

Antifungal Stewardship

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Duke Antimicrobial Stewardship Outreach Network



Duke Center for
Antimicrobial Stewardship
and Infection Prevention



dason.medicine.duke.edu

Disclosures

- Scynexis- grant to my institution (FURI trial)
- Basilea Pharmaceutica- grant to my institution (mold study)
- Patent pending, diagnostic technology, licensed to Biomeme
- UpToDate- Author Royalties
- Meitheal Pharmaceuticals- consultant

Abbreviations

- AFS: Antifungal Stewardship
- AMS: Antimicrobial Stewardship
- DASON: Duke Antimicrobial Stewardship Outreach Network
- IDSA: Infectious Diseases Society of America
- IFD: Invasive Fungal Disease
- NHSN: National Healthcare Safety Network
- TDM: Therapeutic Drug Monitoring

Duke Antimicrobial Stewardship Outreach Network

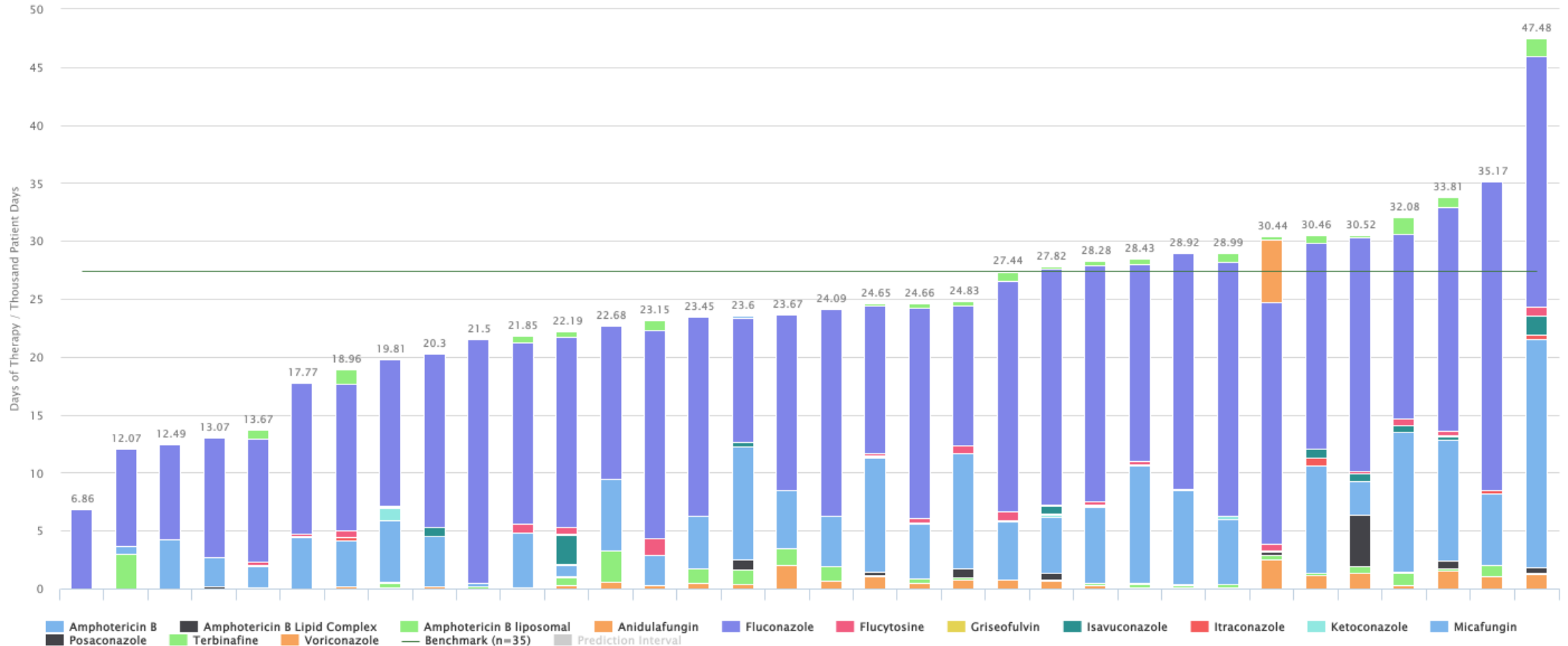
40 community
hospitals

5 states

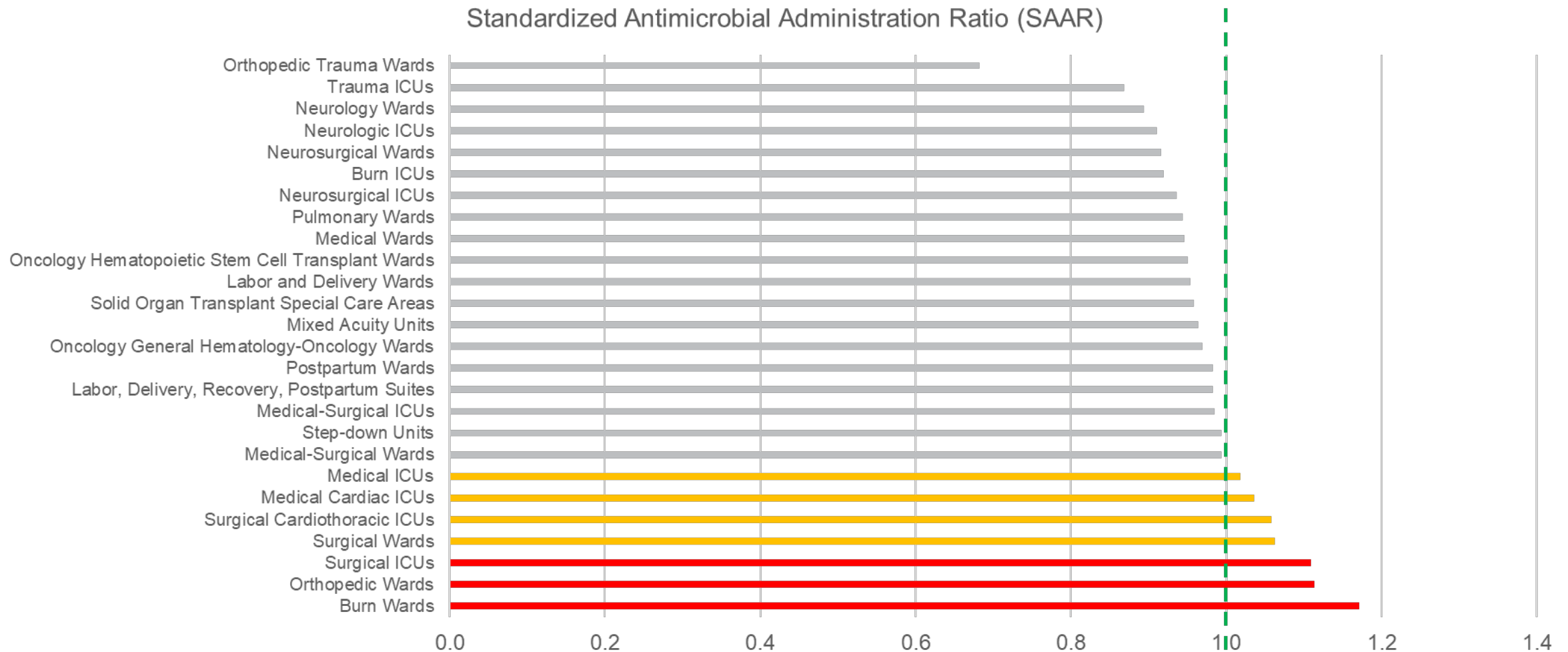
Augusta Health
Carteret Health Care
Chesapeake Regional Medical Center
Conway Medical Center
Granville Medical Center
Iredell Health System
Maria Parham Medical Center
Northern Regional Hospital
Piedmont Athens Regional
Piedmont Atlanta Hospital
Piedmont Augusta Hospital
Piedmont Augusta Summerville
Piedmont Cartersville Medical Center
Piedmont Columbus Regional Midtown
Piedmont Columbus Regional Northside
Piedmont Eastside Medical Center
Piedmont Fayette Hospital
Piedmont Henry Hospital
Piedmont Macon Medical Center
Piedmont Macon North Hospital
Piedmont McDuffie
Piedmont Mountainside Hospital
Piedmont Newnan Hospital
Piedmont Newton Hospital
Piedmont Rockdale Hospital
Piedmont Walton
UNC Health Chatham
UNC Health Johnston
UNC Health Lenoir
UNC Health Nash
UNC Health Rex
UNC Health Rockingham
UNC Health Southeastern
UNC Health Wayne
Sovah Health Danville
Sovah Health Martinsville
Tidelands Georgetown Memorial Hospital
Tidelands Waccamaw Community Hospital
Wake Forest Baptist Health High Point Medical Center
Wilson Medical Center



Variation in Inpatient Antifungal Use DASON Hospitals (2023)



2024 NHSN Report: Antifungal Use in Acute Care Hospital Wards



Variation in Antifungal Use: Acute Care Hospitals

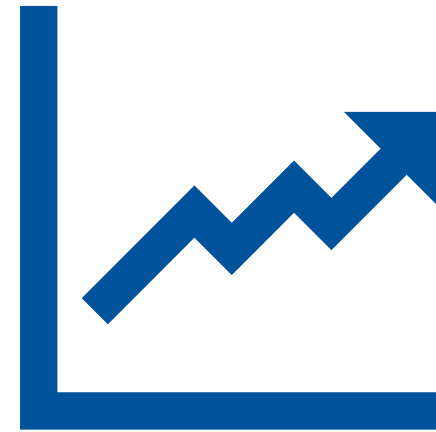
		Percentile Distribution of location-specific SAARs																		
		5th	10th	15th	20th	25th	30th	35th	40th	45th	50th	55th	60th	65th	70th	75th	80th	85th	90th	95th
Critical Care Units/ICUs	Burn ICUs	0.226	0.259	0.290	0.374	0.476	0.497	0.518	0.568	0.614	0.661	0.729	0.771	0.822	0.907	0.984	1.166	1.386	1.673	3.083
	Medical Cardiac ICUs	0.088	0.244	0.347	0.433	0.508	0.566	0.661	0.712	0.757	0.847	0.937	1.003	1.083	1.217	1.344	1.505	1.792	2.027	2.832
	Medical ICUs	0.190	0.301	0.402	0.483	0.559	0.623	0.681	0.740	0.798	0.848	0.908	1.013	1.094	1.179	1.268	1.401	1.537	1.732	2.107
	Medical-Surgical ICUs	0.187	0.306	0.370	0.449	0.503	0.566	0.620	0.675	0.737	0.800	0.868	0.944	1.029	1.132	1.248	1.376	1.549	1.799	2.179
	Neurologic ICUs	0.228	0.307	0.349	0.418	0.460	0.502	0.554	0.571	0.595	0.663	0.785	0.805	0.871	1.029	1.108	1.484	1.727	2.110	2.834
	Neurosurgical ICUs	0.151	0.229	0.266	0.393	0.448	0.504	0.571	0.640	0.715	0.795	0.886	0.936	0.988	1.062	1.262	1.621	1.788	2.230	2.748
	Surgical Cardiothoracic ICUs	0.073	0.118	0.193	0.240	0.301	0.340	0.383	0.450	0.523	0.620	0.686	0.770	0.878	0.993	1.144	1.346	1.651	2.092	2.684
	Surgical ICUs	0.204	0.311	0.345	0.416	0.460	0.533	0.588	0.668	0.729	0.793	0.852	0.954	1.024	1.133	1.287	1.395	1.677	2.145	2.469
	Trauma ICUs	0.176	0.264	0.355	0.418	0.455	0.494	0.583	0.625	0.680	0.724	0.823	0.869	0.984	1.033	1.136	1.167	1.272	1.493	2.082
Wards	Burn Wards	0.116	0.139	0.396	0.514	0.571	0.641	0.644	0.832	0.872	0.972	1.216	1.350	1.429	1.734	1.799	1.982	2.266	3.116	3.367
	Labor and Delivery Wards	0.000	0.000	0.154	0.228	0.288	0.356	0.419	0.490	0.573	0.643	0.752	0.844	0.996	1.228	1.421	1.667	1.970	2.572	4.003
	Labor, Delivery, Recovery, Postpartum Suites	0.000	0.000	0.060	0.168	0.258	0.345	0.426	0.510	0.607	0.697	0.802	0.914	1.052	1.257	1.428	1.807	2.228	2.905	3.776
	Medical Wards	0.236	0.327	0.414	0.478	0.549	0.602	0.664	0.720	0.769	0.836	0.897	0.968	1.044	1.126	1.226	1.330	1.469	1.686	2.062
	Medical-Surgical Wards	0.194	0.303	0.379	0.449	0.509	0.567	0.633	0.692	0.751	0.810	0.872	0.946	1.029	1.124	1.241	1.373	1.545	1.781	2.191
	Neurology Wards	0.216	0.278	0.343	0.399	0.448	0.530	0.580	0.634	0.725	0.771	0.851	0.928	1.010	1.086	1.143	1.243	1.433	1.539	1.955
	Neurosurgical Wards	0.265	0.368	0.447	0.527	0.602	0.622	0.653	0.700	0.742	0.827	0.868	0.971	1.021	1.106	1.220	1.315	1.432	1.750	1.949
	Oncology General Hematology-Oncology Wards	0.206	0.252	0.312	0.357	0.394	0.429	0.464	0.520	0.552	0.611	0.650	0.723	0.807	0.948	1.059	1.262	1.544	2.171	3.031
	Oncology Hematopoietic Stem Cell Transplant Wards	0.323	0.389	0.517	0.556	0.623	0.651	0.727	0.819	0.924	0.946	0.970	1.023	1.072	1.106	1.167	1.276	1.435	1.597	2.175
	Orthopedic Trauma Wards	0.111	0.236	0.292	0.331	0.362	0.407	0.429	0.459	0.496	0.556	0.587	0.695	0.715	0.753	0.865	1.140	1.145	1.431	1.816
	Orthopedic Wards	0.070	0.149	0.229	0.338	0.419	0.490	0.583	0.682	0.783	0.864	0.934	1.029	1.104	1.244	1.383	1.566	1.762	2.052	2.454
	Postpartum Wards	0.000	0.000	0.135	0.229	0.283	0.361	0.438	0.508	0.602	0.677	0.771	0.889	1.024	1.182	1.459	1.754	2.203	2.825	3.983
	Pulmonary Wards	0.231	0.396	0.482	0.566	0.659	0.700	0.755	0.780	0.825	0.870	0.953	0.989	1.089	1.211	1.237	1.311	1.348	1.472	1.721
	Surgical Wards	0.148	0.270	0.356	0.438	0.502	0.577	0.647	0.711	0.775	0.849	0.932	1.020	1.111	1.210	1.332	1.452	1.635	1.865	2.289
Other	Mixed Acuity Units	0.093	0.202	0.301	0.351	0.438	0.486	0.542	0.633	0.688	0.770	0.831	0.918	1.009	1.113	1.233	1.413	1.679	1.994	2.862
	Step-down Units	0.201	0.303	0.389	0.461	0.525	0.586	0.651	0.719	0.775	0.852	0.920	1.000	1.078	1.168	1.300	1.419	1.583	1.846	2.308
	Solid Organ Transplant Special Care Areas	0.251	0.364	0.412	0.424	0.455	0.480	0.552	0.585	0.719	0.780	0.812	1.049	1.183	1.255	1.457	1.547	1.972	2.566	2.864

The Case for Antifungal Stewardship

- Frequent infections in high-risk populations
- New therapies increasing risk of IFDs and Candiduria
 - Checkpoint inhibitors, immunomodulators, etc. (e.g. ibrutinib)
 - SGLT2 inhibitors (eg empagliflozin): increase glucose in the urine
- High morbidity and mortality of IFDs
- Complexity of at-risk patient population (organ function, drug-drug interactions, overlapping toxicities)
- Increased use of prophylaxis in at-risk populations

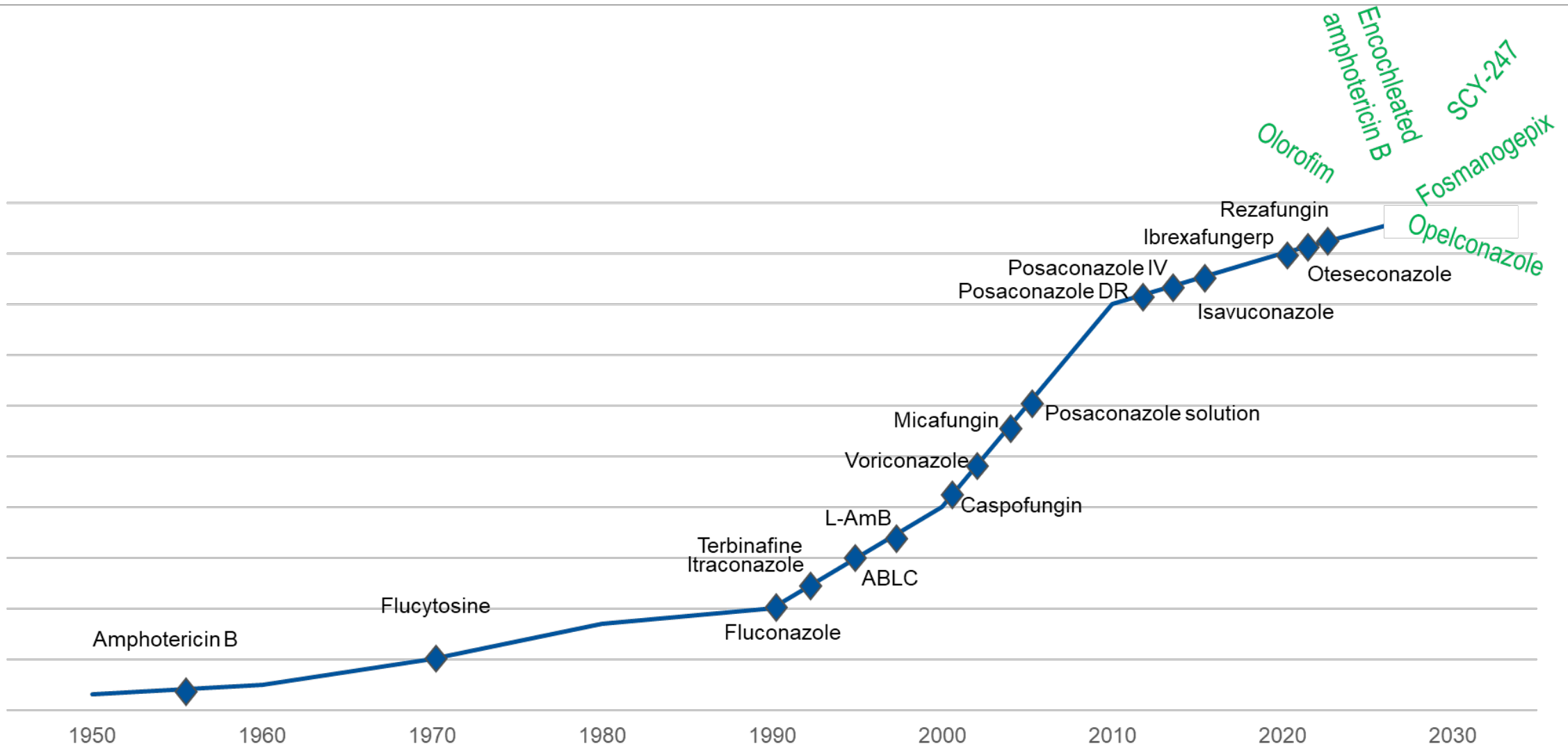
Antifungal Resistance and New Challenges

- *Candida glabrata*
 - Echinocandin and azole resistance
- *Candida parapsilosis*
 - Fluconazole resistance is increasing
- *Candida auris*
 - Multi-drug-resistant
- Aspergillosis
 - Influenza- and COVID-associated cases
 - Azole-resistance is increasing



Alexander BD et al. Clin Infect Dis 2013 ; 56(12): 1724-32. doi: 10.1093/cid/cit136; Escibano P. Front Fungal Biol. 2022. 3: <https://doi.org/10.3389/ffunb.2022.1010782>; Witt LS et al. IDWeek 2023: 2885. Lestrade PPA et al. Clin Microbiol Infect 2019; 25(7): 799-806; Bradley K et al. Emerg Infect Dis 2022; 28(9):1904-1905. Zhao J et al. Eur J Clin Microbiol Infect Dis. 2024; 43(4): 683-692.

Antifungal Drug Pipeline



Adapted from Ostrosky-Zeichner L. *Nature Reviews Drug Discovery*. 2010;9:719-727.

Knowledge gaps among clinicians in regards to fungal infection diagnosis & management

- Differentiating between colonization and infection, assigning IFI category per latest guidelines
- Selecting and interpreting fungal diagnostic tests
- Deciding when and if to initiate antifungal therapy
- How and when to use serological markers ((1,3)- β -D-glucan, cryptococcal antigen) in monitoring response to antifungal therapy
- Indications and protocols for empirical antifungal therapy
- Escalating antifungal therapy in non-responders
- Adjusting antifungals in patients receiving immunosuppressants
- Considerations while using antifungals (selection, dose/duration, toxicities, drug interactions, TDM)

Sachdev J et al. Medical Mycology 2025; 63(2): myaf003. <https://doi.org/10.1093/mmy/myaf003>

Reasons for inappropriate antifungal use

- Inappropriate selection for pathogen
- Inadequate dosage
- Inappropriate antifungal for site
- Inadequate duration
- Lack of adjustment based on susceptibility results
- Inappropriate/too frequent change of antifungal

Sachdev J et al. Medical Mycology 2025; 63(2): myaf003. <https://doi.org/10.1093/mmy/myaf003>

Opportunities for Antifungal Optimization

- Referral tertiary teaching hospital in Tehran, Iran
- 2019-2020
- 151 adults receiving ≥ 24 h of any parenteral antifungal drug

Parameter	Proportion Inappropriate
Diagnostic Workup	58.9%
Patients' followup	58.9%
Indication	18.5%
Time of Administration	28.5%
Selected antifungal agent	10.6%
Dosage	6.6%
Duration of treatment	36.4%
Treatment monitoring	84.1%
Administration technique	12%

Atashgar H et al. J Infect Dev Ctries 2023; 17(3):411-417. doi:10.3855/jidc.16828

Management of Candiduria Among Hospitalized Patients

- Retrospective analysis
- 305 hospitalized patients, 4 U.S. medical centers (Jan 2010- Dec 2013)
- 47% not managed in accordance with IDSA guidelines
- 65% had a catheter at the time of culture
- Reasons for non-adherence:
 - Treatment not indicated
 - Treatment indicated and no antifungal given
 - Inappropriate drug selection
 - Inappropriate antifungal dose
 - Inappropriate antifungal duration

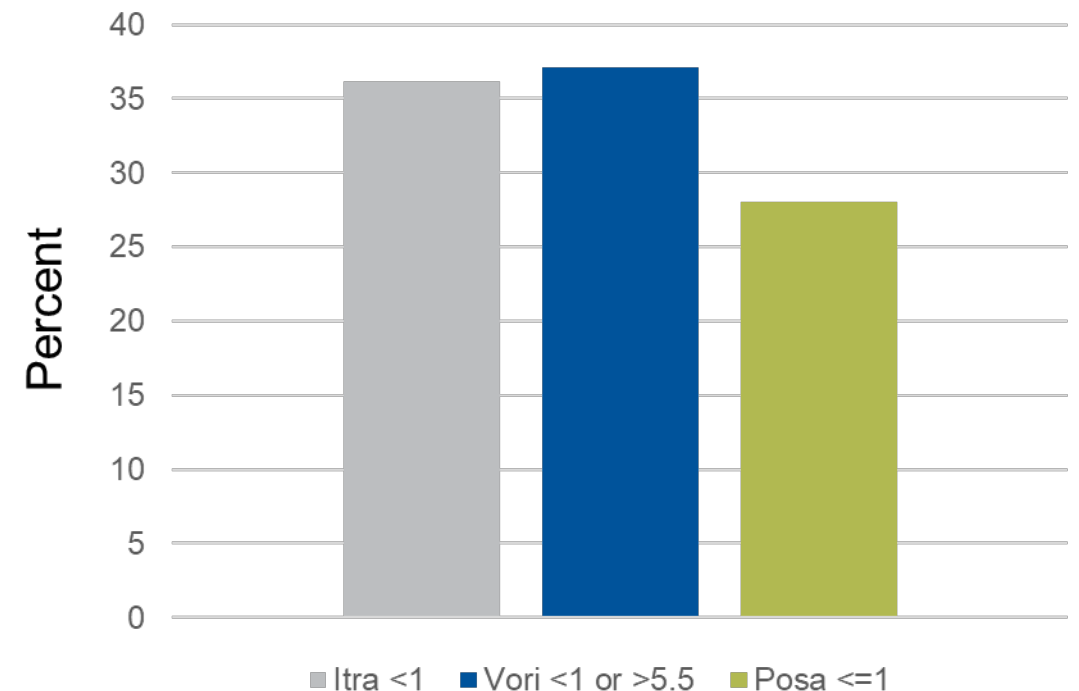


Jacobs D et al. Antimicrob Agents Chemother 2017. 62(1): e01464-17. <https://doi.org/10.1128/AAC.01464-17>.

Azole Therapeutic Drug Monitoring

- 2019-2021 data from >25 U.S. hospitals
- 2623 admissions with itraconazole (≥ 5 days), voriconazole (≥ 3 days), or posaconazole (≥ 5 days)
- Therapeutic drug monitoring (TDM) performed in only **15.8%**
- TDM may be underutilized in some settings

Proportion of First Levels Potentially outside the Therapeutic Range



Benedict K et al. *Open Forum Infectious Diseases*, 2023.10(8):ofad389. <https://doi.org/10.1093/ofid/ofad389>
Benedict K et al. *Open Forum Infectious Diseases*, 2023. 10(9):ofad468. <https://doi.org/10.1093/ofid/ofad468>

CDC: Barriers to performing antifungal TDM

Among survey respondents reporting barriers to performing antifungal TDM:

- 74% reported long turn-around times for send-out tests
- 48% had difficulty coordinating testing logistics
- 39% had uncertainty about recommendations
- 18% had uncertainty about benefits

<https://www.healio.com/news/infectious-disease/20231010/antifungal-therapeutic-drug-monitoring-adherence-high-though-room-for-improvement-exists>

Benedict K et al. *Open Forum Infectious Diseases*, 2023. 10(9):ofad468. <https://doi.org/10.1093/ofid/ofad468>

The State of Antifungal Stewardship: 2017

Antifungal Stewardship in the UK

- 11% Dedicated AFS program
- 43%: AFS as part of AMS
- 26% No AFS program, but monitor antifungal use
- 20% No AFS

Micaleff C et al. J Med Microbiol 2017. 66(11): 1581-1589.

Goals of Stewardship

- **Primary: To appropriately use antimicrobials**
 - Improve therapeutic choices (underuse)
 - Reduce unnecessary use (overuse)
 - Outcomes:
 - Improve patient outcomes and patient safety
 - Decrease emergence of resistance
- **Secondary:**
 - Decrease costs for health system
 - Satisfy regulatory requirements

Core Elements of Stewardship: Establishing the Framework for Optimizing Antifungal Use

- Leadership
- Accountability & Responsibilities
- Expertise
- Education & Practical Training
- Action
- Monitoring & Surveillance
- Reporting & Feedback



Pulcini C et al. Clin Microbiol Infect. 2019 Jan;25(1):20-25; Allegria W and Patel P. J. Fungi **2021**, 7(5), 352; Johnson MD, et al. J Infect Dis. 2020;222(Suppl. 3):S175–198

Expertise on Infection Management

- Experts in IFD management
 - How many have access to medical mycologists?
 - How many have access to ID consultants (with fungal expertise)?
 - How many have access to ID pharmacists?
- Expertise in fungal diagnostics
 - Access to timely conventional and non-culture based diagnostics
 - Early and accurate diagnosis of IFD is one of the most important factors influencing patient outcomes and appropriate prescribing of antifungal therapy

Johnson MD, et al. *J Infect Dis.* 2020;222(Suppl. 3):S175–S198;

3

Performance of Non-Culture Based Diagnostic Tests Varies

Parameter	Serum (1→3)-β-D-Glucan (<i>Candida</i>) [58–60]	Serum Mannan/ Antimannan (<i>Candida</i>) [61]	Blood T2Candida (<i>Candida</i>) [62, 63]	PCR (<i>Candida</i>) [64]	Galactomannan (<i>Aspergillus</i>) [65]	Serum (1→3)-β-D-Glucan (<i>Aspergillus</i>) [66, 67]
Sensitivity	80%	58%	91%	73%	71%	81%
Specificity	80%	93%	98%	95%	89%	78%
PPV/NPV at 2% prevalence (screening ^a)	9% >99%	12.5% 99%	0.5% >99%	16.7% 99%	8% 99%	8% >99%
PPV/NPV at 10% prevalence (screening ^a)	30% 97%	50% 95%	81% 99%	50% 94%	41% 96%	29% 97%
PPV/NPV at 30% prevalence (diagnosis ^b)	<63% 90%	77% 83%	96.4% 96%	74% 81%	72% 87%	62% 91%

Abbreviations: NPV, negative predictive value; PPV, positive predictive value.
^aScreening: asymptomatic patients without localized signs of infection.
^bDiagnosis: symptomatic patients with suspected infection.

- Identify best-use cases for implementation/use of fungal diagnostics
- High negative predictive value: may aid de-escalation of antifungal therapy
- Limited utility if pre-test probability of invasive diseases is <10%
- Improved clinical impact when coordinated with AFS

Johnson MD, et al. *J Infect Dis.* 2020;222(Suppl. 3):S175–S198

Optimizing Diagnostics

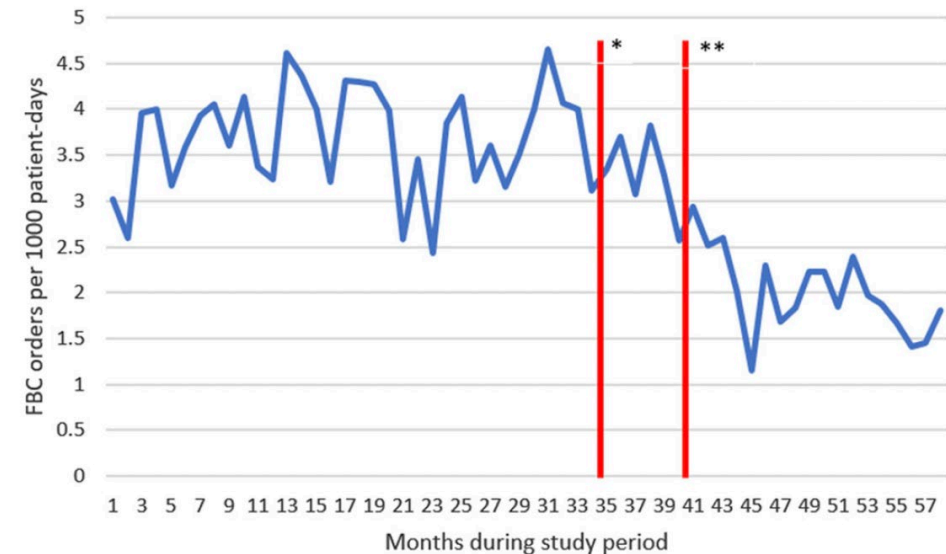
“Beta-D-glucan testing is overused in patients without solid organ/stem cell transplant or hematologic malignancies”

- 355 patients with ≥ 1 beta-d-glucan test
 - Excluded solid organ/stem cell transplant or hematologic malignancy
- 49% had no indication for beta-d-glucan testing
 - Being in an ICU or having cirrhosis were associated with inappropriate testing
- 4% had antifungals started based on beta-d-glucan testing results

Markou et al. Open Forum Infect Dis 2017. 4(Suppl 1): S74.

Fungal Blood Culture Optimization

- Specific fungal blood culture (FBC) bottles are often not indicated
- Routine blood culture bottles will detect *Candida* spp.
- Intervention to reduce contamination and overuse of FBCs
- Decreased FBC utilization without changes in positivity rate, except increased histoplasma isolation
- Order alert: *“Filamentous fungal blood cultures should only be ordered in patients with suspected disseminated infection due to mold or dimorphic fungi such as Histoplasma and Blastomyces”*



Chavez M et al. Infect Control Hospital Epidemiol 2024. 45(3): 384-386; licensed under CC 4.0 <https://bit.ly/4f7whIM>.

4

Education and Practical Training

- 40% of antifungal use was inappropriate with respect to indication, dosage, risk of drug-drug interactions or antifungal susceptibility results
- 1/3 of antifungal agents were routinely underdosed
- Significant knowledge gaps
- AFS programs should develop/utilize targeted training to address these gaps
 - Incorporate into training of students, residents, fellows, personnel

Nivoix Y et al. *J Antimicrob Chemother* 2012; 67:2506–13; Labelle AJ, et al. *Crit Care Med.* 2008;36(11):2967–72; Johnson MD, et al. *J Infect Dis.* 2020;222(Suppl. 3):S175–198

Education and Practical Training

- Significant knowledge gaps in appropriate antifungal prescribing
 - Interpretation of microbiology results
 - Colonization vs infection
 - Indications for prophylaxis vs empiric therapy
 - Antifungal dosing and monitoring
- AFS programs should develop/utilize targeted training to address these gaps
 - Incorporate into training of students, residents, fellows, personnel

Education examples

- Presentations
- Newsletters

Common Scenarios of Antifungal Overuse

YEAST IN SPUTUM	YEAST IN URINE
<ul style="list-style-type: none"> ▪ <i>Candida</i> pneumonia is exceedingly rare, almost always occurs in the setting of distinctly immunocompromised host ▪ <i>Candida</i> in the sputum or respiratory specimens from mechanically ventilated patients rarely requires antifungal therapy 	<ul style="list-style-type: none"> ▪ In asymptomatic patients, most often represents colonization and does not need treated* ▪ If catheterized, may resolve with removal of the catheter. Presence of pyuria & colony count does not differentiate colonization vs. infection

Lookout for encapsulated yeast in sputum → “cryptococcosis” and needs workup

*More serious (consider w/u and treatment): patients with structural abnormalities, those undergoing urinary tract instrumentation, VLBW infants, neutropenic/ severely immunocompromised patients

Current Fungal Infection Reports 2009, 3:21–31
 Jacobs DM, *Antimicrob Agents Chemother* 2018; 62(1): e01464-17.
 Sobel JD, *Clin Infect Dis* 2000; 30(1): 9-24. <https://doi.org/10.1086/313580>



Antimicrobial Stewardship News
 Volume 5, Number 1
 January 2017



Treatment of Candidiasis & Antifungal Stewardship Opportunities

Introduction

Candida are yeasts that are abundant in normal human flora of the skin, mouth, and gut. Disease occurs when natural protective barriers or host defenses are compromised, such as in scenarios of mucositis or

Candiduria

The presence of candiduria usually triggers a physician to consider whether a patient has a *Candida* urinary tract infection (UTI) that requires treatment. In asymptomatic patients, candiduria almost always represents colonization. Removing the indwelling urinary catheter generally eradicates candiduria. A randomized controlled trial evaluating fluconazole vs placebo for 14-

Special scenarios: yeast in urine

Random sample in 4 hospitals: 80% of candiduria patients were asymptomatic

Multicenter randomized trial of fluconazole (14 days) vs placebo for asymptomatic or minimally symptomatic (afebrile) candiduria ($\geq 10^3$ cfu/MI)

Eradication of *Candida* in the urine:

Outcome	Fluconazole	Placebo	p value
Overall (at end of therapy)	79/159 (50%)	46/157 (29%)	<0.001
Two-Weeks after end of treatment	59/87 (68%)	56/86 (65%)	0.7

Similar outcomes 2 weeks after treatment, whether initially treated or not



Jacobs DM, *Antimicrob Agents Chemother* 2018; 62(1): e01464-17.
 Sobel JD, *Clin Infect Dis* 2000; 30(1): 9-24. <https://doi.org/10.1086/313580>

Bloodstream Concentrations of Azoles in Samples Sent for TDM

UTHSC Reference Laboratory Jan 2001-April 2013

Antifungal	Number of levels	Median (ug/mL)	% Below Lower Limit of Assay	LOW	HIGH
Voriconazole	14,923	1.86	14.6%	(<1 ug/mL) 39.2%	(>5.5) 10.4%
Posaconazole	1,548	0.64	9.6%	(<0.7 ug/mL) 58.4%	(>1.25) 19.9%
Itraconazole	689	0.84	38%	(<0.5 ug/mL) 54.6%	Not reported

Wiederhold NP et al. *Antimicrob Agents Chemother.* 2014;58:424-431.

Education Examples: TDM guidance


SIDP
 SOCIETY OF INFECTIOUS DISEASES PHARMACISTS
 Utility of triazole antifungal therapeutic drug monitoring:
 Insights from the Society of Infectious Diseases Pharmacists
 Endorsed by the Mycoses Study Group Education and Research Consortium

McCreary EK et al.
Pharmacotherapy 2023; 43:
 1043-1050.

Azole	Target trough	Toxicity Ceiling for Troughs	Timing
TDM routinely recommended			
Voriconazole	Prophylaxis ≥ 0.5 mg/L Treatment $\geq 1-2$ mg/L	4-5.5 mg/L	Trough, 2-5 days (~2 d with LD, ~5 d without LD)
Itraconazole	Prophylaxis ≥ 0.5 mg/L Treatment ≥ 1 mg/L (based on itra only)	3-4 mg/L (HPLC)	Anytime in dosing interval (troughs typical) ~5-7 days with LD, 10-14 d without LD
Posaconazole	Prophylaxis $\geq 0.5-0.7$ mg/L Treatment $\geq 1-1.5$ mg/L	>3-3.74 mg/L	Trough, 5 days with LD, 7 days without LD
TDM recommended in specific circumstances			
Fluconazole	Not established	Not established	Trough 5-7 days, (sooner with LD)
Isavuconazole	Not established, for treatment some experts recommend $\geq 1-2$ mg/L	Not established	Anytime in dosing interval (troughs typical) ~5-7 days with LD, 10-14 d without LD

Examples: TDM Guidance

MSGERC / Terranova &
Dallas Smith, PharmD, MS, MAS
Melissa Johnson, PharmD, MHS
JoAnne Young MD

Antifungal Therapeutic Drug Monitoring (TDM): Overview

Why TDM?

To achieve blood levels to support efficacy and minimize toxicity

Which drugs?

Triazole antifungals

How to perform TDM in adult patients

Drug	TDM Recommendation		Timing of Samples (after drug initiation, dose change, or change in interacting medications)	Target Trough Range
	Prophylaxis	Treatment		
Itraconazole	Sporanox capsule	✓✓	✓✓	 mg/L 3-4 1 0.5 Tx Range
	Itraconazole suspension	✓✓	✓	
	SUBA-Itraconazole (Tolsura)	Non-applicable	✓	
Posaconazole	Immediate-release suspension	✓✓	✓✓	 mg/L 3-3.75 1-1.5 0.5-0.7 Tx Range
	Delayed-release tablet	✓✓	✓	
	Intravenous	✓✓	✓	
Voriconazole	Tablet	✓✓	✓✓	 mg/L 4-5.5 1-2 0.5 Tx Range
	Intravenous Suspension	✓✓	✓✓	
Isavuconazole	Tablet	Not Available	Consider in situations marked by pharmacokinetic variability (e.g., critical illness, alternative delivery, extremes in weight, etc) or refractory illness.	 mg/L 4.6-5.1 1 Tx Range
	Intravenous	Not Available	Consider in situations marked by pharmacokinetic variability (e.g., critical illness, alternative delivery, extremes in weight, etc) or refractory illness.	

Key

- Therapeutic Upper Range (Toxicity Ceiling)
- Therapeutic Lower Range
- Prophylaxis Lower Range
- ✓✓ Recommended
- ✓ Consider

Next steps? See the companion infographic for a discussion of dosing adjustments to consider.

Resource: McCreary EK, et al. Utility of triazole antifungal therapeutic drug monitoring: Insights from the Society of Infectious Diseases Pharmacists. Endorsed by the Mycoses Study Group Education and Research Consortium. *Pharmacotherapy*. 2023 Oct;43(10):1043-1050. doi: 10.1002/phar.2850. Release date: July, 2024.

Antifungal Therapeutic Dose Adjustment Considerations by Drug

Itraconazole		Posaconazole	
Drug Level (mg/L)	Consider Dose Adjustments	Drug Level (mg/L)	Consider Dose Adjustments
Supratherapeutic: >3-4	Consider dose reduction if the patient is experiencing an adverse event (or transition to another antifungal if clinically appropriate).	Supratherapeutic: >3-3.75	<ul style="list-style-type: none"> Delayed-release tablets: Reduce daily dose by 100 mg and recheck in 5-7 days Oral suspension: Reduce daily dose by 200 mg and recheck in 5-7 days
Therapeutic: 0.5 to 3-4 (depending on indication)	No change	Therapeutic: 0.5 to 3-3.75 (depending on indication)	No change
Subtherapeutic: <0.5 -1 (depending on indication)	<ul style="list-style-type: none"> For capsules, absorption can be increased by taking the medication with an acidic carbonated beverage (such as cola or ginger ale) or stopping or reducing H2RAs and PPIs Change capsules to solutions Increase daily dose by 100-200 mg For solution, take the medication on an empty stomach 	Subtherapeutic: 0.5-1.5 (depending on indication)	<ul style="list-style-type: none"> Delayed-release tablets and IV: Increase daily dose by 100 mg Oral suspension: <ul style="list-style-type: none"> Dose at 200 mg 4 times daily rather than 400 mg BID OR Increase daily dose by 200-400 mg and recheck in 5-7 days (maximum absorbable individual dose is 400 mg) Ensure suspension is taken with a fatty meal or nutritional supplement and an acidic carbonated beverage (such as cola or ginger ale)
		Subtherapeutic: <0.5	<ul style="list-style-type: none"> Delayed-release tablets: Consider q 12h dosing for very low levels Consider other triazoles

Voriconazole		Isavuconazole	
Drug Level (mg/L)	Consider Dose Adjustments	Drug Level (mg/L)	Consider Dose Adjustments
Supratherapeutic: >4.0 (Asians)-5.5 (Non-Asians) ¹	<ul style="list-style-type: none"> If levels are very high, consider holding 1-2 doses and restart at lower dose Oral Tablets: Decrease the daily dose by 50-100 mg and recheck level in 4 days 	Supratherapeutic: >4.6-5.1 (depending on indication)	Consider dose reduction in patients with adverse events; but relationship of levels to toxicity is unclear. Unbound levels of isavuconazole may vary widely, study is needed.
Therapeutic: 0.5 to 4-5.5 (depending on indication)	No change	Therapeutic: 1 to 4.6-5.1 (depending on indication)	No change
Subtherapeutic: 0.5-2.0 (depending on indication)	<ul style="list-style-type: none"> Oral Tablets: Increase daily dose by 50-100 mg and recheck level in 4 days IV: Increase IV therapy by 50% to a maximum of 6 mg/kg 	Subtherapeutic: 0.5-<1	Consider increasing the dose by 186 mg (1 capsule).
Subtherapeutic: <0.5	<ul style="list-style-type: none"> Patient may be a rapid metabolizer; split the dose to q 8h and recheck level in 2 days Evaluate for DDIs and adherence 	Subtherapeutic: <0.5	Double the dose or decrease the dosing interval to q 12h.

¹ Takesue Y et al. *Clin Ther*. 2022 Dec;44(12):1604-1623. doi: 10.1016/j.clinthera.2022.10.005. H2RA = H2 receptor antagonist; PPI = proton pump inhibitor

Resources for implementing TDM:

- SIDP/MSGERC Guidance: McCreary EK et al. *Pharmacotherapy*. 2023 Oct;43(10):1043-1050. doi: 10.1002/phar.2850
- Asian Guidelines: Takesue Y et al. *Clin Ther*. 2022 Dec;44(12):1604-1623. doi: 10.1016/j.clinthera.2022.10.005.
- Medscape continuing education: 5 Things to Know About Antifungal Therapeutic Drug Monitoring. [medscape.com/viewarticle/999522_print](https://www.medscape.com/viewarticle/999522_print)
- University of Michigan Antifungal TDM Guidelines: https://www.med.umich.edu/asp/pdf/adult_guidelines/Antifungal_TDM.pdf

Release date: July, 2024.

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[Antifungal Therapeutic Drug Monitoring \(TDM\): Infographic Resources](https://funguseducationhub.org/fungal-tdm/)
(<https://funguseducationhub.org/fungal-tdm/>)

Education resources



[SIDP Antimicrobial Stewardship Certificate](https://sidp.org/Stewardship-Certificate)
(<https://sidp.org/Stewardship-Certificate>)

[SIDP education programs \(www.sidp.org\)](http://www.sidp.org)

Antifungal PK/Dosing in Special Circumstances

Antifungal	Characteristics	Obesity	Critical Care
Echinocandins	Highly protein bound, metabolized (caspo, mica) or degraded (anidula)	Doses may need increased	Limited data but may need higher doses (may be due to weight)
Flucytosine	Low protein binding, renally eliminated	Lack of data but may consider dosing on IBW	Insufficient data, but renally eliminated
Fluconazole	Low protein binding, hydrophilic, renally eliminated	TBW 12 mg/kg LD, then 6 mg/kg/day	Adjust for renal impairment/dialysis
Itraconazole	Highly protein bound, metabolized (3A4), cyclodextrin in IV	No data- could consider using LBW	Recommend 200 mg IV Q8h x 72h, then 200 mg IV QD-BID; CVVH increases elimination
Voriconazole	Moderate protein binding (58%), metabolized (2C19, 2C9, 3A4), non-linear PK, cyclodextrin in IV	Consider using ABW, limited data	Limited data, highly variable PK; consider 4 mg/kg q12h po for CRRT
Posaconazole	Highly protein bound, partially metabolized, cyclodextrin in IV	Inconclusive, standard doses of DR tablets	Highly variable PK in critically ill, even with IV formulation
Isavuconazole	Highly protein bound, large Vd, metabolized (3A4, 3A5, UGT), linear PK	No change in dose	Limited data but no apparent adjustment

IBW= ideal body weight, TBW= total body weight, LBW= lean body weight, ABW= adjusted body weight

Pyrpasopoulou A et al. J Emerg Crit Care Med 2019; 3:37. Abdul-Aziz MH et al. Intensive Care Med 2020; 46: 1127-53. Amsden JR Curr Fungal Infect Rep 2019; 3:21-32. Mourad A et al. OFID 2017;4(Suppl 1): S292-3. Lyster H et al. Clin Pharmacokinet. 2023; 62(7): 931-942

Other Actions Aiming at Responsible Antimicrobial Use

- ID consultation for patients with IFDs
- Development of institutional bundles and guidelines
- Consider ongoing interventions such as “handshake stewardship rounds”, academic detailing, or post-prescription review and feedback (PPRF)
 - Pre-authorization less effective for AMS than PPRF
- Evaluate quality of antifungal prescribing systematically and use data-driven strategies to optimize AFS interventions
- Additional research is needed to develop/evaluate new tools for AFS

ID Consult/Bundles Improve Quality of Care for Candidemia

EXAMPLE CANDIDEMIA BUNDLE



Susceptibility testing



Follow-up cultures



Dilated ophthalmologic exam



CVC removal

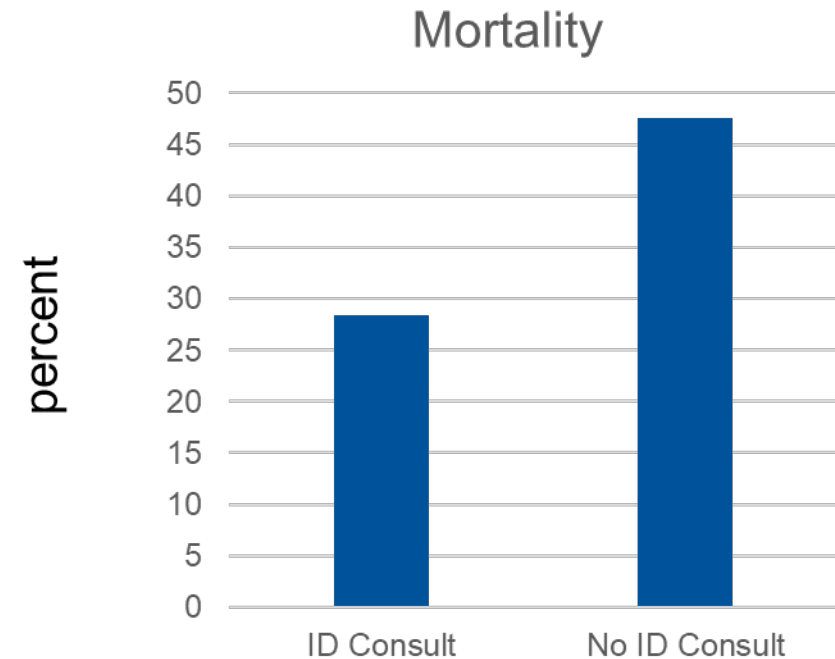


Evaluate other sites



Stepdown/duration of therapy

ID Consult Associated with Lower Mortality



Pappas PG et al. *Clin Infect Dis*, 2016;62(4):e1-e50; Antworth A et al. *Pharmacotherapy*, 2013;33(2):137-143. Mejia-Chew et al. *Lancet Infect Dis* 2019, 19(12): 1336-44; Kobayashi T et al. *Open Forum Infect Dis* 2020, 7(9): ofaa270.

Experience with Antifungal PAF

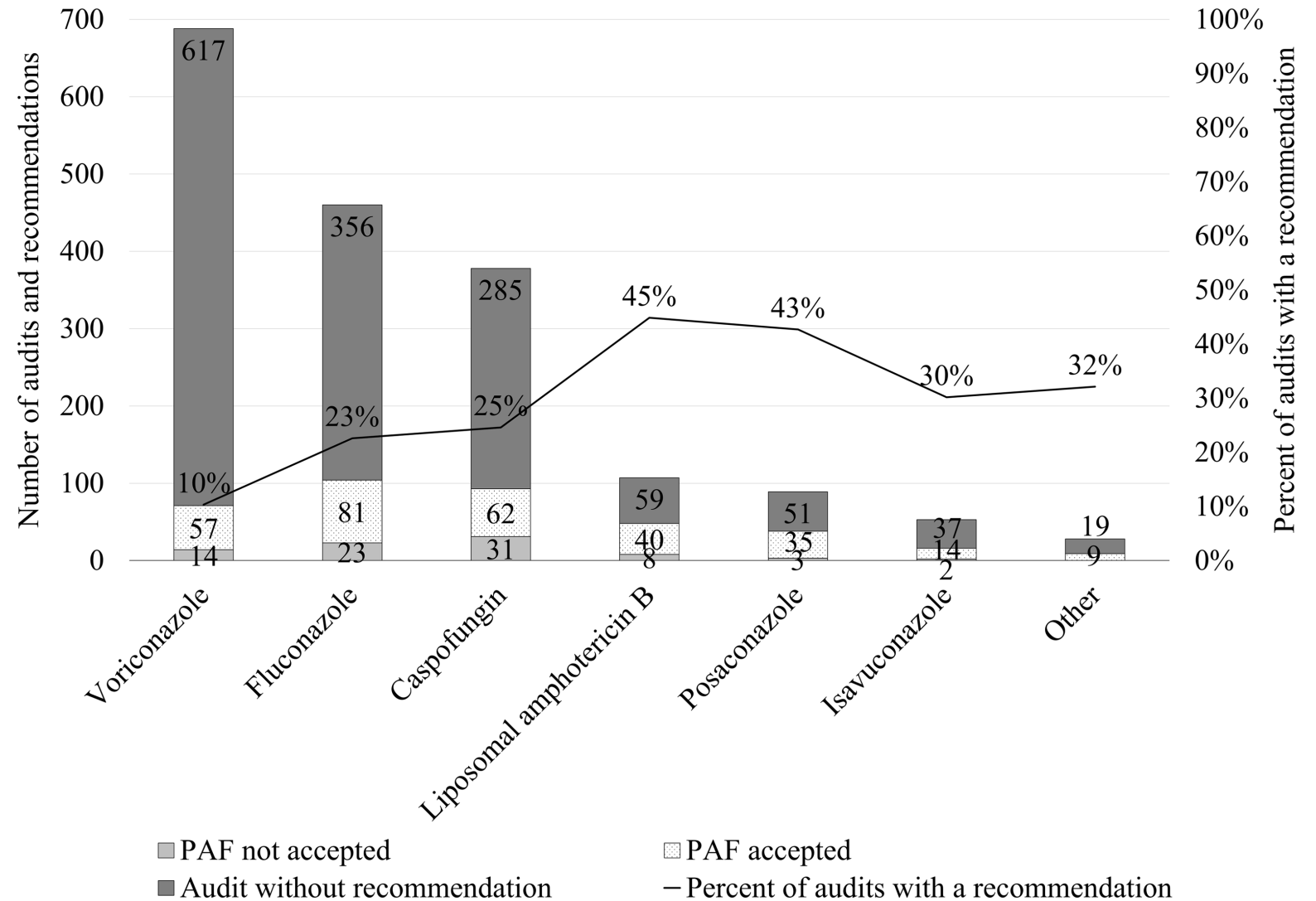
Stanford Pediatric ASP

11/1/2020-10/31/22

1803 antifungal audits

21% resulted in a recommendation

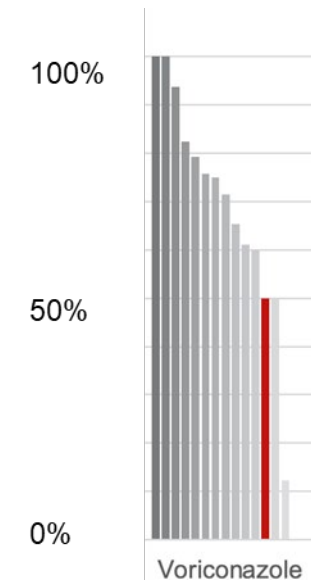
80% acceptance rate



5 Other Essential Actions

- Local surveillance and reporting of IFD to prescribers
- Review of drug–drug interactions with antifungals
- Intravenous to oral transition program
 - Daily report- pharmacist review
 - Automatic switch by pharmacist per policy or recommendation to prescriber
 - Common targets: fluconazole, voriconazole

Proportion of Oral to Total
16 DASON hospitals



Johnson MD, et al. *J Infect Dis.* 2020;222(Suppl. 3):S175–198

Example Performance Measures for AFS

- Mortality (or for prophylaxis, fungal-free survival)
- Length of stay
- Clinical response (treatment success, stable disease, failure)
- Appropriate choice of antifungal agent, dose, route, duration
- Time to (targeted/optimal) therapy
- Adherence with practice guidelines
- Persistent culture positivity/time to culture resolution
- Recurrent or breakthrough infection
- Performance of quality measures (ie, ophthalmologic examination, galactomannan testing, follow-up cultures performed)
- Therapeutic drug monitoring performed/achievement of therapeutic levels

Johnson MD, et al. *J Infect Dis.* 2020;222(Suppl. 3):S175–198

6 Monitoring & Surveillance

- Establish/adapt local surveillance systems for IFDs
- Promote rational diagnostic testing and communicate results to AFS teams to facilitate 'real-time' interventions
- A clinical pharmacist or clinician should screen patient medical records for antifungal drug interactions
- Have access to timely TDM for triazole antifungal agents
- Have access to timely antifungal susceptibility testing
- Perform routine susceptibility testing and develop cumulative antifungal susceptibility reports

Johnson MD, et al. *J Infect Dis.* 2020;222(Suppl. 3):S175–198

Example Cumulative Antifungal Susceptibility Report 2022-2024 Duke University Hospital

Organism	Number of Isolates*	Fluconazole	Micafungin	Voriconazole
Candida albicans	103	100	100	100
Candida glabrata	178	--- (94% S-DD)	97	Not reported (no approved breakpoint)
Candida krusei (2016-2024 due to low isolate numbers)	65	R (intrinsically resistant)	100	82
Candida tropicalis	34	91	100	91
Candida parapsilosis	68	90	94	94

* Invasive sources only (not urine or superficial wound specimens), DUH Antibiogram, 2024

7 Reporting & Feedback

- Track antifungal drug use
- Benchmark antifungal use
- Assess patient-level outcomes whenever possible
- Give directed data feedback to prescribers

Common Numerators

Days of Therapy (DOT)

Defined Daily Doses (DDD)

Common Denominators

1,000 Patient Days

Admissions

Days Present

Inhabitants

Johnson MD, et al. *J Infect Dis.* 2020;222(Suppl. 3):S175–198

AFS Checklist - GAP Analysis

- Practical recommendations to get started:
 - Define achievable objectives
 - Define outcome measures
 - Share reports with prescribers and facility leadership (antifungal use and resistance)
 - Define an improvement roadmap for the next period, with objectives tied to the roadmap & based on the gap analysis

Summary

- Antifungal stewardship is essential to optimizing prevention and management of fungal infections across healthcare settings
- We have identified unique aspects of AFS that align with the Global Core Elements of Antimicrobial Stewardship
- Incorporating these core elements at the local level can facilitate best practices for AFS in various healthcare settings, and ultimately improve quality of care for our patients

Questions

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