



May 24, 2022

Antifungal Stewardship Part 2

Whitney Hartlage, PharmD & Alyssa Castillo, MD

Outline

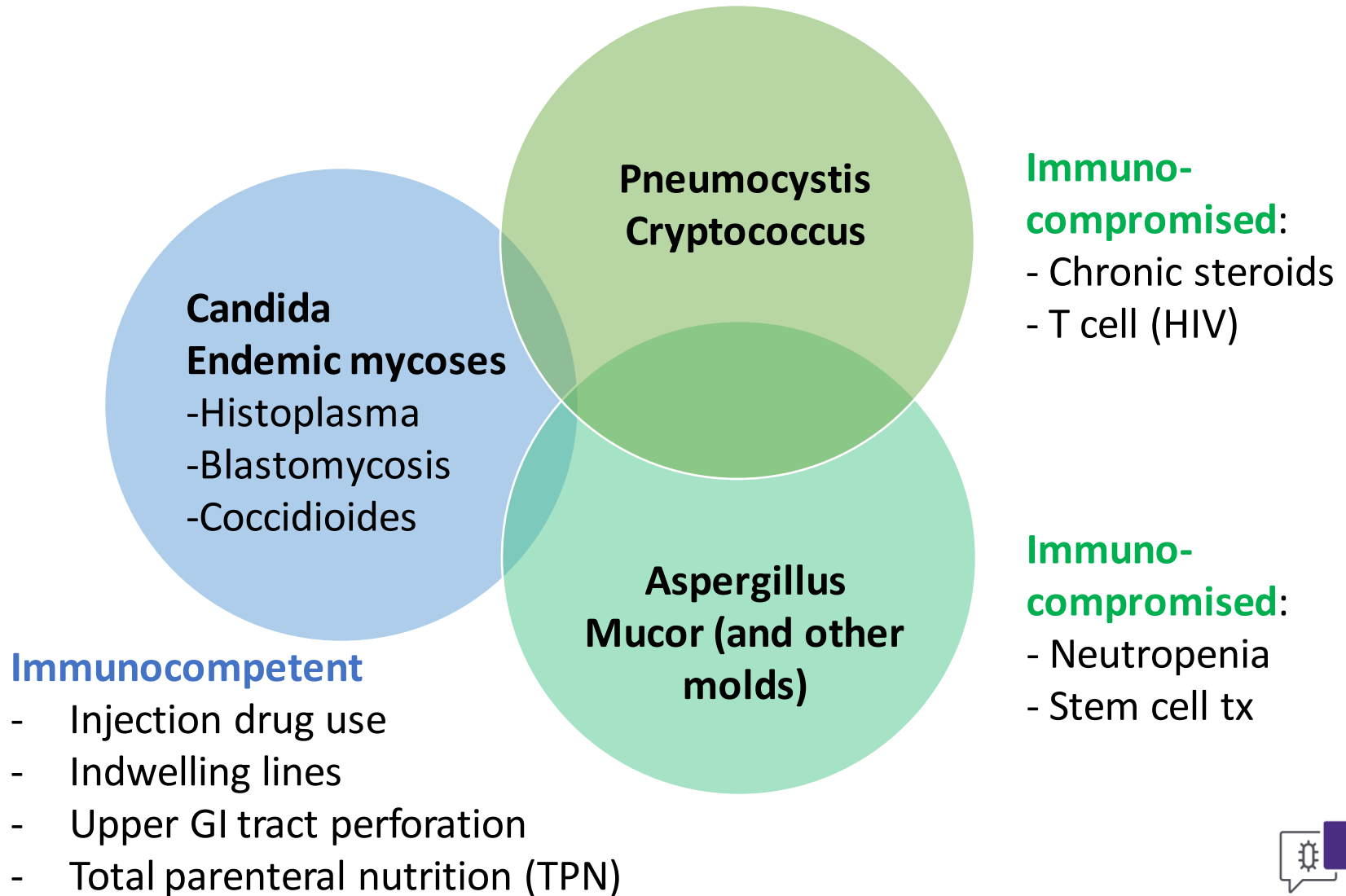
- Part I: Alyssa
 - When to suspect fungal infection
 - Fungal diagnostic testing 101
- Part II: Whitney
 - Implementation of antifungal stewardship (AFS) programs
 - Examples of AFS interventions



Fungal Infections & Diagnostic Testing



Risk Factors for Fungal Infection



Fungal Diagnostic Testing

Culture

- “Routine” Blood Cx:
 - Detect candida spp
 - Typically + at 24-72h
- Fungal Blood Cx:
 - Superior only for:
 - Blastomyces
 - Coccidioides
 - Histoplasma
 - Malassezia

No Culture

- Serologic Testing
 - Coccidioides Ab
- Molecular Testing
- Antigen Detection
 - Histoplasma urinary ag
 - Cryptococcal ag
 - Galactomannan
 - 1,3- β -D-glucan



Fungal Diagnostic Testing

Galactomannan

- **Target:** Diagnosis of invasive aspergillosis
- **Samples:** Serum, BAL
- **Test Characteristics:**
 - BAL: Sens 73%, Spec 89%
 - Serum: Sens 38%, Spec 87%
- **Drawbacks**
 - Cross-reactivity
 - False positives

1,3- β -D-glucan (“Fungitell”)

- **Target:** Broad screening for fungal disease
 - Candida, aspergillus, pneumocystis
- **Samples:** Serum only
- **Test Characteristics:**
 - Candida: Sens 87%, Spec 85%
 - PJP: Sens near 100%
- **Drawbacks**
 - False positives
 - Long TAT
 - Does not detect mucor or cryptococcus



Fungal Diagnostic Testing

Host	Most Common Fungal Infections	Diagnostic Test
Immunocompetent	Candida	Routine blood cultures Tissue fungal stain & culture
	Endemic mycoses	Serologic testing (Coccidioides Ab) Antigen detection (Histoplasma urine ag)
Immunocompromised: - Chronic Steroids - HIV	Pneumocystis	Microscopy, Molecular (PCR) 1,3-β-D-glucan
	Cryptococcus	Cryptococcal antigen (CrAg)
Immunocompromised: - Neutropenia	Aspergillus	Galactomannan
	Molds (mucor)	Molecular diagnostics (PCR) ± Culture

Skeptical of the + Culture?

Colonization is likely when **candida** is identified on culture at the following sites:

Site	Potential Lab Stewardship Intervention
Sputum	“Rapidly growing yeast are rarely a cause of pneumonia”
Urine	No candida subspecies given No susceptibilities given
Skin	Consider: “Yeast is a normal component in skin flora”



Implementation of Antifungal Stewardship (AFS)



Stewardship Overview

**Leadership
commitment and
accountability**

Establish stewardship roles and responsibilities

Drug expertise and action

Implement processes
to promote appropriate management of
infectious syndromes, including empiric and
definitive treatment

**Tracking, reporting, and
education**

Identify and track key stewardship outcome
measures and deliver education that promotes
prescribing



Core Members of AFS



Antifungal Stewardship Members and Support

Physicians	<ul style="list-style-type: none">• Coordinates the AFS program• Leads educations/academic detailing• <u>Diagnostic testing/stewardship</u>• Antifungal drug selection and assessment of treatment response• <u>Development of clinical guidelines and pathways</u>
Clinical pharmacists	<ul style="list-style-type: none">• Coordinates AFS activities• Assessment of baseline antifungal use and benchmarking• <u>Education to clinicians, including physicians and pharmacists, on appropriate antifungal use</u>• Antifungal formulary management• <u>Development of clinical guidelines and pathways</u>
Microbiologists	<ul style="list-style-type: none">• Implement and interpret fungal diagnostics• Implement and validate antifungal susceptibility testing
Infection control professional	<ul style="list-style-type: none">• Provide guidance on infection control practices• Provide guidance on development of surveillance systems



Impact of Treatment Bundles



- Ensure that critical diagnostic tests and source control procedures are performed in a timely fashion when antifungal therapy is started
- A 9-component management bundle was developed for and used to manage 648 nonneutropenic patients with candidemia
 - Clinical success between patients with and without compliance, 92.9% vs. 75.8% ($p=0.011$)

Effective approach toward **improving antifungal prescribing** and **improving patient outcomes**



Treatment Bundle Examples



Invasive candidiasis management bundle	
At the time therapy is being started	<ul style="list-style-type: none">• Obtain 2 blood cultures prior to starting therapy• Removal of existing CVCs within 24h of diagnosis• Initial appropriate selection and dosing of antifungals considering local epidemiology started within 12h of culture• Ophthalmological exam within the first week of diagnosis
After starting therapy	<ul style="list-style-type: none">• 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 3-5d after starting therapy and evaluating the need for alternative therapy based on culture ID and susceptibility• Administration of at least 2 weeks of therapy after clearance of blood cultures• Step-down to oral fluconazole therapy in patients with a favorable clinical course and an isolate with documented susceptibility



Treatment Bundle Examples



Invasive aspergillosis management bundle	
At the time therapy is being started	<ul style="list-style-type: none">Serum galactomannan test repeated twice in patients not on mold-active azole prophylaxisCT imaging of chest and/or sinus/brain in patients with symptoms localized at these signsEarly bronchoscopy (within 48h) with cytology examination and culture of BAL fluid, measurement of galactomannan antigen titer in BALInitial appropriate selection and dosing of antifungal agentsSystematic screening for drug interactions for any patient starting or stopping a triazole antifungal agent
After starting therapy	<ul style="list-style-type: none">Periodic (eg, weekly) testing of serum galactomannan (if aspergillosis) as an adjunct criterion to assess treatment responseTDM of voriconazole and posaconazole and possibly isavuconazole serum levels to document adequate drug exposuresAssessment of therapy appropriateness based on microbiological, culture, or histological resultsRepeat chest CT imaging after 3–4 wk and periodically based on response, to assess infection status and/or progressionStep-down to oral triazole therapy in patients with a favorable clinical course

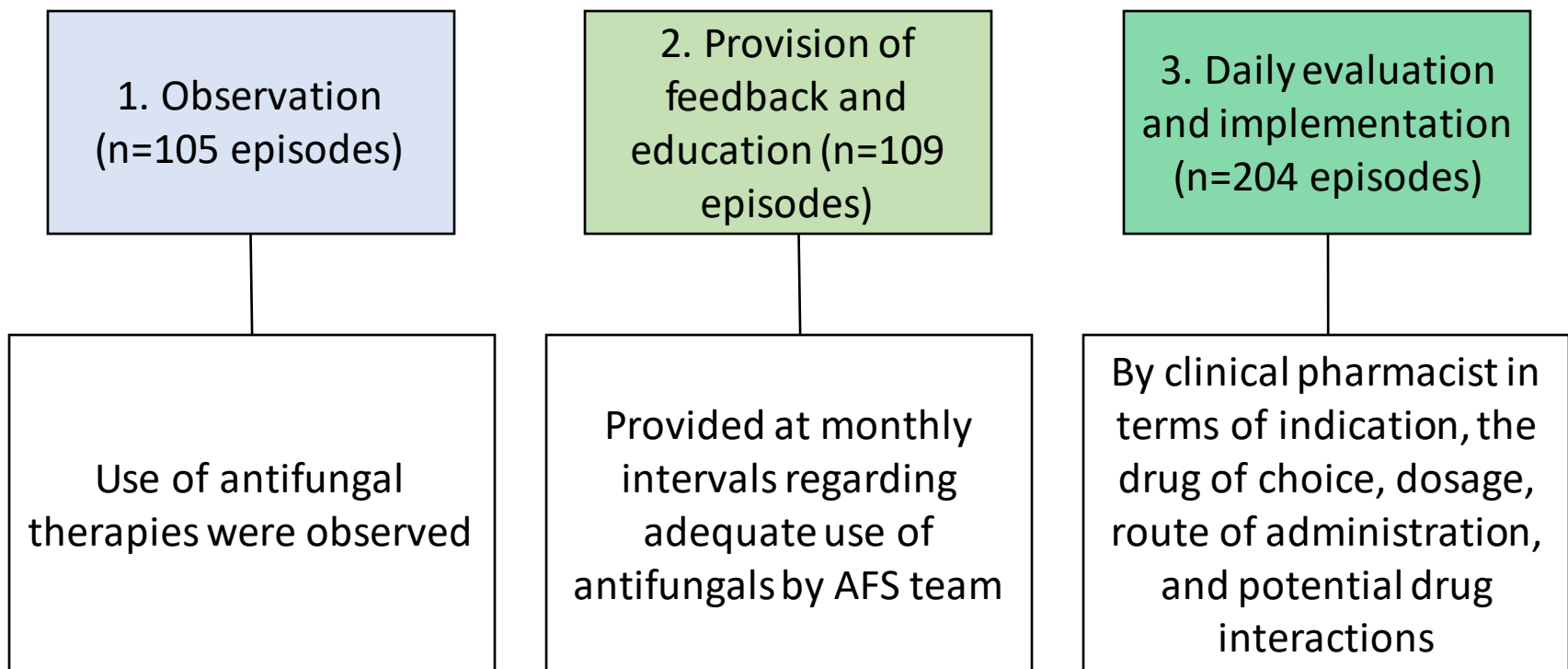


Implementation of Pharmacist-Driven AFS Program



- Prospective, quasi-experimental study

Study periods



Implementation of Pharmacist-Driven AFS Program



- **Overall appropriateness of antifungal use increased significantly** in the third period compared with the remaining two periods (30.5%, 26.6%, and 62.7%, respectively, in the three periods; $p < 0.001$)

TABLE 3 AFS recommendations and acceptance rates

Type of recommendation	No. (%) of recommendations:	
	Made (n = 157)	Accepted (n = 151)
Related to fungal infection		
Diagnosis	3 (1.9)	1 (33.3)
Treatment	108 (68.8)	104 (96.3)
Follow-up	46 (29.3)	46 (100)
Related to treatment		
Initiation of treatment	9 (5.7)	9 (100)
Discontinuation of treatment	25 (15.9)	22 (88.0)
De-escalation	12 (7.6)	11 (91.7)
Drug selection	2 (1.3)	2 (100)
Dose increase	15 (9.6)	15 (100)
Dose decrease	10 (6.54)	10 (100)
Loading-dose selection	8 (5.1)	8 (100)
Administration route	6 (3.8)	6 (100)
Therapeutic drug monitoring	23 (15.9)	23 (100)
pDDI ^a	13 (9.0)	13 (100)
Adverse effects	1 (0.6)	1 (100)
Prescribing error in the order	3 (1.9)	3 (100)
Request for laboratory or radiological examination	30 (19.1)	28 (93.3)

^apDDI, potential drug-drug interaction.

Conclusion: a pharmacist-driven AFS program is practical and achievable and can increase the rate of appropriateness in antifungal therapies



Educational Training and Practical Interventions are Essential



- Development of targeted educational programs to address gaps in knowledge
 - Interpretation of microbiology laboratory results
 - Differentiation of colonization versus infection
 - Indications for prophylaxis versus empiric therapy
 - Antifungal therapy dosing and monitoring
- Ongoing interventions
 - Post-prescription review and feedback
 - Handshake stewardship



Target Educational Interventions for your Audience



- Cross-sectional multicenter survey evaluating prescribing physicians' knowledge about diagnosis and treatment of invasive candidiasis and aspergillosis, and the compliance with current IFI international guidelines

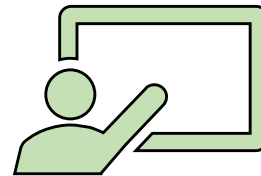
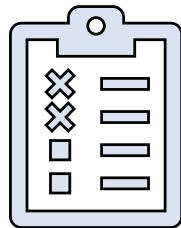
Table 2 Percentage of adequate answers regarding department and physician category

Question	Adequate answer	Overall N = 121	Medical n = 62	ICU N = 52	P	Residents n = 67	Staff n = 54	P
Q1.When <i>Candida</i> is isolated in a urine culture, choose the answer that best describes what you would do:	Start antifungal treatment only in some cases.	69.4	79	63.5	0.09	62.7	77.8	0.08
Q2.On a patient with mechanical ventilation and a probable VAP a tracheal aspirate culture shows <i>Candida</i> sp. Which of the following statements best show your interpretation:	Requires antifungal treatment only if the patient has a high <i>Candida</i> score.	42.1	46.5	38.5	0.44	38.8	46.3	0.46
Q3. In which of the following clinical scenarios you would start <i>Candida</i> prophylaxis?	AML (Acute Myeloid Leukemia) patients on induction chemotherapy.	38	45.2	32.7	0.18	29.9	48.1	0.05
Q4.In your opinion, the best choice for <i>Candida</i> prophylaxis is:	Fluconazole in most of the cases.	88.4	83.9	92.3	0.25	85.1	92.6	0.25



Target Educational Interventions for your Audience

- Results of survey were used to design interactive training courses based on clinical cases



Conclusion: there are serious **lacks in knowledge** in this area that requires a **tailored** educational program as a first step of an AFS implementation



Suggestions for Process and Outcome Metrics for AFS



Metric	Example of Metric
Antifungal drug consumption	Days of therapy per 1000 patient-days OR defined daily dose per 1000 patient-days
Institutional guideline compliance <ul style="list-style-type: none">Choice of drugDoseTherapeutic drug monitoringDe-escalationIV-to-PO conversionUse of diagnostic testsSource control	Proportion of patients: <ul style="list-style-type: none">Treated with drug of choice for indicationPrescribed appropriate dosing for indicationOn azole for whom serum level was checked appropriately from time of initiationWith fluconazole-sensitive <i>Candida</i> for whom therapy was switched from echinocandin to fluconazoleTaking an azole who were switched from IV-to-POIn compliance with institutional recommendations for monitoring serum galactomannanWith candidemia with catheter removal
Prevention strategies in high-risk patients	Episodes of invasive fungal infection in target groups
Treatment of invasive fungal infection	<ul style="list-style-type: none">Proportion of patients with clinical cureProportion of patients with candidemia with recurrent infection
Costs	Total cost of prescriptions per year, stratified by antifungal drug



Approaches when ID Expertise is Limited

- 1) Contract or resource-share with other hospitals
- 2) Utilize resources within a health system network
- 3) Use collaborative organizations to share data and resources (eg, statewide groups in the US, national networks)
- 4) Engage telehealth support for stewardship efforts at the local level
- 5) Identify and train local personnel in AFS principles and best practices



Conclusion

- The development of AFS programs provides a foundation for **improved** communication, diagnosis, and management of IFDs, while **optimizing patient outcomes** and **increasing cost-effectiveness**
- Adoption of these AFS principles will require some **tailoring at the local level** based on the differences between healthcare systems and practices



Thank you!

Questions?

Whitney: WhitHart@uw.edu

Alyssa: AYC20@uw.edu

