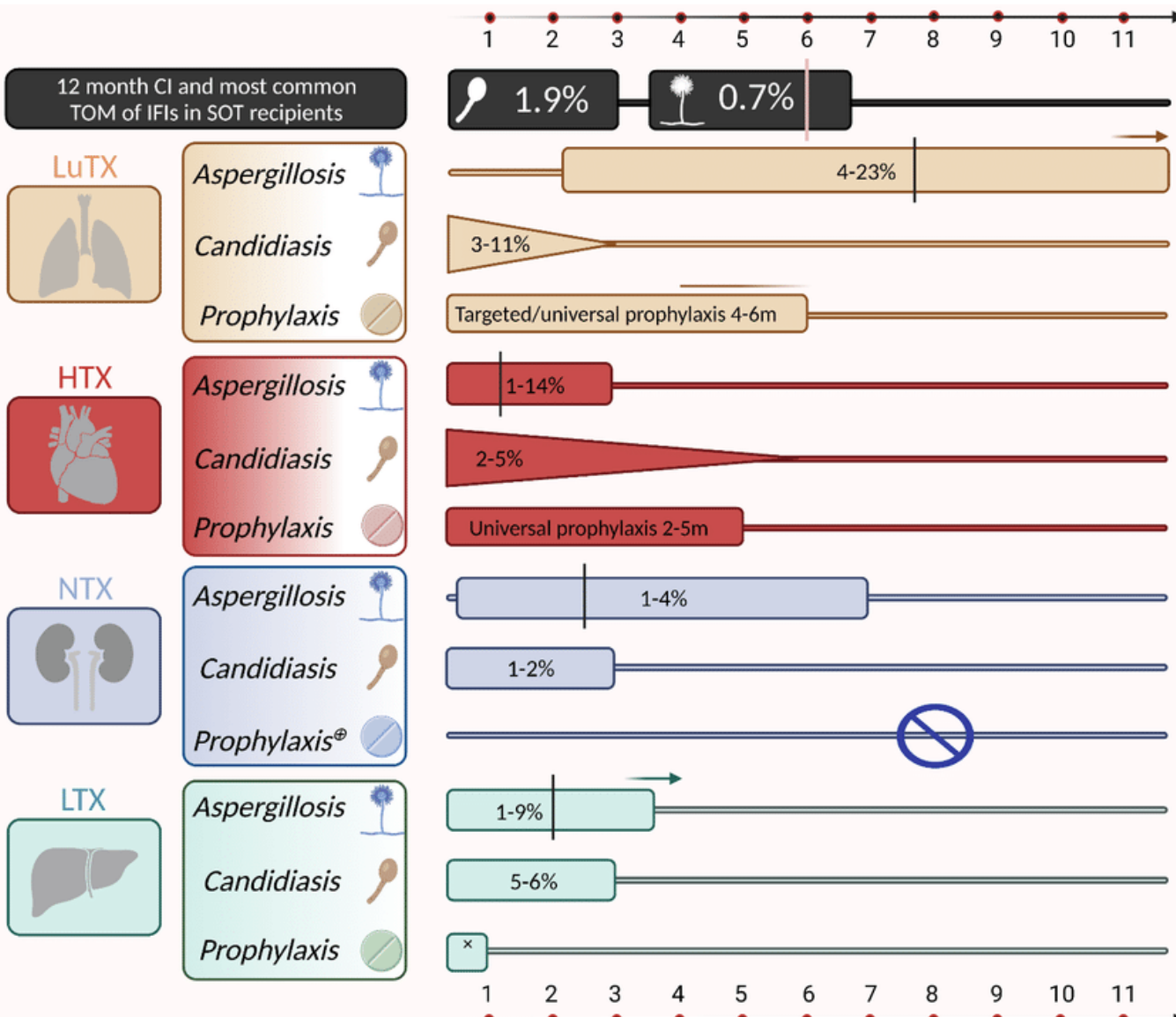
Compared BDG-guided early discontinuation or
continuation of empirical antifungal therapy
against standard care



Rate of patients not on antifungal therapy. The figure shows Kaplan–Meier estimates of the rate of patients not on antifungal therapy according to the (1 → 3)- β -d-glucan-guided (BDG) and the control-group



Opportunities: Antifungal stewardship in SOT



Summary of IFI prevalence and timing when those fungal infections normally occur as well as prophylaxis recommendations for selected organ transplantations and fungal pathogens.

Opportunities: Antifungal stewardship in Hematology

Importance of Antifungal Stewardship in Haematology

Rationale: High costs, toxicity (e.g., amphotericin B), and rising antifungal use justify stewardship.

IFD Burden: Invasive fungal diseases (IFDs) common in haematologic malignancies (e.g., acute leukemia), with high morbidity/mortality.

Risk Factors: Neutropenia duration, chemotherapy cycles, and immunosuppression (e.g., HSCT, GvHD) increase IFD risk.

Emerging Resistance: Azole-resistant *Candida* (e.g., *C. glabrata*) and *Aspergillus* spp. emerging, driven by prophylaxis overuse.

Challenges and Microbiology

Diagnostic Limits: Poor tools (e.g., no rapid tests) lead to empirical overuse; non-culture tests (e.g., galactomannan) may improve stewardship.

Yeasts: *Candida albicans* dominant, but non-*albicans* spp. (*C. krusei*, *C. glabrata*) rise with azole prophylaxis in HSCT.

Moulds: *Aspergillus* spp. (*A. fumigatus*, *A. flavus*) key in HSCT; risk tied to neutropenia and GvHD.

De-escalation Difficulty: Empirical therapy hard to stop without diagnostics, complicating stewardship efforts.

Strategies and Recommendations

Prophylaxis: Azoles (e.g., posaconazole for AML, voriconazole for HSCT) recommended; TDM optimizes dosing (e.g., voriconazole >1 mg/L).

Treatment: Empirical (liposomal amphotericin B) and pre-emptive (diagnostic-driven) strategies used; voriconazole first-line for CNS IFD.

TDM Role: Essential for itraconazole (>0.5 mg/L), voriconazole (>1 mg/L), posaconazole (>0.7 mg/L prophylaxis) to ensure efficacy, reduce toxicity.

Future Needs: Multidisciplinary teams, local guidelines, and better diagnostics (e.g., PCR, CT) to enhance AFS.



Challenges for AFS

Patients with IFD – complex and co – morbidities

Complex diagnostics

High case mortality rates and toxicities

Focus on IFI prevention

Effective surveillance of IFDs

Need for Multidisciplinary team involvement



AFS: UNIVERSAL BARRIERS



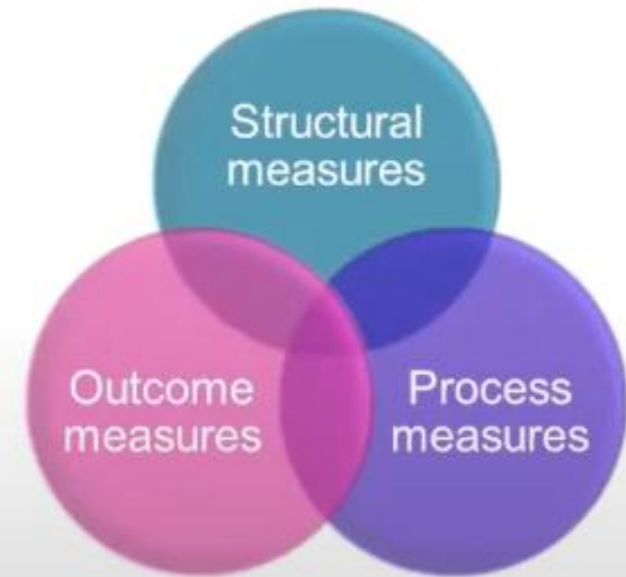
Processes:

- Availability or slow turn around time of diagnostic tests or TDM
- Measurement of quality of prescribing

Structural:

- Lack of staffing (micro, ID, pharmacist)
- Lack of support by administration
- Lack of real time IFD surveillance

Lack of **outcomes** data-most focus on less resource intensive metrics like costs



Micallef C et al, J Med Microbiol 2017; 66:1581; Seo SK et al ICHE 2016:37:1195; Urbancic K unpublished.; Donabedian, A. 2005. Evaluating the quality of medical care. *The Millbank Quarterly*, 83, 4, 691-729.



Summary



- Huge Need for Antifungal Stewardship
- Pharmacists play a critical role in Antifungal Stewardship
 - AFS Interventions
 - AFS - Diagnostic stewardship
 - AFS Opportunities - ICU, Transplant setting
- Pharmacists : Key in Antifungal TDM





THANK YOU



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