Antifungal Stewardship

A Practical Guide to Implementation

Joint Commission Resources

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Overview of Fungal Infections and the Need for Antifungal Stewardship

Chinhak Chun, MD

Introduction

Antimicrobial pharmaceuticals administered to treat infectious diseases face challenges that are different than those encountered by other drugs aimed at noninfectious diseases: living organisms possess an innate ability to adapt to hostile environments, be it the host's defense mechanisms or antimicrobial agents. Microorganisms, including fungi, can develop resistance after exposure to antimicrobial agents. The resistance is then retained within the species through rapid multiplication cycles or transferred to different microorganisms through conjugation and other mechanisms to share plasmids or chromosomes. The emergence of antimicrobial resistance has far-reaching serious consequences on patient safety, quality of healthcare, and economic outcomes.[1-3]

The Emergence of Multi-drug Resistant and More Virulent Organisms

The past 20 years have seen the emergence of multi-drug resistant organisms (MDROs), initially observed in bacteria and followed by other microorganisms including fungi.[4] MDROs are not only developing resistance to a dwindling number of effective antimicrobial agents, but they are also becoming increasingly virulent, with escalating morbidity and mortality.[2,3]

For example:

- Since the introduction of fluconazole and itraconazole, *Aspergillus*, one of the most virulent molds, has replaced *Candida* as the most common fungal pathogen in hematopoietic stem cell transplant recipients[5]
- "Breakthrough" fungal infections due to Zygomycetes, voriconazole-resistant *Candida glabrata*, and other molds cause highly fatal infections to the recipients of hematologic stem cell transplantation after these patients had received voriconazole for prophylaxis or treatment of aspergillosis[6]
- The emerging multi-antifungal resistant *C. auris* is responsible for serious infections in multiple geographic locations. The resistance is at least temporally associated with increased use of the antifungals, especially fluconazole and the newer antifungal class, echinocandins[7]

These events are similar to severe outcomes of infections caused by multi-drug resistant bacteria. *Clostridium difficile* (*C. difficile*)-associated disease is now a global problem, an undeclared pandemic. In Canada, the epidemic in the last decade caused by the *C. difficile* BI/NAP1/027 strain was responsible for a 3-fold increase in risk-adjusted mortality.[8] The emergence of this strain coincided with the emergence of resistance to the fluoroquinolone class of antimicrobial agents.[9]

Bacteremia caused by Methicillin-Resistant *Staphylococcus aureus* (MRSA), relative to Methicillin-Susceptible *S. aureus* (MSSA) bacteremia, is associated with a 3-fold increase in mortality and prolonged hospitalization.[1] The outcomes were similar for hospitalized patients when infected with multi-drug resistant *Pseudomonas* or *Enterobacter*.

Strategies to treat fungal infections appropriately face additional challenges. In addition to the increasing incidence of antifungal resistance, invasive fungal infections tend to occur in patients who are immunocompromised. The most severe form of fungal infections, invasive fungal disease (IFD), are unique to patients receiving neutrophil-depleting chemotherapy for malignant diseases, transplantation-related immunosuppressive treatment, very low birth weight infants, and children with malignant disease or inborn errors of the immune system. Mortality associated with invasive infections caused by *Aspergillus, Mucorales*, and other molds in immunosuppressed patients often exceed 50% despite antifungal therapy.[10]

Financial Burden of Antibiotic Resistance

Infections caused by antibiotic-resistant microorganisms are not only associated with a high risk of mortality, but also significant financial expenditures worldwide.[1-3] Aside from the cost of antimicrobials and medical treatment, intangible costs arising from death, disability, grief, pain, and suffering cannot be underestimated.

Many antibiotic management efforts aimed at a single antibiotic between 1981 and 2008, before the advent of the more organized antimicrobial stewardship program (ASP), were successful in reducing antibiotic and antifungal costs.[11-14] The social and economic impact of well-organized widespread ASPs

could be significant. The critical question is whether antimicrobial stewardship programs are going to stop or even reverse the speed of expanding antimicrobial resistance.

Antimicrobial Stewardship

The current strategies to stem the tide of surging pathogenic bacterial resistance is to expedite the production of more effective antimicrobial agents and simultaneously influence the prescribing practices of medical professionals.[15] The response to the first strategy has not been very promising.[16] The second strategy to promote the rational use of antimicrobials, universally known as antimicrobial stewardship, has been promoted by the World Health Organization (WHO), Centers for Disease Control and Prevention (CDC), and other professional healthcare organizations.

Since 2007, the Infectious Disease Society of America (IDSA) published 2 antimicrobial stewardship program guidelines, and the CDC introduced seven core elements of antimicrobial stewardship program.[17-20] The major accrediting organizations, such as The Joint Commission and Joint Commission International, have added accreditation requirements to their standards specific to ASPs.[21,22]

Antifungal Stewardship

There is a compelling need for evidence-based antifungal stewardship programs that are designed to impact patient care across many medical specialties in healthcare organizations and overcome the obstacles described above.[13,23] Antifungal stewardship programs require multidisciplinary collaboration, careful planning, leadership support, and financial resources to be successful.[13]

Antifungal stewardship faces additional challenges compared to antimicrobial stewardship.

- There is a lack of consistently reliable noninvasive and rapid diagnostic tests. While blood cultures serve that purpose for bacteria, many fungi do not grow in conventional blood culture media. Fungal cultures may take days or weeks. Gram stain has a limited role except for *Candida* and *Sporothrix*. Noninvasive laboratory tests for biomarkers are not available for many fungal pathogens, and if available, are not universally affordable[24]

Antifungal stewardship programs require multidisciplinary collaboration, careful planning, leadership support, and financial resources to be successful.[13]

- Biopsies or other invasive methods used to obtain tissue specimens may increase the risk to the patient, and require expertise to interpret the histochemical test results
- The appropriate selection of antifungal drugs depends on timely isolation and identification of the pathogen followed by the susceptibility testing, including minimum inhibitory concentrations (MICs) and clinical breakpoints for multiple antifungal agents. These processes require a well-equipped and staffed microbiology laboratory. Such facilities may not be available for all hospitals and other health system entities[25,26]
- The strength of clinical recommendations and the quality of evidence for antifungal prophylaxis, treatment regimens, dosing, and duration of therapy by international professional

organizations are not consistently ranked high by the IDSA-United States Health Service grading system ("a strong recommendation and the high quality of evidence"). There are also few randomized clinical trials for many IFDs[25,26]

- Adherence to published recommendations for antifungal therapy by clinicians is often poor, without stewardship activities[13,27]; however, inappropriate antifungal use for *Candida* species isolated from urine declined more than 50% with antifungal stewardship and education[23]
- Clinicians with no formal training in the management of fungal diseases prescribe antifungals frequently.[13] Only a small portion of antifungal prescriptions are generated from the hematology/oncology departments caring for immunocompromised patients[13]
- Multiple antifungals prescribed for empiric treatment are often deemed unnecessary as only a small proportion of patients receiving such therapy have a proven infection[13,28]
- Even basic, older generation antifungals may not be readily available in developing countries, and the price of antifungals fluctuates widely[24]
- Many antifungal agents are associated with toxicities and drug-drug interactions. In particular, the triazole class of antifungals is associated with multiple drug-drug interactions
- Therapeutic drug monitoring in plasma is useful in optimizing the safety and efficacy of antifungals. For example, the triazoles exhibit patient-to-patient variabilities in absorption with pharmacogenetic differences and may require more frequent monitoring of plasma concentrations.[29] Resources to provide the antifungal plasma concentrations or pharmacokinetic data may not be readily available

Fungal Infections and Antifungal Strategy

Fungal infections will be reviewed in this section with a summary of clinical presentations, symptoms, and diagnostic strategy. The diagnosis will address the laboratory tests that include both conventional (culture, special stain, and serology) and emerging tests for biomarkers.

The empirical and prophylactic use of antifungals should be limited to clearly defined patient populations and supported by evidence-based guidelines from professional organizations. Breakthrough infections caused by equally virulent fungi are known to occur after prophylaxis.[30,31]

ASPERGILLUS

Aspergillus is the cause of sinusitis, bronchopulmonary, and central nervous system infections. It has emerged as the most frequent cause of invasive pulmonary infections in patients with immune systems that have been compromised due to a variety of illness, including induction chemotherapy for acute myelogenous leukemia, bone marrow or solid organ transplantation, Acquired Immune Deficiency Syndrome (AIDS), and prolonged corticosteroid therapy for lung diseases. Four species of *Aspergillus* are associated with the majority of invasive fungal infections: *A. fumigatus*, *A. flavus*, *A. terreus*, and *A. niger.*

Central Nervous System Infection

In 2012, the CDC reported a US multistate outbreak of fungal meningitis. While the index case had fungal meningitis caused by *Aspergillus fumigatus*, the majority of cases of fungal meningitis were due to *Aspergillus* and *Exserohilum rostratum*, a very rare cause of human fungal disease.[32] The patients were mostly immunocompetent. The outbreak was associated with contaminated methylprednisolone used for epidural and intra-articular injections.[32] The source of the contamination was traced to a single pharmaceutical compounding facility that did not adhere to aseptic compounding procedures. The fungi were identified from the environmental samples as well as unused medications found at the facility.

The distinction between invasive and noninvasive aspergillosis is determined by the immune status of the patient, rather than the anatomical location of the infection. While the isolation of *Aspergillus* from the tissue is always a sign of invasive disease, its isolation from the respiratory secretions, especially from patients who have been on prolonged corticosteroids for chronic obstructive pulmonary disease (COPD), may indicate colonization.[33] The mortality from invasive aspergillosis treated with antifungals and surgical debridement ranges from 20% (invasive sinusitis) to 90% (cerebral aspergillosis).[10]

Allergic Bronchopulmonary Aspergillosis (ABPA)

ABPA is a manifestation of an allergic response to *Aspergillus*. Patients experience a cough with mucus production, wheezing, shortness of breath, and intermittent fever. ABPA is more severe and protracted in the presence of advanced bronchiectasis or cystic fibrosis.

Aspergilloma

A mass of *Aspergillus* hyphae may develop in preexisting lung cavities of patients with chronic lung disease, including tuberculosis. Diagnosis depends on the isolation of *Aspergillus* from sputum and the high titers of *Aspergillus* antibodies along with the radiographic evidence of a fungus ball. Patients with aspergilloma can be asymptomatic and not require antifungal treatment but can develop potentially serious complications such as hemoptysis. The decision to treat aspergilloma depends on the ongoing assessment of asymptomatic patients—worsening cough, hemoptysis, high antibody titers in serum, and changing radiographic appearances of the aspergilloma are indications of an invasion.

Sinusitis

Aspergillus sinusitis in immunocompetent patients can be locally invasive, destroying the bony structure of the paranasal sinus. In immunocompromised patients, an extension of the infection, rhinosinusitis, to the orbit and intracranial space may cause altered vision, cavernous sinus thrombosis, and other central nervous system infections.[34,35] An ulcerative nasal lesion with eschar or nonsensitive area are clues to fungal infection.[10] Symptoms include fever, cough, nasal discharge, feeling of obstruction or congestion, headache, and epistaxis.

Tracheobronchitis

Invasive infection causing pseudomembrane formation and ulceration of the trachea and bronchi occur in patients with AIDS and recipients of lung transplantation.[36,37]

Lung and Disseminated Infection

The most common manifestation of severe aspergillosis is invasive pulmonary aspergillosis (IPA). IPA occurs in patients with granulocytopenia, immunosuppressive chemotherapy, systemic corticosteroids, and bone marrow or stem cell transplantation.[10]

Symptoms may include a cough, hemoptysis, and pleuritic chest pain in association with a rapidly progressive lung infiltrate to nodules, necrotizing pneumonia, and cavitation. Characteristic radiographic findings are "halo" or "air-crescent" signs best demonstrated by computed tomography. Disseminated aspergillosis may also cause brain abscesses, mycotic aneurysm, endocarditis and bone infections.

Diagnosis will involve the following:

- Visualization of septate, branching hyphae on secretion or tissue stained with Gomori's methenamine silver (GMS) or periodic acid-Schiff (PAS)
- Isolation of *Aspergillus* from the respiratory secretion including bronchoalveolar lavage, or tissue
- Serology: (1-3)-β-D-glucan (BDG), matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS)
- Polymerase chain reaction (PCR)

Note: The isolation of a fungus or the diagnosis of a fungal infection can be complex. In each section of this chapter where tests for diagnosis are provided, it should be noted that more tests will build a stronger diagnosis. They are considered, in the best case scenario, to all be beneficial or required; however, depending on the institution, not all may be available.

The most common manifestation of severe aspergillosis is invasive pulmonary aspergillosis (IPA).

- Treatment can be either targeted or empiric. Prophylaxis is indicated in allogenic stem-cell transplantation, induction chemotherapy for acute leukemia, neutropenia with acute myelogenous leukemia, myelodysplastic syndrome, or significant graft-versus-host disease. Treatment is typically not warranted for asymptomatic, immunocompetent patients with radiographically stable aspergilloma; aspergillus isolated from the respiratory secretion in an asymptomatic, or immunocompetent patients without evidence of pulmonary infection[10]

BLASTOMYCES DERMATITIDIS

Blastomyces dermatitidis is endemic in North America along the Great Lakes, St. Lawrence River, Mississippi River, and Ohio River. Infection occurs when airborne conidia are inhaled.

Pulmonary Blastomycosis

Pulmonary disease is the predominant manifestation of *B. dermatitidis* infection, with the potential for widespread dissemination. A skin infection may occur alone, but it is considered a marker for multiorgan infection.[10] Symptoms include a chronic cough with hemoptysis and pleuritic chest pain. Fever is not always present. Radiographic appearances are not characteristic.

Diagnosis will involve the following:

- Demonstration of the characteristic broad-based budding yeast either by potassium hydroxide (KOH) smear or fungal stain of the tissue
- Secretion, body fluid, and tissue cultures
- Chemiluminescent DNA probe is commercially available and provides rapid results when there is sufficient culture material
- Serologic methods vary in sensitivity and specificity. PCR is more specific, but not readily available commercially. Antigen detection test in urine is sensitive, but cross-reaction occurs with *Histoplasma*, *Paracoccidioides*, and *Penicillium*

Note: The isolation of a fungus or the diagnosis of a fungal infection can be complex. In each section of this chapter where tests for diagnosis are provided, it should be noted that more tests will build a stronger diagnosis. They are considered, in the best case scenario, to all be beneficial or required; however, depending on the institution, not all may be available.

CANDIDA

Candida species as a whole have been relatively sensitive to most systemic antifungal drugs for decades, except for *C. krusei*, which is inherently resistant to the first-generation azoles. Recently, a multi-drug resistant *C. auris* has emerged in multiple countries, including the US *C. auris* has been found to be resistant to fluconazole (86% of 35 isolates), amphotericin B (43%), and echinocandins (3%).[7,38,39] It has been isolated from blood, wounds, and otic specimens of patients with multiple comorbidities with extensive healthcare exposure, in both acute and chronic care facilities. At least 2 nosocomial outbreaks have been observed.[38]

Colonization

Understanding the difference between colonization and infection is the first step in the prudent use of antifungals. *Candida*, being the normal commensal of the human body, is found on the skin, gastrointestinal tract, female genital tract, expectorated sputum, or in urine without evidence of infection. *Candida* and the host are in a commensal relationship.

Differentiating colonization from infection is a critical step in deciding whether to treat *Candida* or any other fungus as a pathogen. Patients colonized with *Candida* do not require treatment unless a decision to use prophylaxis is made due to severe immunosuppression or critical illness in the intensive care unit.[40] Colonization of the urine may occur without prior exposure to antimicrobial agents and is often associated with indwelling bladder catheters. Patients often have no signs of infection such as fever, urinary tract discomfort, or painful voiding.

Another example of colonization is *Candida* isolated from expectorated sputum or tracheal secretions obtained from asymptomatic patients without concomitant oropharyngeal lesions or lower airway infection. Colonization usually occurs during or after antimicrobial treatment or prolonged use of corticosteroids.

A. NONINVASIVE INFECTION

Cutaneous Candidiasis

Dermatitis in the axilla, groin, under the breast or skin folds, is seen in obese patients especially with diabetes. Itching, irritation, and discomfort are common symptoms.

Oropharyngeal Infection

Antimicrobial or chemotherapy is the usual antecedent. White plaques or patches appear in clusters, or the lesions appear as a membrane that covers the oropharynx. The lesions do not come off the surfaces of the involved area by peeling or scraping. Coinfection due to herpes group virus or aphthous ulcers may cause ulcerating lesions.

Symptoms vary from asymptomatic to severe, including pain and difficulty swallowing. Ulcerating lesions due to herpes virus group or aphthous mucositis may cause severe pain and difficulty swallowing.

Vulvovaginal Infection

Infection occurs in association with prior antimicrobial administration, oral contraceptive use, intrauterine devices, Human Immunodeficiency Virus (HIV) infection, diabetes, and pregnancy. Common symptoms are itching and discharge, dysuria, and dyspareunia. Diagnosis is made by the appearance of the lesion aided by a wet mount or potassium hydroxide (KOH) test of vaginal discharge.

Lower Urinary Tract infection

Chronic indwelling bladder catheters are the usual predisposing condition. Patients may not mount fevers or other signs or symptoms of infection. Colonization of the bladder in this setting must be differentiated from infection to avoid unnecessary antifungal therapy.

Balanitis

Vesicles on the penis change into lesions resembling thrush. Severe itching and burning sensation are the main symptoms. *Candida* balanitis can be acquired through sexual intercourse.

B. NONINVASIVE, BUT POTENTIALLY SERIOUS INFECTION

Chronic Mucocutaneous Candidiasis

A rare syndrome that starts early in life and is associated with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED).[10] Patients experience a severe and recurrent form of mucocutaneous infections, onychomycosis, vaginitis, and esophagitis. Chronic and disfiguring skin lesions may occur on the face, scalp, and hands.

Esophageal Infection

Esophagitis often coexists with oropharyngeal infections and shares the underlying host factors. Chronic consumption of alcohol is also a predisposing factor. Coinfection with herpes group virus frequently occurs in immunocompromised patients. Infection may spread to the stomach and duodenum. Esophageal perforation has been reported.[41, 42]

Symptoms include pain on swallowing in the substernal area (odynophagia) which varies from mild to severe enough to prevent swallowing altogether. Herpetic coinfection increases the severity and duration of pain.

Diagnosis is made from the symptoms and confirmed by the appearance during the esophagogastric endoscopy or by the microscopic examination and culture of the esophageal tissue.

Tracheobronchitis

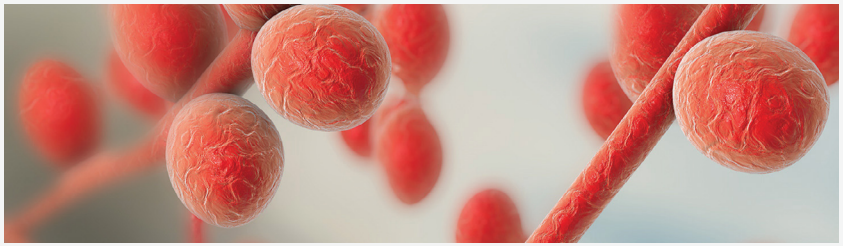
Mild infections are self-limited and associated with a persistent cough.[43] For critically ill patients in the intensive care unit (ICU) and immunocompromised patients, tracheobronchitis may be the source of bloodstream and lower airway infections.

C. INVASIVE INFECTION

Endocarditis

Candida endocarditis usually involves prosthetic heart valves. Other predisposing factors include intravenous drug use and indwelling central-line associated fungemia.

Understanding the difference between colonization and infection is the first step in the prudent use of antifungals.



Images included throughout are not intended to reflect the specific fungal species summarized within the manual.

Physical examination may reveal a new heart murmur, fever, and embolic manifestations. Endophthalmitis secondary to fungemia can cause pain and a decrease in visual acuity that could result in blindness. Endophthalmitis may occur from fungemia without endocarditis.

Esophagitis in Critically Ill and Immunosuppressed Patients

There are multiple case reports of esophageal perforation due to *Candida* esophagitis in children, elderly patients with multiple comorbidities, and recipients of hematopoietic stem cell transplantation.[41, 42] These patients abruptly develop perforation of the esophagus followed by severe sepsis. The usual symptoms and indolent clinical courses common to the immunocompetent patients were not evident before the perforation occurred.

Antifungal prophylaxis could be started in high-risk patients in adult ICUs with a high rate (>5%) of invasive candidiasis.[44]

Hepatosplenic Candidiasis (Chronic Disseminated Candidiasis)

Candidemia and neutropenia precede the onset of persistent and occasionally high fever, right upper quadrant pain, nausea, and abnormal alkaline phosphatase. These symptoms start during the recovery period from immunosuppression. Small abscesses develop in the liver, spleen, and kidneys. Computed tomography, ultrasound, or magnetic resonance imaging may visualize these abscesses. Prolonged antifungal therapy with corticosteroids is usually indicated.[10,44]

Peritonitis

Peritoneal seeding of *Candida* can occur secondary to the perforation of the abdominal viscus, abdominal surgery, or as a complication of peritoneal dialysis. The perforation of the upper gastrointestinal tract is prone to *Candida* peritonitis and abscess. Fever, abdominal pain, and tenderness are usually present. Diagnosis depends on predisposing factors as well as a Gram stain, cultures, and white blood cell (WBC) count of the dialysis effluent or ascites. The proportion of WBC count greater than 50% is supporting evidence of peritonitis.

In dialysis-associated peritonitis, the effluent may appear cloudy or contain debris. The catheter should be removed immediately if fungal peritonitis is confirmed. The duration of antifungal treatment is 2 weeks after catheter removal. Intraabdominal instillation of an antifungal drug is not recommended.[45]

Tracheobronchitis, Pneumonia, and Empyema

Invasive tracheobronchitis and pneumonia are life-threatening diseases in critically ill patients in the ICU and immunocompromised patients. *Candida* pneumonia is rare, but acute respiratory failure due to pneumonia has been associated with a mortality rate of up to 90%.[45] For patients in the ICU, risk factors include corticosteroid treatment, diabetes mellitus, liver cirrhosis, COPD, and influenza.[44] Most patients require mechanical ventilation due to respiratory failure. Symptoms include a cough, fever, and shortness of breath. Empyema may cause pleuritic chest pain.

Osteoarticular Infection

Bone and joint infections occur from fungemia or direct inoculation of conidia from contiguous sources such as trauma, surgery, intravenous drug use, or as a complication of

contaminated injectable medications. Joint infections and discitis are painful, whereas vertebral osteomyelitis could develop slowly with vague discomfort at the onset.

Central Nervous System Infection

Candidemia, trauma, infected ventricular shunts, and contaminated surgical procedures are the most frequent sources. AIDS is also a predisposing factor.[46] Meningitis is the most frequent manifestation, but multiple microabscesses can occur. Diagnosis in newborns is difficult. Symptoms include fever, headache, stiff neck, irritability, and altered sensorium.

A diagnosis can be made via the following:

- *Candida* species stain as Gram-positive yeasts with buds, nonseptate pseudohyphae, or both
- Culture from blood, body fluid, secretion, and tissue
- Serologic test: Beta-D-glucan (BDG), T2 Magnetic Resonance Assay, PNA-FISH, MALDI-TOF, T2Candida

Note: The isolation of a fungus or the diagnosis of a fungal infection can be complex. In each section of this chapter where tests for diagnosis are provided, it should be noted that more tests will build a stronger diagnosis. They are considered, in the best case scenario, to all be beneficial or required; however, depending on the institution, not all may be available.

Treatment can be empiric or targeted to the culture results.[44]

- Empiric
  - Critically ill patients in the ICU with risk factors for invasive candidiasis (devices including indwelling intravascular catheters) and no other known cause for fever. Clinical assessment of risk factors, surrogate markers for invasive candidiasis, and culture data from nonsterile sites should be reviewed
  - Immediate therapy in patients in septic shock with the above risk factors
- Targeted
  - When cultures demonstrate growth of *Candida* spp. It is recommended to obtain susceptibility test on all isolates when possible

Antifungal prophylaxis could be started in high-risk patients in adult ICUs with a high rate (>5%) of invasive candidiasis.[44]

DO-NOT-TREAT[44]

- The growth of *Candida* from respiratory secretions (IDSA guidelines offer no qualification to this recommendation. However, the decision should be based on the assessment of the patient)
- Asymptomatic candiduria except for neutropenic patients, very low birth weight infants, and patients scheduled for urologic manipulation

COCCIDIOIDES SPECIES

Coccidioides immitis has been reclassified into 2 species, *C. immitis* and *C. posadasii*. *C. immitis* infections are concentrated in California, whereas *C. posadasii* has been isolated from patients in other states and other countries.[47,48] Inhaled arthroconidium transforms into a spherule, which starts the inflammatory reaction. A single arthroconidium is sufficient to cause respiratory infection. Up to two-thirds of all infections due to *Coccidioides* species are mild enough not to prompt medical evaluation. The severity of the initial respiratory infection frequently does not correlate with the likelihood of the late-onset complications.[47] Pregnancy is a distinct risk factor for the development of severe and disseminated coccidioidomycosis.

Respiratory Infection

Respiratory infections include several stages of an early primary infection of pneumonia, a nodular or cavitary disease, and chronic fibrocavitary pneumonia. Pulmonary nodules and cavities appear at any stage. The transitional process may take several weeks to several months. Early symptoms include a cough, chest pain, shortness of breath, arthralgia, and fever. The illness resembles community-acquired pneumonia associated with rheumatologic, cutaneous, or systemic complaints.[48,49]

Erythema nodosum and erythema multiforme may occur. Chest radiographic findings are abnormal in more than half of patients with early infection. While most early respiratory infections resolve without complications, diffuse pulmonary infiltrates and respiratory failure may occur in patients with cellular immunodeficiency, including HIV-infected patients with the $CD4^+$ counts less than 100 cells/mm^3 or with rare mutations involving interferon-γ, interleukin 12, and other cellular immune pathways.

The coccidioidal cavity may close over time, cause respiratory symptoms, become a nest for mycetoma or rupture into the pleural space, which requires prompt surgical intervention for decortication and resection of the cavity, as well as antifungal therapy.[48]

Chronic fibrocavitary pneumonia characterized by pulmonary infiltrates and pulmonary cavitation is associated with diabetes mellitus and preexisting pulmonary fibrosis.

Extrapulmonary Disseminated Infection

Risk factors for dissemination include the later stages of pregnancy, advanced HIV infection, therapies to prevent solid organ rejection after transplantation, long-term and high-dose corticosteroid treatment, tumor necrosis factor inhibitors, and Hodgkin's lymphoma.[47,48] Skin is the most common target of dissemination followed by joints and bones.

Coccidioidal meningitis develops within 6 months of the initial infection. Complications may include hydrocephalus (especially common in children), vasculitis, and abscesses.

DIAGNOSIS

- Identification of spherules by cytology or KOH preparation. Hematoxylin and eosin stain (H & E) and special stains (calcofluor stain, PAS)
- The culture of the fungus from various specimens
- Serological testing: Enzyme-linked immunosorbent assay (EIA), immunodiffusion for complement-fixing antibodies (IDCF), complement fixation (CF), and precipitin tests
- Radiographic results are often not specific

Note: The isolation of a fungus or the diagnosis of a fungal infection can be complex. In each section of this chapter where tests for diagnosis are provided, it should be noted that more tests will build a stronger diagnosis. They are considered, in the best case scenario, to all be beneficial or required; however, depending on the institution, not all may be available.

TREATMENT

- Empiric treatment is recommended for suspected infection
- Targeted treatment is indicated when growth is confirmed[50]

PROPHYLAXIS

- All patients undergoing organ transplantation in an endemic area without active infection should receive prophylactic therapy
- No prophylaxis for recipients of biological response modifiers (BRMs) without active infection (screen with *Coccidioides* serology before initiation of BRMs)

DO-NOT-TREAT[48]

- An asymptomatic pulmonary nodule or cavity when there are no overt immunosuppressing conditions

- A nonmeningeal initial infection during the first trimester of pregnancy: No therapy with close monitoring (an option with the weak recommendation, low evidence)

CRYPTOCOCCUS NEOFORMANS

An encapsulated fungus transmitted through inhalation, *Cryptococcus* demonstrates an affinity for the respiratory and central nervous systems. *C. neoformans* transformed from a relatively uncommon human pathogen to one of the most prevalent, with the advent of immunocompromised human populations, including those infected with HIV. At the beginning of the HIV pandemic, cryptococcal meningoencephalitis was a common presenting illness that defined AIDS. The distinct polysaccharide capsule enhances pathogenicity by producing multiple detrimental effects on human defense mechanisms.[51] Rarely, *Cryptococcus neoformans* var. *gattii*, *C. laurentiis*, and *C. albus* cause infections.

Pulmonary Infection

The manifestations of lung involvement range from asymptomatic colonization to life-threatening pneumonia. In the severely immunosuppressed patient, fever, chest pain, and shortness of breath are associated with rapidly progressive pneumonia. Many patients with pneumonia may present with CNS infection at the onset of the disease. The radiographic appearance of the lungs is not characteristic and may resemble pneumocystosis and other opportunistic lung infections. The examination of cerebrospinal fluid (CSF) for evidence of meningeal involvement is indicated if the pulmonary disease is associated with a positive cryptococcal antigen in the serum.[51]

For the immunocompetent host with a noncalcified nodule(s) but no pulmonary symptoms, treatment rather than observation is recommended.[51] Repeatedly positive sputum cultures for *Cryptococcus* in the immunocompetent host, but without a pulmonary lesion, cryptococcal antigen in serum, or *Cryptococcus* isolated from the CSF and urine may represent endobronchial colonization. Antifungal treatment is not recommended.[51]

Central Nervous System Infection

Cryptococcus spreads to the meninges through the bloodstream from the lungs. A headache, fever, cranial nerve palsies, altered sensorium, or defects in cognitive functioning may evolve over several weeks. The spectrum of infection ranges from meningitis, meningoencephalitis, and a space-occupying lesion(s). CSF examination with India ink preparation demonstrates distinct encapsulated yeast. In patients with AIDS, the higher burden of cryptococci in the CSF results in higher antigen titers and slower response to therapy. The possibility of coinfection with *Toxoplasma gondii*, tuberculosis or CNS lymphoma needs to be considered. The advent of highly effective antiretroviral therapy has reduced the incidence of CNS cryptococcosis, but the mortality and morbidity are still high in sub-Saharan Africa.[52] Globally, cryptococcal meningitis is responsible for 15% of AIDS-related deaths.[53]

Eye involvement occurs in almost half of patients with meningitis.[51]

Skin Infection

A skin lesion that resembles a papule, ulcer, skin cancer or acne vulgaris is usually a marker of disseminated infection. A biopsy should be considered in immunocompromised hosts at risk of cryptococcosis.

Other rare cryptococcal infection sites include bone, genitalia, and the prostate gland.

Diagnosis can be made via the following:

- Direct examination of body fluids with India ink preparation
- Special stain (Gomori's methenamine silver, mucicarmine, or Fontan-Mason) on tissue
- The culture
- Serology: Latex agglutination, ELISA, Lateral Flow Assay (LFA)

Note: The isolation of a fungus or the diagnosis of a fungal infection can be complex. In each section of this chapter where tests for diagnosis are provided, it should be noted that more tests will build a stronger diagnosis. They are considered, in the best case scenario, to all be beneficial or required; however, depending on the institution, not all may be available.

PROPHYLAXIS[54]

- HIV-infected patients
  - Not routinely recommended in the United States and Europe
  - Recommended in areas with limited HAART availability, high levels of antiretroviral drug resistance, and a high burden of disease

DO-NOT-TREAT

- Positive sputum cultures for *Cryptococcus* in an immunocompetent patient, but without a pulmonary lesion, cryptococcal antigen in serum, or *Cryptococcus* isolated from the cerebrospinal fluid and urine[51]

FUSARIUM

Of more than 50 fusarium species, 12 species cause human infection. *F. solani*, *F. oxysporum*, and *F. verticillioides* are the most frequent pathogens. Inhalation of fusarial conidia and wounds contaminated with the fungus that is commonly found in soil are the usual portals of entry to the human body.

The spectrum of infections ranges from a superficial skin infection, catheter-associated bloodstream infection, and contact lens-associated keratitis to disseminated infection.

Eye Infection

Fusarium solani is a common cause of fungal keratitis associated with trauma and patients that use contact lenses. Topical natamycin and amphotericin B are the traditional initial treatment, but topical voriconazole is also effective. Visual loss, corneal perforation, and endophthalmitis may occur.

Skin Infection

Preexisting skin lesions progress to invasive infection in immunocompromised patients. They start as papules or painful nodules and turn purple and necrotic. These lesions are often the first manifestation of dissemination.

Disseminated Infection

Prolonged neutropenia due to hematologic malignancy and severe T-cell immunodeficiency are predisposing factors for invasive and disseminated infection. Symptoms of disseminated infection include fever and myalgia unresponsive to an empiric antimicrobial agent. Prognosis is especially poor in immunocompromised patients with persistent neutropenia and recent corticosteroid therapy.

The intrinsic resistance of *Fusarium* to antifungals explains the high mortality rate of 50% to 80% in patients with persistent neutropenia. However, despite the intrinsic resistance, in vitro testing remains useful because many *Fusarium* species show species-specific antifungal profile.[55]

DIAGNOSIS

- Isolation from tissues or body fluids. In a tissue, fusaria may resemble *Aspergillus*
- Blood culture: Positive in 50% of disseminated infections
- Serology: A positive (1, 3)-β-D glucan test and a negative galactomannan differentiates *Fusaria* from *Aspergillus*
- Matrix-assisted Laser Desorption Ionization Mass Spectrometry (MALDI-TOF MS) for *F. fujikuroi* complex
- PCR in blood and tissues

Note: The isolation of a fungus or the diagnosis of a fungal infection can be complex. In each section of this chapter where tests for diagnosis are provided, it should be noted that more tests will build a stronger diagnosis. They are considered, in the best case scenario, to all be beneficial or required; however, depending on the institution, not all may be available.

HISTOPLASMA CAPSULATUM

Histoplasmosis is acquired by inhalation of mycelia and microconidia. *Histoplasma* is responsible for a broad spectrum of pulmonary as well as disseminated infections.

Eye Infection

A multifocal chorioretinitis presumably caused by *Histoplasma* infection, referred to as presumed ocular histoplasmosis syndrome (POHS), is associated with blind spots and distorted vision at a later stage of the infection. *Histoplasma* is not present in eye lesions consisting of neovascularization, uveitis, or choroiditis. Circumstantial evidence of *Histoplasma* infection includes a positive skin test to histoplasmin, intrathoracic calcification, and geographic association to the endemic region.[56] In 2003, products of *H. capsulatum* DNA were identified in the macular and midchoroidal uvea of an enucleated eye from a patient who had been diagnosed with POHS.[57]

Pulmonary and Mediastinal Infection

Acute primary infection of the lung for most patients is no different in clinical manifestations from other mild respiratory infections, including influenza. Typical symptoms are fever, headache, cough, and chest pain. The symptoms usually subside within 10 days. Erythema nodosum and erythema multiforme may occur during the early stages. Chest radiographic findings include patchy infiltrates that eventually calcify. Perihilar, as well as mediastinal, lymphadenopathy is characteristic but not pathognomonic.

Acute primary infection of the lung for most patients is no different in clinical manifestations from other mild respiratory infections, including influenza.

Acute pericarditis may occur as a delayed manifestation of acute infection in less than 10% of patients.[56] *Histoplasma* is not present in the pericardial tissues or pericardial effusion. The patients respond to anti-inflammatory agents.

Chronic cavitary pulmonary histoplasmosis is associated with the preexisting emphysematous pulmonary disease. Thickening of the walls of the bullae with subsequent necrosis and increasing fibrosis is common and ultimately results in the formation of large persistent cavities.[58] Granulomatous mediastinitis or mediastinal granuloma is a complication of the infection of mediastinal lymph nodes. Mediastinal fibrosis, or fibrosing mediastinitis, is an uncommon complication of pulmonary infection. Fibrosis of the mediastinal structures progresses as a result of infected mediastinal lymph nodes.[58]

Progressive Disseminated Infection

Acute progressive disseminated histoplasmosis may occur during acute infection in the elderly and very young (less than 2 years of age), but primarily in immunosuppressed patients, including those infected with HIV.[58] The infection progresses rapidly with diffuse pulmonary infiltrates leading to acute respiratory distress syndrome and multiorgan failure with a high rate of mortality. Bone marrow biopsy and culture is needed to confirm the diagnosis.

Chronic progressive disseminated histoplasmosis occurs in mostly older adults who are not overtly immunosuppressed. These patients have no obvious immunosuppression, but their macrophages cannot effectively kill *H. capsulatum*.[58] A specific defect in the cellular immune response to the organism could be the underlying factor. Common symptoms are fever, malaise, anorexia, and weight loss. Characteristic well-circumscribed and deep ulcers develop on the tongue and oral cavity, as well as the labia, glans of the penis, intestinal tract, endovascular structures, the central nervous system, and adrenal glands. Hepatosplenomegaly, chronic granulomatous hepatitis, chronic meningitis, bone infection, and endocarditis can occur.[56,58]

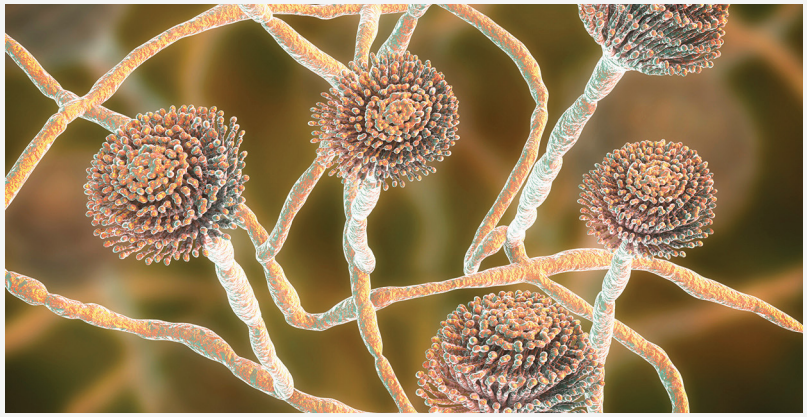
DIAGNOSIS

- Histopathology: Special stain on tissues: Periodic acid-Schiff (PAS) stain, Gomori's methenamine silver (GMS), Grocott silver
- Peripheral blood smear in disseminated infection (intracellular organisms in neutrophils)
- The culture of bone marrow, tissues, and body fluids
- Serology: Complement fixation, immunodiffusion, (high false-negative results), and latex agglutination
- Western blot, ELISA, PCR

HIV infected patients with CD4 <150 cells/mm^3 and potentially other immunosuppressed patients should be considered candidates for prophylaxis. Treatment should be undertaken for documented infections. The selection of the treatment agent will depend on the site and the severity and duration of the infection.[59]

DO-NOT-TREAT[59]

- Mild-to-moderate acute pulmonary infection of less than 1 month



The isolation of a fungus or the diagnosis of a fungal infection can be complex. In each section of this chapter where tests for diagnosis are provided, it should be noted that more tests will build a stronger diagnosis. They are considered, in the best case scenario, to all be beneficial or required; however, depending on the institution, not all may be available.

- Mediastinal fibrosis (treatment may be warranted if clinical findings cannot differentiate mediastinal fibrosis from mediastinal granuloma)[59]
- Mediastinal lymphadenitis
- Pulmonary nodule (histoplasmoma)

MUCORMYCOSIS

Mucorales is one of the 2 orders in the class Zygomycetes, the other being Entomophthorales. Mucormycosis is used synonymously with zygomycosis. Most human infections are caused by the 3 genera—*Rhizopus*, *Lichtheimia*, and *Mucor*. Infection develops after inhalation of sporangiospores or direct inoculation.

Mucormycosis has emerged as the third most common invasive mycosis after aspergillosis and candidiasis in patients with hematological and allogeneic stem cell transplantation, prolonged neutropenia, poorly controlled diabetes mellitus, and less frequently, the recipients of organ transplantation.[60,61] Iron-overload situations, with or without medications to manage this condition, increase the risk. Patients with no immunosuppression may develop a cutaneous infection. Other predisposing conditions are trauma and voriconazole prophylaxis in immunocompromised patients. Increase in mucormycosis has also been linked with the increasing use of voriconazole, and zygomycetes isolated from patients who had received voriconazole were resistant to voriconazole treatment.[30]

Skin Infection

Contaminated bandages, trauma, and burns may lead to superficial infection. Symptoms include pain, warmth, excessive redness, or swelling around a wound. The skin infection may spread to muscles and other organs by way of vascular invasion. The typical presentation of cutaneous mucormycosis is a necrotic eschar accompanied by surrounding erythema and induration.[30]

Rhino-orbital-cerebral Infection

A fulminant process that starts from the nose, extending into the facial structures (including the palate and eyes) causes pain, fever, swelling, headache, and proptosis. A black eschar is a characteristic manifestation of advanced skin involvement. Symptoms include facial pain, headache, and fever. Altered mental status indicates the invasion of the central nervous system. Brain abscess, thrombosis of the cavernous sinus, and carotid artery may occur. Fatality is high regardless of treatment.[61]

Pulmonary Infection

Persistent fever, shortness of breath, cough, and chest pain are common early symptoms. Imaging test results are not different from other opportunistic infections. Bronchial obstruction and hemoptysis from endobronchial mucormycosis, pulmonary artery aneurysms, and cavitary pneumonia may also occur. The air-crescent sign, similar to aspergillosis, may be present. The combination of multiple lung nodules and pleural effusion seen in the early stage could differentiate mucormycosis from other infections. Mortality of mucormycosis of the lung is greater than 80%.[61]

Gastrointestinal Infection

Abdominal pain, nausea, vomiting, and gastrointestinal bleeding are the most common symptoms. Infection may occur in any part of the gastrointestinal tract including the spleen, liver, and pancreas. Diagnosis is usually made postmortem because

the initial presentation is nonspecific. Endoscopic biopsy and specific diagnostic tests should be considered. Gastrointestinal mucormycosis can also involve the liver, spleen, and pancreas.[61]

Disseminated Infection

- Dissemination can originate from any form of mucormycosis. The infections described above including skin lesions may be the source or the results of dissemination. As dissemination typically occurs in people with multiple comorbidities, it may be difficult to recognize early symptoms related to mucormycosis.[30,61]

DIAGNOSIS

- 1, 3, beta-D-glucan test is negative (differentiation from aspergillosis)
- Culture and histopathology of tissue
- The special stain of sputum or body fluids (KOH, calcofluor white, GMS)
- DNA probes after PCR

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PARACOCCIDIOIDES BRASILIENSIS

Paracoccidioidomycosis occurs only in Latin American countries between 23˚ N and 34˚ S.[62] The fungus is transmitted by inhalation, but its habitat is not well-defined. Infected patients are predominantly male and are not immunocompromised.

Pulmonary Infection

The lungs are the primary target organs. There are 2 clinical presentations: a juvenile form, which is more acute and severe, and a chronic adult form.[62] A cough with occasional hemoptysis and shortness of breath are nonspecific symptoms. The radiographic findings include bilateral extensive pulmonary infiltrates, cavities, bullae, and emphysema.

Other Infections

Mucocutaneous encrusted ulcers often coexist with pulmonary infections. Mucous membrane ulceration of the mouth and nose may spread to the lymphatic system. Systemic infections involving multiple organs may occur.

Diagnosis may involve the following:

- A wet mount of various specimens reveal characteristic translucent walls with multiple budding
- Histopathology and the culture
- Serology: Agar gel immunodiffusion test, complement fixation test

Note: The isolation of a fungus or the diagnosis of a fungal infection can be complex. In each section of this chapter where tests for diagnosis are provided, it should be noted that more tests will build a stronger diagnosis. They are considered, in the best case scenario, to all be beneficial or required; however, depending on the institution, not all may be available.

SCEDOSPORIUM SPECIES[63,64]

The genus *Scedosporium* consists of 2 medically significant species: *Scedosporium apiospermum* (and its sexual state *Pseudallescheria boydii*) and *Scedosporium prolificans*. *Scedosporium* spp. are increasingly recognized as causes of invasive infections in immunocompromised patients. The organisms cause a broad spectrum of infections, including mycetoma, colonization of the airways, sinopulmonary infections, extrapulmonary infections, and disseminated infections.

Sputum colonization may occur in patients with AIDS, cystic fibrosis, bronchiectasis, and recipients of liver or lung transplants.

The treatment of *Scedosporium* spp. is often difficult, particularly as numerous small abscesses are not amenable to surgical intervention, as inadequate debridement impedes the penetration of systemic antifungals. The addition of GM-CSF and interferon-gamma (IFN-γ) has been shown to increase the antifungal activity of PMNs due to the enhancement of phagocytosis and oxidative burst leading to increased hyphal damage.

DIAGNOSIS

Scedosporium can be misidentified as other molds such as *Aspergillus* spp. and *Fusarium* spp.

- Skin culture from skin infections in nonimmunosuppressed patients
- Blood and tissue culture from immunosuppressed patients

SPOROTHRIX SCHENCKII

S. schenckii infection is most often limited to the skin and subcutaneous tissues and is associated with minor trauma while handling plant matter.[65] Scratches or bites from animals, especially cat-bites, also cause skin infection. Symptoms depend on the site of infection. Skin infections typically start with a painless small bump that turns into a chronic ulcer. Lymphatic systems are often involved. Bursitis and septic arthritis can occur. In rare cases, the infection disseminates to the lungs and central nervous system in patients with alcohol abuse or immunosuppression.

DIAGNOSIS:

- Skin biopsy for special stain and culture
- Serology: Latex agglutination test

Note: The isolation of a fungus or the diagnosis of a fungal infection can be complex. In each section of this chapter where tests for diagnosis are provided, it should be noted that more tests will build a stronger diagnosis. They are considered, in the best case scenario, to all be beneficial or required; however, depending on the institution, not all may be available.

Other Rare Fungi[66]

Rare groups of fungi that exist as commensals occasionally cause invasive infections in patients with intravascular catheters or a compromised immune system. Isolation of these fungi from blood or tissue should not be considered contamination. These fungi are:

Dematiaceous and other dark-walled fungi, *Lacazia loboi*, *Malassezia furfur*, *Penicillium marneffei*, *Pichia anomala*, *Rhodotorula* spp., *Rhinosporidium seeberi*, *Saccharomyces cerevisiae*, *Trichosporon* spp., *Exserohilum*, and *Wangiella jeanselmei*.

Conclusions

The treatment of fungal infections is becoming increasingly complicated due to myriad reasons, including increased numbers of immunocompromised patients, increasing resistance of fungi to antifungals, and emerging new pathogenic fungi. Invasive fungal infections are treated either preemptively, empirically, or prophylactically with antifungals because of the potential for serious morbidity and high mortality.

Antifungal therapy is fraught with challenges due to the inherent characteristics of fungi and antifungals and the development of resistance, and lack of compliance with accepted clinical practice guidelines and recommendations on the treatment of fungal infections. Resource-poor regions of the world often cannot afford the older generation antifungals that have been available in the market for decades.

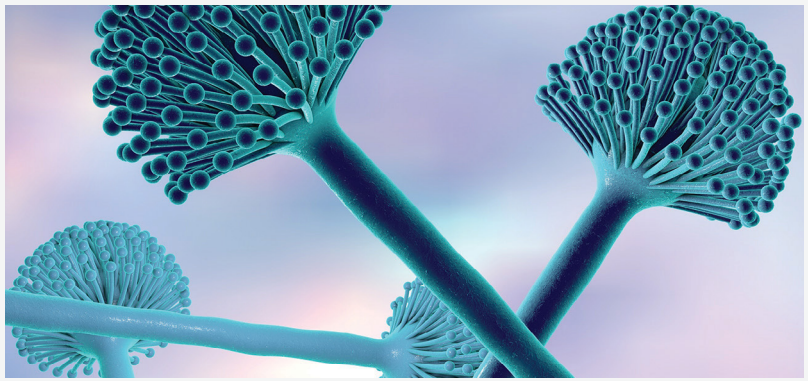
In these contexts, the need for antifungal stewardship becomes ever more important to provide guidance on the use of the limited number of antifungals not only prudently, but parsimoniously. During the formative years of antifungal stewardship in the past several years, a consensus on the effective antifungal stewardship program has emerged.

Implementing a robust antifungal stewardship program will be detailed in the other chapters of this resource, however in summary, for the antifungal stewardship program to be successful, it is:

- Chartered with a full administrative and financial support of the top management of the organization
- Inclusive of all patient care departments or services
- Built around an interdisciplinary group of interested, influential healthcare professionals with infectious disease experience, including pharmacists and physicians
- An ongoing activity
- Inclusive of patients and families

The antifungal stewardship program needs written policy and procedures that include:

- The program's vision, mission, measurable performance indicators, and staffing needs
- An educational plan for staff as well as patients and families
- Meeting schedules, a standing agenda and additional topics for discussion



Not all initial efforts for antifungal stewardship will be able to include all of the elements highlighted above. Each program should attempt to prioritize the initial needs based on the scope, complexity, and available resources of the organization.

- The program's accountability to the applicable oversight mechanism of the hospital
- A statement on neutrality by building a firewall between the staff of the program and the pharmaceutical industry and representatives and, if applicable, a purchasing department of the organization
- A clearly defined interventional methodology

The antifungal stewardship program should be monitored for effectiveness. Examples of measurable indicators are:

- The quantity of antifungals prescribed or the expenditure on the purchase of antifungal over time.
- Defined daily dose (DDD), days of treatment (DOT), or the total doses or costs of antifungals prescribed may be used
- The pattern or trend of antifungal resistance. An antibiogram published regularly and shared with caregivers
- The proportion of interventions accepted by the caregivers

The activity of the antifungal stewardship program may also include:

- Controlling the size of the antifungal formulary
- Preapproval for all or selected antifungal prescription or order
- Stopping or changing antifungal treatment or adjusting the dose based on the reports from the microbiology laboratory
- Development of guidelines for fungal infection
- Educating hospital staff
- Providing clinical breakpoints, the plasma concentration of antifungals, and other pharmacokinetic services to the clinicians in collaboration with the local or regional laboratory
- Ongoing monitoring of the efficacy of the antifungal stewardship program

Not all initial efforts for antifungal stewardship will be able to include all of the elements highlighted above. Each program should attempt to prioritize the initial needs based on the scope, complexity, and available resources of the organization. The effectiveness should then be monitored for continuous performance improvement, using its own indicators or some of the examples described in this resource.

References

1. Cosgrove SE. The relationship between antimicrobial resistance and patient outcomes: Mortality, length of hospital stay, and health care costs. *Clin Infect Dis*. 2006;42(Suppl 2):S82-9.

2. Eliopoulos GM, Cosgrove SE, Carmeli Y. The impact of antimicrobial resistance on health and economic outcomes. *Clin Infect Dis*. 2003;36(11):1433-37.

3. Founou RC, Founou LL, Essack SY. Clinical and economic impact of antibiotic resistance in developing countries: A systematic review and meta-analysis. *PLoS ONE*. 2017;12(12):e0189621. doi:10.1371/journal.pone.0189621.

4. Gulshan K, Moye-Rowley WS. Multidrug Resistance in Fungi. Eukaryot Cell. 2007;6(11):1933-1942. Accessed June 17, 2018.

5. Kontoyiannis DP, Marr KA, Park BJ, et al. Prospective surveillance for invasive fungal infections in hematopoietic stem cell transplant recipients, 2001-2006: an overview of the Transplant-Associated Infection Surveillance Network (TRANSNET) Database. *Clin Infect Dis*. 2010;50 (8):1091-100.

6. Imhof A, Balajee SA, Fredricks DN, Englund JA, Marr KA. Breakthrough fungal infections in stem cell transplant recipients receiving voriconazole. *Clin Infect Dis*. 2004;39(5):743-46.

7. Lockhart SR, Etienne KA, Vallabhaneni S, et al. Simultaneous emergence of multidrug-resistant *Candida auris* on 3 continents confirmed by whole-genome sequencing and epidemiological analyses. *Clin Infect Dis*. 2017; 64 (2):134-140.

8. Labbé AC, Poirier L, MacCannell D, et al. *Clostridium difficile* infections in a Canadian tertiary care hospital before and during a regional epidemic associated with BI/NAP1/027 strain. *Antimicrob Agent Chemother*. 2008;52(9):3180-3187.

9. Pépin J, Valiquette L, Cossette B. Mortality attributable to nosocomial *Clostridium difficile*–associated disease during an epidemic caused by a hypervirulent strain in Quebec. *CMAJ*. 2005;173(9):1037-1042.

10. Edwards JE. *Candida species*. In Mandel G, Douglas R, Bennett J, eds. Principles and Practice of Infectious Diseases. 6th ed. Philadelphia, PA: Churchill Livingstone, 2005:2938-57.

11. Oberjé EJM, Tanke MAC, Jeurissen P. Antimicrobial stewardship initiatives throughout Europe: proven value for money. *Infect Dis Rep*. 2017;9(1):42-47.

12. Impact of antibiotic stewardship program interventions on costs. https://www.cdc.gov/antibiotic-use/healthcare/evidence/asp-int-costs.htm. Accessed June 10, 2018.

13. Muñoz P, Valerio M, Bouza E. Antifungal stewardship in daily practice and health economic implications. *Mycoses*. 2015;58(suppl 2):S14-25.

14. Haque A, Hussain K, Ibrahim R, et al. Impact of pharmacist-led antibiotic stewardship program in a PICU of low/middle-income country. *BMJ Open Qual*. 2018;7(1):e000180. doi:10.1136/bmjoq-2017-000180. Accessed June 17, 2018.

15. Infectious Diseases Society of America. The 10 by '20 Initiative: pursuing a global commitment to develop 10 new antibacterial drugs by 2020. *Clin Infect Dis*. 2010;50(8):1081-83.

16. Boucher HW, Talbot GH, Benjamin DK, et al. 10 × '20 Progress—development of new drugs active against Gram-negative bacilli: An update from the Infectious Diseases Society of America. *Clin Infect Dis*. 2013;56(12):1685-94.

17. WHO global strategy for containment of antimicrobial resistance. http://www.who.int/drugresistance/WHO_Global_Strategy_English.pdf. Accessed June 10, 2018.

18. Core elements of hospital antibiotic stewardship programs. https://www.cdc.gov/antibiotic-use/healthcare/implementation/core-elements.html. Accessed June 17, 2018.

19. Dellit TH, Owens RC, McGowan JE, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clin Infect Dis*. 2007;44(2):159-77.

20. Barlam TF, Cosgrove SE, Abbo LM, et al. Implementing an antibiotic stewardship program: guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. *Clin Infect Dis*. 2016;62(10):1197-1202.

21. Joint Commission on Hospital Accreditation. APPROVED: new antimicrobial stewardship standard. *Jt Comm Perspect*. 2016;36(7):1, 3-4, 8.

22. 6th Edition in Depth: The Importance of Antibiotic Stewardship [news release]. Oak Brook, IL: Joint Commission International; March 14, 2017. https://www.jointcommissioninternational.org/6th-edition-in-depth-the-importance-of-antibiotic-stewardship. Accessed June 17, 2018.

23. Apisarnthanarak A, Yatrasert A, Mundy LM, et al. Impact of education and an antifungal stewardship program for candidiasis at a Thai tertiary care center. *Infect Control Hosp Epidemiol*. 2010;31(7):722-27.

24. Kneale M, Bartholomew JS, Davies E, et al. Global access to antifungal therapy and its variable cost. *J Antimicrob Chemother*. 2016;71(12):3599-3606.

25. Clinical and Laboratory Standards Institute. Performance Standards for Antifungal Susceptibility Testing of Yeasts, M60. https://clsi.org/media/1895/m60ed1_sample.pdf. Accessed June 17, 2018.

26. Clinical and Laboratory Standards Institute. Performance Standards for Antifungal Susceptibility Testing of Filamentous Fungi, M61. https://clsi.org/media/1896/m61ed1_sample.pdf. Accessed June 17, 2018.

27. Muñoz P, Rojas L, Cervera C, et al. Poor compliance with antifungal drug use guidelines by transplant physicians: A framework for educational guidelines and an international consensus on patient safety. *Clin Transplant*. 2012;26(1):87-96.

28. Falci DR, Stadnik CMB, Pasqualotto AC. A review of diagnostic methods for invasive fungal diseases: challenges and perspectives. *Infect Dis Ther*. 2017;6(2):213-23.

29. Bellini C, Antonini P, Emmani S, et al. Malignant otitis externa due to *Aspergillus niger*. *Scan J Infect Dis*. 2003;35(4):284-88.

30. Kontoyiannis DP, Lionakis MS, Lewis RE, et al. Zygomycosis in a tertiary-care cancer center in the era of *Aspergillus*-active antifungal therapy: a case-control observational study of 27 recent cases. *J Infect Dis*. 2005;191(8):1350-60.

31. Skiada A, Lanternier F, Groll AH, et al. Diagnosis and treatment of mucormycosis in patients with hematological malignancies: guidelines from the 3rd European Conference on Infections in Leukemia. *Haematologica*. 2013;98(4):492-504.

32. Multistate outbreak of fungal meningitis and other infections – case count [news release]. Atlanta, GA: Centers for Disease Control and Prevention; October 30, 2015. https://www.cdc.gov/hai/outbreaks/meningitis.html. Accessed June 2018.

33. American Thoracic Society. What is allergic Broncho-pulmonary Aspergillosis (ABPA)? *Am J Respir Crit Care Med*. 2014;190(6):3-4.

34. Peral-Cagigal B, Redondo-González LM, Verrier-Hernández A. Invasive maxillary sinus aspergillosis: A case report successfully treated with voriconazole and surgical debridement. *J Clin Exp Dent*. 2014;6(4):e448-51.

35. DelGaudio JM, Swain RE Jr, Kingdom TT, et al. Computed tomographic findings in patients with invasive fungal sinusitis. *Arch Otolaryngol Head Neck Surg*. 2003;129(2):236-40.

36. Paterson DL, Singh N. Invasive aspergillosis in transplant recipients. *Medicine (Baltimore)*. 1999;78(2):123-38.

37. Denning DW, Follansbee SE, Scolaro M, et al. Pulmonary aspergillosis in the acquired immunodeficiency syndrome. *N Engl J Med*. 1991;324(10):654-62.

38. Tsay S, Welsh RM, Adams EH, et al. Notes from the field: ongoing transmission of *Candida auris* in health care facilities - United States, June 2016-May 2017. *MMWR Morb Mortal Wkly Rep*. 2017;66(19):514-5.

39. Arendrup MC, Prakash A, Meletiadis J, et al. Comparison of EUCAST and CLSI reference microdilution MICs of eight antifungal compounds for *Candida auris* and associated tentative epidemiological cutoff values. *Antimicrob Agents Chemother*. 2017;61(6):e00485-17.

40. Chapman SW, Dismukes WE, Proia LA, et al. Clinical Practice Guidelines for the Management of Blastomycosis: 2008 Update by the Infectious Diseases Society of America. https://academic.oup.com/cid/article/46/12/1801/296953. Accessed June 17, 2018.

41. Gock M, Schäfer M, Perren A, et al. Fatal Esophageal Perforation Caused by Invasive Candidiasis. *Ann Thorac Surg*. 2005;80(3):1120-2.

42. Tran HAM, Vincent JM, Slavin MA, et al. Esophageal perforation secondary to angio-invasive *Candida glabrata* following hemopoietic stem cell transplantation. *Clin Microbiol Infect*. 2003;9 (12):1215-8.

43. Johnson DC. Chronic *candida bronchitis*: A consecutive series. *Open Respir Med J*. 2012;6:145-9.

44. Pappas P, Kauffman CA, Andes D, et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2009:48(5):503-35.

45. Li P, Szeto CC, Piraino B, et al. ISPD peritonitis recommendations: 2016 update on prevention and treatment. *Perit Dial Int*. 2016;36(5):481-508.

46. Casado JL, Quereda C, Oliva J, et al. Candidal meningitis in HIV-infected patients: analysis of 14 cases. *Clin Infect Dis*. 1997;25(3):673-6.

47. Calgiani J. Bennet J. *Coccidioides* species. In Mandel G, Douglas R, Bennet J, eds. *Principles and Practice of Infectious Diseases*. 6th ed. Philadelphia, PA: Churchill Livingstone; 2005:3040-51.

48. Galgiani JN, Ampel NM, Catanzaro A, et al. 2016 Infectious Diseases Society of America (IDSA) clinical practice guideline for the treatment of coccidioidomycosis. *Clin Infect Dis*. 2016;63(6):e112-46.

49. Tsang CA, Anderson SM, Imholte S, et al. Enhanced surveillance of coccidioidomycosis, Arizona, USA, 2007-2008. *Emerg Infect Dis*. 2010;16(11):1738-44.

50. Thompson GR 3rd, Barker BM, Wiederhold N. Large-scale evaluation of *in vitro* amphotericin B, triazole, and echinocandin activity against *Coccidioides* species from U.S. institutions. Antimicrob Agents Chemother.61(4):e02634-16.

51. Perfect JR. *Cryptococcus neoformans*. In Mandel G, Douglas R, Bennet J, eds. *Principles and Practice of Infectious Diseases*. 6th ed. Philadelphia, PA: Churchill Livingstone; 2005:2997-3012.

52. Jarvis JN, Harrison TS. HIV-associated cryptococcal meningitis. *AIDS*. 2007;21(16):2119-29.

53. Rajasingham R, Smith RM, Park BJ, et al. Global burden of disease of HIV-associate cryptococcal meningitis: an updated analysis. *Lance Infect Dis*. 2017;17(8):873-81.

54. Perfect JR, Dismukes WE, Dromer F, et al. Clinical Practice Guidelines for the Management of Cryptococcal Disease: 2010 Update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2010;50:291–322.

55. Al-Hatmi, AMS, Curfs-Breuker, I, de Hoog GS, et al. Antifungal Susceptibility Testing of Fusarium: A Practical Approach. Journal Fungi. J Fungi. 2017;(3):19; doi:10.3390/jof3020019. Accessed June 13, 2018.

56. Wheat LJ, Stein L, Corya BC, et al. Pericarditis as a manifestation of histoplasmosis during two large urban outbreaks. *Medicine* (Baltimore). 1983;62(2):110-9.

57. Spencer W, Chan C, Shen DF, et al. Detection of *Histoplasma capsulatum* DNA in lesions of chronic ocular histoplasmosis syndrome. *Arch Ophthalmol*. 2003;121(11):1551-5.

58. Kauffman CA. Histoplasmosis: a clinical and laboratory update. *Clin Microbiol Rev*. 2007;20 (1):115-32.

59. Wheat LJ, Freifeld AG, Kleiman MB, et al. Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2007;45:807-25.

60. Petrikkos G, Skiada A, Lortholary O, et al. Epidemiology and clinical manifestations of mucormycosis. *Clin Infect Dis*. 2012.54;(Suppl 1):S23-34.

61. Sugar A. Agents of mucormycosis and related species. In Mandel G, Douglas R, Bennet J, eds: *Principles and Practice of Infectious Diseases*. 6th ed. Philadelphia, PA: Churchill Livingstone; 2005:2973-84.

62. Restrepo A, Tabón AM. Paracoccidioides brasiliensis. In Mandel G, Douglas R, Bennet J, eds: *Principles and Practice of Infectious Diseases*. 6th ed. Philadelphia, PA: Churchill Livingstone; 2005:3062-68.

63. Cortez K, Roilldes E, Quiroz-Telles F, et al. Infections Caused by *Scedosporium* spp. *Clin Microbiol Rev*. 2008;21(1):157-97.

64. Cooley L, Spelman D, Thursky K, et al. Infection with *Scedosporium apiospermum* and *S. prolificans*, Australia. *Emerg Infect Dis*. 2007;3(8):1170-7.

65. Kauffman C, Bustamante B, Chapman S, et al. Clinical practice guidelines for the management of sporotrichosis: 2007 update by the Infectious Disease Society of America. *Clin Infect Dis*. 2007;45(10):1255-65.

66. Hospenthal DR. Uncommon fungi. In Mandel G, Douglas R, Bennet J, eds: *Principles and Practice of Infectious Diseases*. 6th ed. Philadelphia, PA: Churchill Livingstone; 2005:3068-79.

CHAPTER 2:

Making a Business Case for Antifungal Stewardship

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Case Scenario

A multi-hospital integrated delivery system that includes a 1000 bed academic medical center with 17 additional community hospitals, varying in size, recently completed its Strategic Plan for the years 2018-2021. The Communication Plan for the Strategic Plan included meeting with clinical and administrative leaders throughout the system to share the new Together Everybody Achieves More (TEAM) Strategies for success. Historically, the organization had been challenged with less than desirable metrics related to cost, access, and quality. With the new 2018-2021 Strategic Plan, TEAM Strategies for improvement placed emphasis on the alignment of organizational, departmental and clinical outcome goals.

Case Scenario (cont.)

Goals were created that would require quarterly status reports for clinical, quality, and financial improvements. A new incentive plan was introduced for clinical and administrative leaders that included not only required documentation of improvements from baseline related to clinical and financial metrics; but, documentation of examples of the TEAM Strategy. Leaders had to provide examples of the synergy that occurs when clinical and organizational leaders collaborate to enhance quality of care and reduce costs.

The Pharmacy and Infection Prevention and Control Departments report to the Vice-President (VP) and Chief Quality Officer for the system. During the past year, the VP received Pharmacy financial reports that were over budget primarily due to increased antifungal purchases. Infection Prevention and Control Department reports showed increased rates of Multi-Drug Resistance Organisms (MDROs) and *Clostridium difficile* (*C. difficile*) infections that exceeded other comparable organizations as reported on the Centers for Medicare and Medicaid Services (CMS) Hospital Compare website. Based on these reports, the VP requested that the Pharmacy and Therapeutics Committee and the Infectious Disease Prevention Committee develop a TEAM Strategies action plan to address the increased antifungal agent purchases and the adverse patient safety and quality of care issues associated with patient infections. The clinical and administrative leaders decided to evaluate the implementation of an Antifungal Stewardship Program.

Introduction

Antibiotics have saved lives and transformed modern medicine, but they are becoming less effective, due to overuse and the development of MDRO's. Too often antibiotics are used inappropriately, putting patients at risk for developing antibiotic-resistant infections, *C. difficile* infections, as well as other clinical complications. The primary tenants of Antibiotic Stewardship Programs (ASP) are to provide patients the right antibiotic, at the right time, at the right dose and duration of therapy that is streamlined and targeted to the infection being treated.[1] Antimicrobial Stewardship (AMS) and ASP have focused on the appropriate use of antibiotics while antifungal agents have received less attention. Antifungal stewardship (AFS) programs are being incorporated into existing AMS programs at many institutions, because of the high cost of antifungal drugs and the specialized patients to whom they apply.[2] There are many variations of a Stewardship Program; however, the elements of AMS and AFS have much in common with a focus on ensuring the proper use of antimicrobials (antibiotics and antifungals) to

Goals of an antifungal stewardship program:

- *focus on ensuring the proper use of antimicrobials (antibiotics and antifungals)*
- *provide the best patient outcomes, lessen the risk of adverse effects*
- *promote cost-effectiveness*
- *reduce or stabilize levels of microbial resistance*

provide the best patient outcomes, lessen the risk of adverse effects, promote cost-effectiveness, and reduce or stabilize levels of microbial resistance. The AMS focus has been on patient outcomes, preventing toxicity, minimizing cost, and prevent/limit the development of antimicrobial resistance. Both AMS and AFS programs should be developed with a goal to change and direct antimicrobial/antifungal use at a healthcare institution to improve both clinical and financial outcomes, and may employ any number of individual strategies.[3] AMS is designed to ensure the future effectiveness of antimicrobial agents. AFS shares this purpose but is specific to the management of invasive fungal diseases (IFDs) and the high-risk patient populations that are at risk for developing IFDs.

A combination of strategies may be necessary to achieve the desired outcomes of appropriate use of antimicrobials (antibiotics and antifungals). These strategies should be designed with the prevailing local conditions (ie, antimicrobial/antifungal resistance patterns) and target population (eg, immunocompromised patients) in mind. Increased use of antifungal agents and the development of antifungal resistance necessitate optimization of antifungal prescribing. The details for how to develop and implement an ASP have been well described in the 2016 Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) Guidelines.[4] The guidelines will be very beneficial in the process of developing and implementing an AFS. The purpose of this chapter is to make a business case for developing and implementing a comprehensive AFS program.

Implementation of an AFS program:

Overview

A business case is intended to gain the buy in of key decision-makers on the merits of a course of action. It is a key part of the development of a project: a project brief describes what needs to be done, a project plan explains the steps of the project, and the business case sets out why the project is important. A comprehensive business case explains the problem/challenge, identifies all of the viable options to address problem/challenge, and allows decision makers to decide which course of action will be best for the organization.[5]

Developing a business case proposal for AFS should be the responsibility of the senior clinical executive. Although this individual may delegate the actual development of the proposal, he or she provides the appropriate oversight and support. To ensure that an optimal plan for developing a proposal is created, a process improvement team should be established. The Antifungal Stewardship Business Case starts with defining the problem. That is, the "business need" to be solved. Key stakeholders and subject matter experts will be engaged to present what is required to solve the problem and develop alternative approaches to solutions, based on which option is the most cost-effective and efficient.

A business case details the project deliverables, how they will be achieved, what it will cost, and how long it will take. This chapter provides information to assist in meeting the challenges of proposing an AFS Program in the hospital setting with pitfalls to avoid and barriers to overcome. The process presented involves developing a proposal to obtain institutional support for AFS, assembling and leading the AFS core team, analyzing current institutional practices, developing processes to meet AFS goals, and analyzing and reporting data demonstrating the impact of AFS. A multidisciplinary effort with the support of C-Suite Executives, and clinical and financial leaders is essential for success in the business case approval process. This chapter will identify the essential elements of AFS business case development including the following:

- Organizational Assessment of Antifungal Opportunities for Improvement (Gap Analysis)
- Factors to Consider in the Development of a Business Case for Antifungal Stewardship
- Planning Strategically for the Business Case Proposal
- Communicating with the C-Suite Leadership
- What Does Excellence Look Like?
- Conclusions

Organizational Assessment of Antifungal Opportunities for Improvement (Gap Analysis)

The starting point in developing or enhancing a successful AFS is an organizational readiness assessment. Key questions to ask include:

- What are the challenges and opportunities the organization is facing?
- What is the current state, what is the desired future state, and why?
- Does the organization have the right infrastructure to begin the intended change process?
- Does the organization have the right culture to embrace the work?

Ensuring readiness prior to beginning the development of the business case for AFS identifies gaps in the culture and organizational structure that need to be addressed. Transparency and collaboration among clinical and financial leadership teams and across stakeholders will be the driving force behind the assessment.

The AFS should be based on the Centers for Disease Control (CDC)'s Core Elements of an Antibiotic Stewardship Program. The CDC has identified core elements that demonstrate the importance of defined leadership and a coordinated multidisciplinary approach. The core elements are identified in Figure A at right.

C-Suite leadership commitment to the stewardship program is an essential element of success. This leadership commitment sets the stage for accountability throughout the entire organization, and ensures that the stewardship program is properly resourced to achieve the goals. Leaders in Medicine, Nursing, Pharmacy, and the C-Suite are key stakeholders, and must be fully engaged in all stewardship efforts.

Munoz and colleagues identified seven essential elements of antifungal stewardship programs in their article regarding AFS in daily practice.[7] A comparison of the two approaches is provided in Table I. Essential elements presented by Munoz and colleagues are like the CDC but reflect specific differences in the body of knowledge related to populations at risk, diagnostic considerations, and treatment differences for invasive fungal infections (IFIs). Both presentations of core elements for an AFS emphasize that there is not a "one size fits all" solution to implementing stewardship and programs can be deployed via a variety of different mechanisms depending on specific institutional needs.

Figure A: Core Elements[6]

The CDC has developed an excellent tool to serve as a readiness checklist that may be shared with senior management, a senior leader for quality, purchasing directors, clinic managers, nurse managers, key physician leaders, risk managers, pharmacy leaders, infection preventionists and hospital epidemiologists, laboratory staff and information technology staff. For ease of use, the checklist is divided into two sections, one for those just beginning a program, the other for those who wish to enhance an existing program. This CDC Checklist is a tool to assess a stewardship program.[8]

Factors to Consider in the Development of a Business Case for Antifungal Stewardship

A. The Joint Commission and Other Regulatory and Accrediting Agencies

TJC's antibiotic stewardship accreditation standard, Medication Management (MM) Standard MM.09.01.01, effective January 1, 2017, assists in the efforts to improve antibiotic use in hospitals in the United States. Following participation in a White House Forum on Antibiotic Stewardship in June of 2015,

Table I. Comparison of Recommended Elements that Comprise a Stewardship Program

Essential Elements of an AFS Program in Daily Practice as Presented by Munoz et al.[7]	CDC Core Elements for an Antibiotic Stewardship Program[6]
Creation of a Collaborative Group on Mycosis and Antifungal treatment	Leadership commitment
Pre-AFS audit and identification of main AF prescribers	Accountability
Educational programs to offer trainees knowledge in IFI diagnosis and management in clinical practice	Drug expertise
Local guidelines and clinical flowcharts	Actions to improve antimicrobial use
Pharmacy alerts regarding new AF prescribed on a daily basis	Tracking of utilization and outcomes
Implementation of rapid serological and molecular diagnostic tests	Reporting utilization and outcomes
Bedside intervention	Education

The Joint Commission developed the antimicrobial stewardship standard for hospitals, critical access hospitals, and nursing care centers.[9] Extension of this standard to Ambulatory Health Care and Office-based Surgery accreditation programs is anticipated in 2019. Joint Commission standards are the basis of an objective evaluation process that can help healthcare organizations measure, assess and improve performance. The TJC antibiotic stewardship standard will assist in the development of an AFS program with a focus on important patient, individual, and organization functions that are essential to providing safe, high quality antifungal care. Compliance with the standard will help in an organization's efforts to continue accreditation with TJC.

In response to the escalating problem of antibiotic resistance, President Obama implemented an Executive Order that led to the National Action Plan on Combating Antibiotic-Resistant Bacteria.[10] The plan mandates that CMS issue new Conditions of Participation (CoP), to advance compliance with the CDC's Core Elements of Hospital Antibiotic Stewardship Programs. Therefore, in 2016 CMS proposed a similar requirement to TJC in the hospital CoP.[11] Under the rule, hospitals would be required to have hospital-wide infection prevention and control and antibiotic stewardship programs for the surveillance, prevention, and control of healthcare-associated infections and other infectious diseases, and for the appropriate use of antibiotics. Additionally, the organizations must designate leaders of the infection prevention and control program and the antibiotic stewardship program respectively, who are qualified through education, training, experience, or certification. CMS states that institutions should develop and implement an ASP based on national guidelines. These guidelines can include recommendations put forth by the CDC, the Infectious Diseases Society of America (IDSA), the Society for Healthcare Epidemiology of America, and the American Society of Health System Pharmacists (ASHP).

Based on the foregoing discussion, AMS programs are nationally mandated. Data supporting the effectiveness of hospital ASP have been well documented and comparable results should be expected with hospital AFS. Many studies have shown that these programs can improve patient outcomes and reduce antibiotic resistance while saving money by utilizing cost saving and cost avoidance strategies.

The National Quality Forum (NQF) has been instrumental in promoting appropriate antibiotic use spearheaded by the publication of the *National Quality Partners (NQP) Playbook: Antibiotic Stewardship in Acute Care*. NQP's Antibiotic Stewardship Action Team addresses the national priority of antibiotic stewardship to improve public health and patient safety. The Playbook seeks to provide concrete strategies and suggestions for organizations committed to implementing successful ASP programs in acute-care hospitals.[12] The strategies in the Playbook not only pertain to antibacterials but also other antimicrobials such as drugs to fight viruses (antivirals), parasites (antiparasitics), and fungi (antifungals). This publication is supportive of the National Action Plan and links to the CDC Core Elements.

The World Health Organization (WHO) has made addressing antibiotic resistance a strategic priority. A global action plan on antimicrobial resistance was endorsed at the World Health Assembly in May 2015, and has five strategic objectives[13]:

1. Improve awareness and understanding of antimicrobial resistance
2. Strengthen surveillance and research
3. Reduce the incidence of infection
4. Optimize the use of antimicrobial medicines
5. Ensure sustainable investment in countering antimicrobial resistance

The expectation is for organizations worldwide to develop their antimicrobial resistance action plans in line with the global plan. The President's Executive Order and related National Action Plan, the CMS Rule and TJC's Medication Management antimicrobial stewardship standard are examples of approaches within the US consistent with the WHO Action Plan on Antibiotic Resistance. As is evident in this discussion, multiple stakeholders are accountable for prevention of AMR, and for timely and appropriate treatment of Hospital Acquired Infections (HAIs), including hospitals and health plans. For AFS programs to achieve sustainability and succeed, they will need leadership and funding support. Regulatory and accreditation standards can help ensure that support.

B. Impacts of Invasive Fungal Infections

IFDs have a lower incidence relative to infections caused by multi-resistant bacteria, but their health and economic burden are substantial. Pharmacy costs inclusive of antifungal agents are a major determinant of IFD-attributable hospital costs. High drug costs and the toxicities of antifungal agents are the principal rationale for AFS while antifungal resistance is an emerging but less prevalent issue. The high mortality/morbidity associated with IFDs, including adverse impact on curative chemotherapy, combined with suboptimal diagnostic tools, has driven the overuse of antifungal drugs.[2]

Inappropriate antifungal use has contributed to the global increase in antifungal resistance, increased morbidity and mortality, and has played a role in the shift in the etiology of IFDs. Challenges to the appropriate use of antifungals include the unspecific clinical manifestations of IFDs, mainly in immunocompromised and critically ill patients, the poor sensitivity of culture-based microbiologic tests and the pressure to start treatment early due to the high morbidity and mortality of these infections. Empiric antifungal therapy can be both unnecessary and costly.[7]

C. Impacts of Sub-Optimal and Inappropriate Antifungal Use

The estimated annual cost of drug-related morbidity and mortality resulting from non-optimized medication therapy was $528.4 billion, equivalent to 16% of total US healthcare expenditures in 2016.[14] Antimicrobial expenditures across all sectors experienced a decrease of 2.3%, with antibacterials accounting for the largest decrease (-6.5%) and antifungals experiencing the largest increase (4.5%). The portion of antibacterial expenditures attributable to each sector in 2016 was consistent with past findings, with the majority in the retail sector followed by nonfederal hospitals. Except for clinics (2.4% growth), all sectors experienced a decrease in antibacterial expenditures.[15] This decrease is likely attributable to national initiatives to decrease antimicrobial resistance, and efforts to increase antimicrobial stewardship in the community, acute care, and long-term care settings. The direct costs of these infections, in addition to the morbidity and mortality attributable to them as noted above, make a compelling case for comprehensive medication management achieved from an AFS Program.

D. Potential Benefits of an AFS Program

The team preparing an AFS business case proposal needs to ensure that it clearly states the clinical and financial benefits of such a program. The goal of AFS is to achieve optimum clinical outcomes and ensure cost-effectiveness of therapy

while minimizing unintended consequences of antifungal use, including toxic effects, selection of pathogenic organisms, and the emergence of resistance. The characteristics of stewardship programs may vary but generally consist of a range of interventions that can be selected and adapted to fit the infrastructure of any hospital.

Effective stewardship ensures that every patient gets the maximum benefit from the antifungals, avoids unnecessary harm from allergic reactions and side effects, and helps preserve the life-saving potential of these drugs for the future. Improving the appropriate use of antimicrobials in general, have not only demonstrated these benefits but have also been shown to improve outcomes and save healthcare facilities money in pharmacy costs. According to a CDC report, Antibiotic Resistance Threats in the US, ASPs will decrease antibiotic resistance, *C. difficile* infections, and costs and will improve patient outcomes. Further, ASPs help reduce length of stay in hospitals and improve patient care outcomes, which is a benefit to the patient and to the hospital.[16] However, with the widespread use of antibacterials and with increasing numbers of high-risk patients, the emergence and increased rates of serious invasive fungal infections have been seen.

A focus on antibiotic stewardship programs have led to decreases in bloodstream infections caused by resistant bacteria. However, those decreases have resulted in fungal infections such as *Candida*, which is becoming the most common cause of healthcare-associated bloodstream infections in many hospitals across the United States. The development of a few classes of antifungal agents has provided the ability to treat these invasive infections, but just like bacteria, some fungi have developed resistance and no longer respond to the antifungals that are used to treat them. According to the above report, an estimated 46,000 healthcare-associated *Candida* infections occur among hospitalized patients in the United States each year. Roughly 30% of patients with bloodstream infections (candidemia) with drug-resistant *Candida* die during their hospitalization. CDC estimates that each case of *Candida* infection results in 3–13 days of additional hospitalization, and a total of $6,000–$29,000 in direct healthcare costs. Based on these estimates, resistant *Candida* infections may add millions of dollars in excess costs to US healthcare expenditures each year.[16] Although most of the resistance of concern is in *Candida* species, resistance in other fungi also occurs. It's not yet known whether decreasing the use of certain antimicrobial agents can reduce *Candida* infections, but appropriate use of antibacterials and antifungals as described with stewardship programs, is one of the most key factors in fighting drug resistance.

Antimicrobial expenditures had increased by an average of 14.4% annually in the years preceding ASP implementation, decreased by 9.75% in the first year of the program and remained relatively stable in subsequent years, with overall cumulative cost savings estimated at $1.7 million.[17]

While cost reduction may not be the primary objective of a stewardship program, in an ASHP report on the clinical and economic outcomes of a prospective ASP, antimicrobial expenditures, had increased by an average of 14.4% annually in

the years preceding ASP implementation, decreased by 9.75% in the first year of the program and remained relatively stable in subsequent years, with overall cumulative cost savings estimated at $1.7 million.[17] The benefits documented in these reports would logically apply to AFS as well.

E. Barriers to Approvals and Implementation of AFS

Most organizations have limited resources and competition for these resources may be significant. Therefore, a business case for an AFS Program must be strong and based on thorough strategic planning. Proposals must be compelling and based on sound arguments and solid data. The proposal should provide justification for the program based on the specific institutional costs and documented consequences of inappropriate antifungal use (ie, adverse effects, resistance, morbidity, mortality, and HAI). TJC published a free MDRO toolkit, titled "What Every Health Care Executive Should Know: The Cost of Antibiotic Resistance," to assist organizations with a thorough understanding of the clinical and financial adverse impacts of inappropriate antibiotic use. The toolkit discusses stewardship aims that are applicable to AFS Program development and enhancements.

The business case proposal should outline the goals of the AFS based on the scope of the problems identified and available resources. The goals presented in the proposal should be presented as SMART (Specific, Measurable, Attainable, Relevant, and Timely). Short- and long-term goals should be identified through a formal strategic planning process to address anticipated challenges.

Challenges are varied and may differ according to each hospital and healthcare model. The multi-disciplinary team will need to develop strategies to address each of the real and perceived challenges. Based on a survey of infectious diseases physician members of the IDSA Emerging Infections Network (EIN), the multi-disciplinary team will need to address the following for a successful business case proposal[18]:

- Insufficient resources, including funding, time, and people
- Competing initiatives
- Lack of leadership and provider awareness of the value of AFS
- Lack of information technology support and/or inability to get data
- Other specialties alienated by an AFS
- Multiple infectious disease groups within a facility that may provide inconsistent recommendations

Organizational and Individual Sources of Resistance to Change

When developing an AFS business case proposal, it is important for an improvement team to identify potential organizational and individual barriers, and resistance to change. Implementation of an AFS program can be more complicated, more challenging and take longer than expected, in the absence of thorough strategic planning. In addition to identifying which antifungals to target, it is essential to gain approval from diverse stakeholder groups, secure information technology support, get "buy-in" and "ownership" from key influential prescribers, and educate widely to achieve reductions in antibiotic usage. Each hospital must establish AFS protocols and policies and procedures based on their unique staffing, resources, existing practices and organizational culture.

The primary aim of AFS programs is to optimize antifungal drug use and an essential element of the program is to ensure that there is integration of specialist experience and knowledge to tackle the issues related to inappropriate use of antifungal drugs. The core members of the AFS team should consist of

individuals who possess sufficient knowledge of, and experience in, the clinical management of relevant patient populations, fungal epidemiology and susceptibility patterns, the laboratory diagnosis of IFD, pharmacokinetics (PK) of antifungal drugs, dosing and drug–drug interactions.

The first step in the development and implementation of AFS is to build a multidisciplinary team encompassing the necessary expertise to ensure optimal AFS programs and services and to address organizational and individual barriers to change. Optimal composition of an AFS team includes a clinical pharmacist, microbiologist, adult and pediatric Infectious Disease Specialists, nursing, and hematologists. The clinical pharmacist should have specialized infectious diseases understanding of the underlying mechanisms and scientific evidence for different antifungal agents, as well as extensive knowledge of drug PKs to be able to offer institution-specific recommendations on how to manage drug–drug interactions and select the most suitable antifungal for a given clinical condition and IFD.

An important function of a multi-disciplinary team is to evaluate organizational readiness for change specific to antimicrobial stewardship. The credibility of the team depends on the knowledge and experience of its members and the roles they have within their organization. In addition, to be effective, members of the AFS team need to possess effective communication and networking skills, and the ability to collaborate and show a willingness to share responsibilities.[19]

Organizations would be wise to invest in a Project Management Office for a systematic approach to project identification, prioritization, and implementation. Adding an individual with the skills of change management to the multi-disciplinary team is the best way to plan, track, automate, and report on work, enabling you to move from idea to impact. Change management expertise empowers collaboration, drives better decision making, and accelerates innovation. A detailed discussion of the benefits of change management skills is beyond the scope of this chapter, but should not be minimized in the consideration of the importance of such an individual within the multi-disciplinary team.

F. Transitions in Care

When delivering a business case proposal for AFS, organizations should consider the various failure points in care transitions. A complete discussion of the opportunities to improve appropriate use of antifungals across the continuum of care is beyond the scope of this chapter. However, making the connection to other ongoing quality and patient safety initiatives (eg, medication reconciliation), regulatory/accreditation requirements, and operational efficiencies is important for garnering support and achieving a successful AFS proposal. AFS can improve transitions in care by promoting communication effectiveness across disciplines, eliminating handoff errors, and facilitating the transfer of patient care plan information to stakeholders across the continuum of care. A successful business case should help leadership make the connection between clinical quality, reduced costs, and medication safety by highlighting outcomes such as a reduction of ADEs or hospital readmissions due to medication discrepancies carried across the continuum of care.

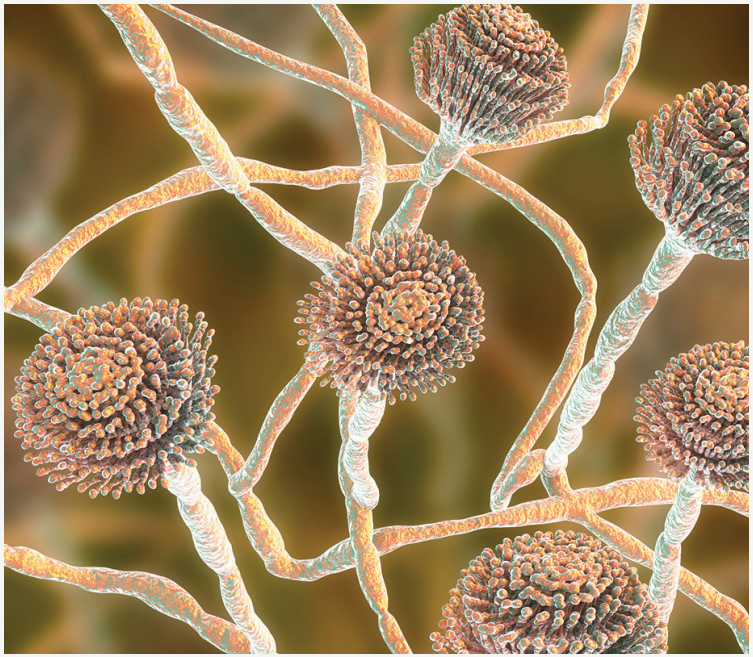
Planning Strategically for the Business Case Proposal

A. A Systematic Approach to Proposal Development

The business case for AFS should be based on a systematic approach to the proposal development to ensure that the following questions are answered[20]:

- What is AFS?
- What is the purpose of AFS?
- What is the impact to patient outcomes?
- What are the primary functions (eg, reduce MDROs) and secondary functions (eg, reduce costs) of AFS?
- What is the Return on Investment (ROI) or Return on Value (ROV)?
- Are there alternatives to AFS? If so, what are the pros and cons of the alternatives?

It is imperative that clinical and financial leaders work together from the beginning of any planning process. While an extensive number of reports of the successes of AMS and ASPs have improved awareness, and understanding of the importance of attention to antimicrobial stewardship, the reality is that healthcare, and the organizations that provide it are fundamentally businesses, and there are numerous competing priorities to ensure financial stability and sustainability. Viewed through the lens that AFS is one of several competing priorities, there is a risk that the healthcare industry will continue to view spending of time and human resources on AMS and AFS programs as solely a cost center. As the current healthcare system is shifting from volume-based reimbursement and fee



It is imperative that clinical and financial leaders work together from the beginning of any planning process.

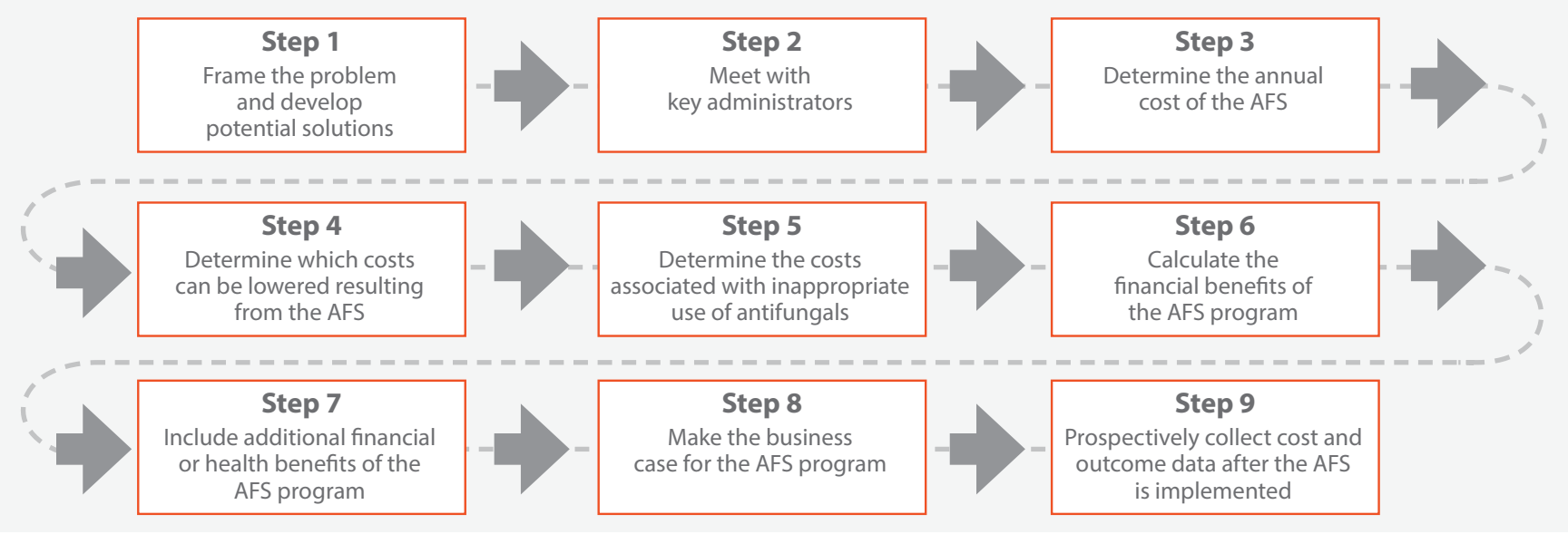
for service to value-based reimbursement, now more than ever healthcare leaders must acknowledge that stewardship is critical to providing value.

Following the organizational assessment (gap analysis) mentioned previously in this chapter, the AFS team leaders must clarify the organization's pathways for business cases and ensure that the approved processes are followed. There will be several steps that your team must take in presenting your case. Depending on the organization, the business plan may need to be presented to multiple key stakeholders and committees. A business case proposal should be built on data that define the problem. The AFS leaders must determine what components are relevant to your business case, including hard and soft dollars, and gather all the clinical and financial data needed. Clinical and financial colleagues can work together to brainstorm and think creatively about what metrics will be most persuasive, particularly when it comes to soft dollars. It is important to remember that the data you include in your business case should be meaningful and compelling.

B. Essential Components of a Business Case Proposal for Antifungal Stewardship to the C-Suite

When of all the relevant clinical and financial data have been gathered, a business case needs to be drafted that is a persuasive presentation of the compelling need for an AFS. Some organizations expect a proposal to be presented as a document to be read thoroughly by decision-making and leadership committees. Therefore, including a brief story as part of your business case may make your proposal more compelling. It puts a human face and experience on something that has occurred within your organization. Likewise, consider whether a brief overview of a root cause analysis (RCA) of an event may be suitable. The process of completing a business case analysis can be broken down into the 9 specific steps shown in Figure B.

Figure B: Process of Completing a Business Case[21]



Based on these steps, some key points to remember are:

- The business case proposal should clearly define and explain the problem of antifungal resistance in the organization and how AFS will address this issue
- AFS leaders should meet with key clinical and organizational leaders in which the leaders provide data that demonstrate that the organization has a problem and to seek leadership support to conduct a multidisciplinary team analysis of the problem and propose potential solutions
- Clinical leaders should work collaboratively with the Finance Department to determine the ROI or ROV for AFS, which should be included in the business case proposal
- Organizational leaders are less receptive to information from medical literature than from the organization's specific experiences and costs. The approach used to make the "pitch" for a business case to develop the AFS should be organization specific and address the unique needs of the organization
- To complete a business case analysis, the estimated cost savings and other financial benefits that result from the AFS must be calculated after the total costs of the program have been deducted
- Ensure that the AFS team leaders develop and assess basic process improvement skills and staff knowledge of process improvement

C. Core Content of Business Case Proposal

Proposals typically include cover letters, details of the major phases in a project, a project schedule, organizational duties, and a cost breakdown of the various components. It is extremely important for AFS leadership to understand the type of proposal that will meet the expectations of senior leaders. Explore whether there's an organizational template that must be used. The core content of a business case proposal typically includes the following[22]:

- Management summary – Summarize the key points within each business case section, ideally on one page
- Project background – Identify the issue, opportunities, and business strategy requirements that the proposed project will address. Discuss any other options that you have considered and rejected as potential solutions and why. Identify any clinical and financial consequences of not approving the project. Give information on the key stakeholders who have been involved in developing the project proposition, and explain the work that's already taken place in earlier project phases or in dependent projects
- Objectives – State what the project will deliver using "SMART" (Specific, Measurable, Attainable, Relevant, and Timely) objectives
- Scope – Define what the project will deliver. Be clear about what is in the scope, and what's out of scope. You may find it helpful to list processes or process areas, geographical areas, departments/functions, equipment, systems or stakeholder groups as a way of being clear about what is in scope

- Dependencies – Identify any project dependencies. For example, state clearly if your team is in any way dependent on work from another team to complete the project
- Risks – Identify the critical risks within the project. State how you plan to eliminate, reduce or manage these risks, and determine the implications of not doing so
- Costs and resources – Clearly lay out your project budget. In addition, highlight resources that you're depending on, but that don't need cash expenditure. These resources may include things like IT hardware, people, equipment, and rooms that are already available. In these cases, state the amount of these resources that you'll need, and highlight where you expect these resources to come from

Clearly state any assumptions that support the cost estimates in the business case, as well as any numbers that you've left out. For example, if it has been assumed that there's sufficient data storage capacity already available, state this. Areas that are often forgotten in budgets include expenses for staff who must attend project events (such as workshops or business testing exercises) and extra systems hardware capacity. Managers often have problems getting hold of the resources they need for their projects. Therefore, it's important to have key stakeholders give upfront approval, and understand the resources that the project will need.

- Benefits – State the benefits that the project will deliver. These should include both qualitative and quantitative benefits
- Milestones – State your project time line. If the project must be delivered by a certain date to achieve legal or internal deadlines, state this. Also, be clear about the implications of the project starting, or not starting, by a certain date
- Project Evaluation – How projects are evaluated will depend on the organization and its mission

The business case is a key document in the initial stages of a project. It details how the project will proceed, and it's the key document that decision-makers need to decide whether to approve and fund your project. It sets the baseline for the project's scope, costs, and time lines, which means that it's a key document for determining whether the project is judged as a success or a failure. As such, take care with this document – after all, anything that's wrong, left out or misunderstood could is likely to cause problems later.[22]

The business case is a key document in the initial stages of a project.

Business case formats and templates may vary, based on organizational guidelines. As such, in the tools section of this chapter, an example of a generic business case template is provided.

D. Strategies for Fostering "Buy-In" and "Ownership"

Multiple stakeholders are accountable for prevention of AMR, and for prevention as well as timely and appropriate treatment of HAIs. As such, a variety of approaches are needed to obtain "buy-in" and even "ownership" of the AFS. Stakeholders are more likely to buy into a concept if the end point is mutually desirable and meet the clinical needs of the patients and the financial needs of the organization.

Keep in mind that people are persuaded more by emotion than reasoning, and stories are a powerful way to engage your audience's emotions. Take your ideas and concepts and humanize them through stories. Also, people don't typically remember the words we say, they remember the pictures we create for them. The following step-by-step guide illustrates the story development process necessary to achieve the needed support AFS programs[23]:

- Goal Setting: Determine your buy-in objective. What action do you want your audience to take regarding your idea, proposal, product, service or organization?
- First Step: Establish your strategic storyline. To generate the action you want, what is the "big picture" or vision of a positive future you want your audience to see?
- Second Step: Develop your storyline that target your audience's agenda. What are this audience's needs, wants and future goals? In the future you are projecting, what are the three most important ways in which this audience's agenda will be fulfilled? Outcomes data can be included in the proposal to help persuade administrators and clinicians to support AFSs. (Additional data and metrics will be reviewed in another chapter). When presenting outcomes, a key point is to remember to place emphasis on the data of most interest to the individual administrator or clinicians. The rank order will vary depending on the recipient.

Order of Importance of Outcomes for Administrators	Order of Importance of Outcomes for Clinicians
Money saved	Improved outcomes
Reduced adverse drug events	Decreased antifungal resistance
Improved outcomes	Research
Decreased antifungal resistance	Reduced adverse drug events
Research	Reduced costs

- Third Step: Call your audience to action. Ask for a commitment or first step toward the action you want

Typically, an audience is interested in the ROI or Return on Value and how the project relates to the organizational strategic objectives. In some organizational situations, you may not be able to present the case in person and will have to submit documents that must "speak for themselves". Stakeholders must be able to comprehend the case without your voice-over.

It is very important to make a clear distinction between "buy-in" and "ownership" and not present them as if they were the same. "Ownership" is when you own or share the ownership of an idea, a decision, or an action plan; it means that you have participated in its development, that you chose on your own accord to endorse it. It means that you understand it and believe in it. It means that you are both willing and ready to implement it. "Buy-in" is the opposite: someone else or some group of people

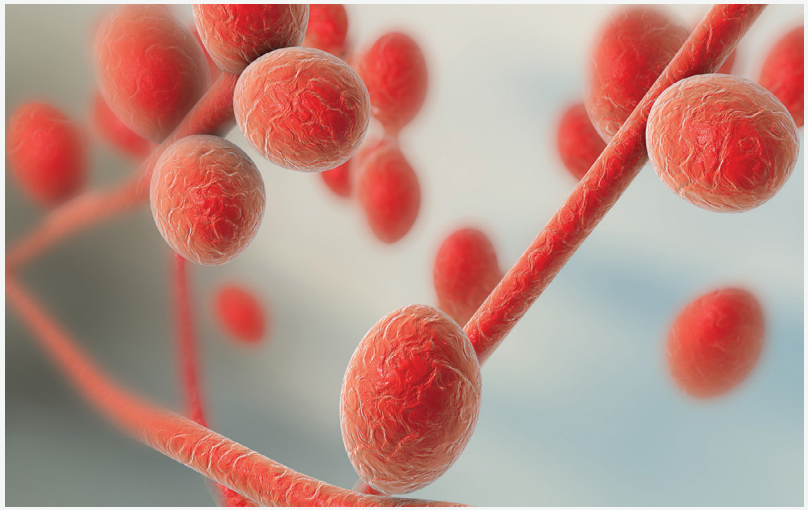
has done the development, the thinking, the planning and now they must convince you to come along and implement their ideas/plans. A key point to remember is that if leaders made the effort to involve UPFRONT all the people that will be involved later in the planning and implementation there would be no need for buy-in for the simple reason that there would be "ownership".[24]

AFS leaders will want to meet with all key stakeholders to validate strengths of the proposal and to address stakeholder concerns and issues, barriers and resistance to gain support, engagement and commitment. This is a crucial step in developing a business case proposal that is sometimes overlooked.

E. From Proposal to Action Plan

Highly reliable organizations influence clinical and administrative leaders to work together collaboratively as one united team to solve problems. AFS leaders should consider reviewing the following eight steps from the Institute for Healthcare Improvement (IHI) for achieving patient safety and high reliability in their organizations that would be beneficial in the implementation of AFS[25]:

1. Address strategic priorities, culture, and infrastructure
2. Engage key stakeholders
3. Communicate and build awareness
4. Establish, oversee, and communicate system-level aims



AMS emphasizes the need for appropriate utilization of drug resources, cost containment, and reduction in antimicrobial resistance rates.

5. Track/measure performance over time, and strengthen analysis
6. Support staff and patients/families impacted by medical errors
7. Align system-wide activities and incentives
8. Redesign systems and improve reliability

The business case should have a project charter that spells out the nature and scope of the work. At a minimum, the charter identifies:

- Name of project sponsor
- Benefits to the organization
- Objectives
- Time frames
- Budget

An action plan has three major elements:

1. Specific tasks: what will be done and by whom?
2. Time line: when will it be done?
3. Resource allocation: what specific funds are available for specific activities?

The action plan should ensure accountability for achieving specific tasks by target deadlines and includes:

- Strategies to reduce the risk of failure
- Responsibility for oversight of the implementation
- Ongoing measurement to determine the effectiveness of the actions
- Objectives of an AFS and the benefits anticipated from each objective
- Resources required to achieve objectives
- Timetable for achieving objectives
- Person(s) responsible for carrying out the objectives
- Evaluation and control processes

Communicating with the C-Suite Leadership

The first step in communicating with the C-Suite will be to determine who will be your audience. Depending on the structure of your organization this might include board members, Chief Financial Officer (CFO), Chief Operating Officer (COO), Chief Medical Officer (CMO), Chief Nursing Officer (CNO), Chief Quality Officer (CQO), and other members of the C-Suite. Understanding your audience, the terminology that is meaningful to them, and what drives their decision-making processes are a critical for the success of your AFS proposal. A strong business case presentation must be clear and easy to understand for non-subject matter experts. The presenters must be confident and enthusiastic about the project, and this is reflected in the quality and detail of the analysis that is in the document and the thoughtful responses to questions.

- Before communicating with the C-Suite, use the following as a checklist to ensure that you have covered all bases. If an answer is "no" to any of the questions, the case will need to be reworked. Did the case...
- Align business case objectives with strategic priorities?
- Identify and address stakeholder objectives?

- Lay out a clear business need and frame it as a compelling story?
- Identify champions and sponsors?
- Engage clinical and financial subject matter experts?
- Double check the numbers and clarify all assumptions?
- Document consideration of all viable options to solve the problem?
- Present a clear action plan for implementation once approval is received?

Challenges of Reporting Metrics (See Chapter 4 for Metric discussion in detail). Successful design and completion of AMS studies present numerous challenges and unanswered questions. Uncertainty remains regarding the appropriate metrics to use to determine the efficacy and/or effectiveness of a stewardship intervention. Most of the studies published to date have focused on antibiotic costs and/or antibiotic utilization.[26] However, published data on AFS programs consistently report cost savings or at least containment of costs, with no significant changes in clinical outcomes and sometimes reduction in resistance and improvement in the quality of care.[7] Senior leaders, such as the CQO will be interested in the following questions:

- What percentage of patients admitted to the hospital or treated by the hospital are experiencing conditions requiring the use of antifungal agents?
- What types of conditions are patients experiencing requiring the use of antifungal agents?
- Where in the organization are patients experiencing these conditions?
- Are such conditions increasing or decreasing?
- What are the drug costs per patient-day and per admission before and after the implementation of an AFS?
- What type of comparison data (qualitative and quantitative) can be used to justify the AFS before and after implementation?
- What do benchmark data (qualitative and quantitative) with "like" organizations before and after implementation reveal?
- What is the impact of publicly reported data?

What Does Excellence Look Like?

A successful AFS is focused on patient-centered care. An example of the scope of activities of a successful ASP with an emphasis on AFS is provided within the appendices section of this chapter. The following characteristics demonstrate excellence in an AFS Program:

An organizational vision is widely communicated

Accountability for performance

AFS values and organizational values are aligned

Key processes deliver optimal clinical, economic, and patient outcomes

System in place to measure and report the value of the AFS

Organizational goals for healthcare improvement are positively affected by the AFS across the continuum of care

ASP processes and outcomes meet and exceed standards of regulatory and accrediting agencies

Use of established best practices as a key component of the AFS strategy

Technology is safely adopted into care processes

Conclusions

The primary goal of AMS is to optimize clinical outcomes while minimizing unintended consequences of antimicrobial overuse. AMS emphasizes the need for appropriate utilization of drug resources, cost containment, and reduction in antimicrobial resistance rates.[27] While there is a considerable amount of literature describing the implementation and impact of various stewardship initiatives targeting antibacterial agents, fewer experiences have been published focusing on the more limited collection of drugs with activity against fungal pathogens or AFS. However, published data on AFS programs consistently report reduced inappropriate use of antifungals, cost and resistance; they also improve the quality of care of patients with proven invasive fungal diseases.[7]

AMS targets inappropriate or unnecessary antibacterial use. It has been estimated that upward of 50% of antibacterial use in the inpatient setting in the USA is inappropriate. Similarly, recent investigations into antifungal drug use have revealed that an alarming 57% of overall antifungal prescriptions were not optimal based on the use of an antifungal adequacy score, clearly establishing a similar need for stewardship of antifungal agents.[28]

Healthcare C-Suite executives, infection preventionists, infectious disease specialists, pharmacists specializing in infectious diseases, and other healthcare facility leaders and clinicians play a critical role in building a sustainable AFS program. The C-Suite leadership commitment sets the stage for accountability throughout the entire organization, and ensures that the stewardship program is properly resourced with people, time, and money to achieve AFS goals. It is helpful to encourage a culture of transparency with results towards the program target by sharing outcomes with all key stakeholders. Experience demonstrates that AFS can be implemented effectively in a wide variety of hospitals and health systems and that success is dependent on defined leadership and a coordinated multidisciplinary team approach.

Most organizations have a rigorous, careful process for allocating funds to projects. They may also have a set of priorities or considerations against which projects are assessed. Investigate the templates and guidelines available within your organization before you start writing your business case. Explore whether there's a template that you must use (and which parts of this are mandatory or optional). Identify who approves business cases for the level of investment that your project requires, and determine the assessment criteria for project approval.

As no new classes of antifungal agents have been approved since 2000, invasive fungal infections, particularly due to organisms demonstrating intrinsic and acquired resistance, are an expanding public health threat in some of the most vulnerable patient populations. Although antifungal resistance has been slow to emerge, compared to the breadth and frequency of bacterial resistance, there is every reason to believe this will become a widespread issue. Efforts to mitigate this trend will require a multifaceted approach as discussed in this chapter regarding making the business case for AFS.[29]

Points to remember include:

1. The high costs and high contribution of antifungal agents to the management of IFDs along with their recognized toxicities is the principal justification for AFS and
2. Practice guidelines adapted to the local context following collaboration with institutional leaders are the cornerstone of AFS and should be available at the point of care with linkage to expert prescribers.

Tools

The CDC Assessment Tool

This checklist will assist hospitals in assessing key elements needed for creating an AFS program that ensures optimal antifungal prescribing and appropriate use. To access the checklist, go to **http://bit.ly/1pgmuw4**.

CDC Core Elements of Hospital Antibiotic Stewardship Programs

This document summarizes core elements of successful hospital ASPs and complements existing guidelines on ASPs from organizations including the IDSA in conjunction with SHEA, ASHP and The Joint Commission.
To download, go to **http://bit.ly/1mkf6MJ**.

Fact Sheet

Just like antibiotics cure bacterial infections, antifungal medications save lives by curing dangerous fungal infections. And just like some bacterial infections are resistant to antibiotics, some fungi no longer respond to the antifungal medications that are designed to cure them. Review this fact sheet to understand the problem, its cause and what can be done.
https://www.cdc.gov/fungal/antifungal-resistance.html

Example of a Business Case Template:

Business Case Template. Adapted from: Australian Government, Department of Health and Ageing, Departmental Business Case Template, April 2010. Toolkit for implementation of the Australian Infection Control Guidelines (AICG) 2010
https://safetyandquality.gov.au/wp-content/uploads/2012/02/BusinessCaseTemplate.pdf

C-Suite Reports

Consider a Quarterly Executive Summary Report as it is important to keep Executive Leadership informed of the efforts of an AFS. The following template can be used to develop an Executive Summary Quarterly Report:

1. Introduction: Provide a brief overview of the purpose and goals of the AFS.
2. Antifungal usage data (eg, DOTs or DDDs normalized for 1,000 patient-days): Team members may want to limit this data only to high-profile antifungals or antifungals that have been targeted by various stewardship initiatives.
3. Financial metrics include current data and compare it to a pre-program baseline and the previous year. Provide graphs of metrics over time. Examples of metrics include:
   - Antifungal expenditures per patient-day and per admission
   - Rate of acceptance of AFS recommendations
   - Rate of adherence to institutional AFS guidelines, care bundles, and policies and procedures for antifungal use
   - Antifungal costs compared to budget
   - Savings (include cost containment/avoidance)
   - Antifungal costs per patient day
   - Antifungal costs per admission
4. Summary of patient-level interventions: Team members may list the number of each major type of intervention (eg, number of therapy de-escalations and number of antifungal regimen changes to cover an "uncovered" pathogen) and the total number of interventions.
5. Summary of activities: Provide a summary of completed, ongoing, and planned AFS initiatives.
6. Outcomes of initiatives: Provide examples of outcomes, such as improved clinical outcomes and decreased use of a specific antimicrobial.

Appendices

A. Adapted from Antibiotic Stewardship Program Evaluation Checklist. Big Book of Checklists. JCR 2016.

This checklist lists elements that should be present in an antifungal stewardship program. You can use it to evaluate the completeness and quality of your organization's program. Answers to all questions should ideally be Y for Yes (unless they aren't applicable).

Organization: _____

Date of Review: _____ **Reviewer:** _____

Leadership Commitment	**Y**	**N**	**N/A**	**Comments**
Has leadership issued a formal statement supporting efforts to improve and monitor antifungal use?				
Has antifungal stewardship been incorporated into job descriptions and performance reviews?				
Has enough staff time been allocated to antifungal stewardship-related activities?				
Does the antifungal stewardship program receive budgeted financial support for its activities?				
Accountability	**Y**	**N**	**N/A**	**Comments**
Has a multidisciplinary team been assembled to oversee and take responsibility for the program?				
Does the team include a physician leader and a pharmacy leader?				
Does it include patient and family representatives?				
Have team leaders been trained in infectious diseases and/or antifungal stewardship?				
Broad Interventions	**Y**	**N**	**N/A**	**Comments**
Do your policies require documentation of dose, duration, and indication in the medical record?				
Does your program have facility-specific treatment recommendations based on national and state guidelines?				
Do physicians review an antifungal's appropriateness 48 hours after the initial order (antibiotic time-out)?				
Do certain restricted antifungals require approval by a physician or pharmacist prior to dispensing (pre-authorization)?				
Does a physician or pharmacist review courses of therapy for specified antifungals (prospective audit with feedback)?				

Pharmacy-Driven Interventions	Y	N	N/A	Comments
Does the pharmacy use automatic changes from intravenous to oral antibiotic therapy, as appropriate?				
Are doses adjusted in cases of organ dysfunction?				
Does the pharmacy optimize doses to treat organisms with reduced susceptibility?				
Does your system use automatic alerts to avoid redundant therapies?				
Does your system use time-sensitive automatic stop orders for specific antibiotics?				
Diagnosis- and Infection-Specific Interventions	**Y**	**N**	**N/A**	**Comments**
Do you have specific interventions in place for common infections, such as community-acquired pneumonia and urinary tract infections?				
Tracking and Reporting	**Y**	**N**	**N/A**	**Comments**
Does your program have a system for evaluating its effectiveness?				
Does your program have a system for improving outcomes and performance?				
Does the team evaluate whether policies and processes are being followed?				
Does your organization track rates of common infections, such as *C. difficile*?				
Does your organization track antifungal use at the unit- and/or facility-wide level?				
Are the results of these evaluations and analyses shared with relevant staff?				
Do prescribers receive direct, personalized communication about how they can improve their antifungal stewardship?				
Education	**Y**	**N**	**N/A**	**Comments**
Does your program educate or train relevant staff on ways to improve antifungal use?				
Does your program educate patients and families on ways to improve antifungal use?				
Does the team share regular updates on resistance and infectious disease management at the national and state levels, with relevant staff?				

B. Sample Business Case for an AFS Program at City Hospital

(Adapted with permission from A Business Case for an Antimicrobial Stewardship Program, **www.IDologist.com**. accessed 07-09-2018).

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Executive Summary

Antimicrobial (antibiotic and antifungal) resistance and escalating healthcare costs have brought worldwide attention to antimicrobial use. In the late 1990s, the World Health Organization, the European Union and the US Centers for Disease Control urged healthcare leaders to address antimicrobial misuse in an effort to combat antimicrobial resistance.[1-4] The development of bacteria for which no effective antibiotics exist, coupled with an antibiotic development pipeline which has dried up, has heightened such concerns. More recently, the Infectious Diseases Society of America, and the Society for Healthcare Epidemiology of America have advocated for hospitals to establish formal programs in an effort to combat hospital-acquired infections and antimicrobial resistance.[5, 6]

Stewardship programs are privileged in that they present the opportunity of achieving the Institute for Healthcare Improvement's triple aims by improving the health of the hospital population (by reducing resistance), improving the patient experience (by improving the quality and reliability of antimicrobial/antifungal use), and by reducing healthcare costs.[7] In this document we present the business case for developing a stewardship program with an emphasis on antifungals at City Hospital, which would serve to improve the quality of care and patient safety while reducing costs.

Overview of Antifungal Stewardship

Antifungal stewardship programs are multidisciplinary initiatives whose primary aim is to optimize antifungal use. The Infectious Disease Society of America (IDSA) and the Society for Health Care Epidemiology of America (SHEA) published guidelines

for antimicrobial stewardship in 2007 that may be applied to antifungal use.[6] Antifungal stewardship, as with antimicrobial stewardship, is broadly defined as a practice that ensures the optimal selection, dose and duration of antifungals that leads to the best clinical outcome for the treatment or prevention of infection while producing the fewest possible side effects and the lowest risk for subsequent resistance.[8] Antifungal stewardship programs may contain a variety of interventions that are complementary to effective infection prevention and control programs.

Antifungal stewardship programs use a variety of interventions to achieve their outcomes, based on local culture, needs, resources, and expertise. Significant improvements in microbiological outcome (eg, prevalence of antibiotic-resistant bacteria) and clinical outcomes (eg, mortality and length of hospital stay) were also noted in some studies. Most programs can expect to achieve a reduction in costs from the successful implementation of antifungal stewardship programs.[6]

Antimicrobial/Antifungal Stewardship at City Hospital

There is currently no antimicrobial/antifungal stewardship program at City Hospital. The Infectious Diseases Consult Service assesses appropriateness of antimicrobial/antifungal therapy only when consulted, but primarily is a consultancy service that aids is diagnosis and management of outlying conditions. Prevention and management of outbreaks of multidrug-resistant pathogens is under the auspices of the hospital's Infection Prevention and Control Program, but they have no mandate to effect antimicrobial/antifungal stewardship.

Evaluating the Need for Antifungal Stewardship

Antifungal stewardship, if properly supported, can offer net present-value cost-savings of $XXXXX over 5 years **[For this appendix, please insert your cost savings]**. These savings **only include antifungal costs**, and do not address the anticipated reduction in costs realized through infection prevention and control, inpatient bed utilization, and patient safety. Such a program, when working in concert with Infection Control, would serve as a model for Quality Improvement and Assurance, and assist in the development of programs of high priority within the hospital:

a) Patient safety

b) Audit and control of multidrug-resistant organisms

c) Transitional care from hospital-to-home

Based on the above information and considerations, City Hospital should fund and develop an antifungal stewardship program, consisting of an infectious diseases physician, a clinical pharmacist dedicated to antimicrobial stewardship, and information and decision support from the pharmacy, infection control, the microbiology laboratory, and medical informatics.

Scope of Business Case Analysis

In developing recommendations for antifungal stewardship at City Hospital, the business case outlines business objectives, stakeholder needs and requirements, and cost-benefit analysis.

Details of program implementation, epidemiological and quality-of-life measures, and indirect cost-savings/avoidance are excluded from the business case analysis. **(See Appendix E.)**

It is assumed that the principles on which the IDSA guidelines for antimicrobial stewardship have been developed are applicable to City Hospital.[6]

Business Objectives

1. To identify and lower inappropriate antifungal use—reducing the expenditure on antifungals at City Hospital.
2. To decrease the rate of hospital-acquired infections associated with multi-drug resistance.
3. To develop guidelines, policies, and measures for streamlining prophylactic, empiric, and definitive antifungal therapy—thereby reducing length-of-stay, mortality, and other undesirable clinical issues.
4. To develop an out-patient intravenous antimicrobial treatment program in order to optimize transition from the in-patient arena to the out-patients arena, reduce length of stay for patients requiring long-term intravenous antimicrobial therapy, and increase patient safety following hospital discharge.

Stakeholder Assessment

The key constituents of antifungal stewardship at City Hospital fall into three broad categories: business stakeholders, partners/support, and end-user/target.

Business Stakeholders

Business stakeholders are represented by City Hospital administration—primarily the Corporate Quality Committee, Pharmacy & Therapeutics Committee, Infection Control, and Microbiology. They are the primary customer, steward, and initiating sponsor related to the business objectives above. As such, antifungal stewardship must satisfy City Hospital's obligations to be fiscally responsible while delivering the utmost quality in healthcare.

Partners/Support

Partners/support represent the internal and external stakeholders who will assist in the implementation of antibiotic stewardship and facilitate the organizational and cultural changes required to achieve the business objectives. Microbiology, Infectious Diseases, Infection Control, and Informatics represent the primary partners/support stakeholders—as functional units within the organization responsible for achieving specific elements of City Hospital's vision and mission.

End-user/Target

The end user/target represents clinical staff providing care and the patients receiving care. They are the individuals specifically affected by antimicrobial stewardship. As such, they represent secondary sponsors who must be kept informed, if not engaged, in the proceedings of antimicrobial stewardship.

For further information regarding stakeholder roles, needs, and requirements, please refer to Appendix D.

Deliverables Associated With Antifungal Stewardship

Deliverables associated with antimicrobial stewardship activities that ensure appropriate antimicrobial therapy are as follows:

- Guidance on streamlining prophylactic therapy
- Guidance on streamlining empiric therapy
- Guidance on optimizing therapy associated with a definite diagnosis

- Outline diagnostic methods and microbiological culturing practice that leads to prescribing of antifungals
- Surveillance and reporting of antifungals and associated resistance
- Infection control recommendations to avoid the transmission and onset of infection
- Education and feedback measures regarding antifungal use, resistance, and diagnosis of infection

Existing Antimicrobial/Antifungal Stewardship at City Hospital

There is no committee or working group at City Hospital regularly addressing antimicrobial stewardship or antifungal utilization. Although there is an Antibiotic Formulary Committee that reports to the Pharmacy & Therapeutics Committee (which reports to MAC), this committee does not have the mandate nor is resourced to evaluate antimicrobial/antifungal utilization.

Antimicrobial Stewardship Proposed by the IDSA

In January 2007, the IDSA provided guidelines for the infrastructure, support, and activities required for antimicrobial stewardship.[6] This business case shares much of the basic elements of the IDSA recommendations.

Core members of antimicrobial/antifungal stewardship program include an infectious diseases physician and an infectious disease trained pharmacist, along with any administrative and IT support required for effective implementation of antimicrobial stewardship.

Table 1. Antimicrobial/Antifungal Stewardship Members and Support

Infectious diseases physician	• Coordinates the antimicrobial stewardship program • Leads educational/academic detailing
Clinical pharmacist with infectious diseases training	• Coordinates antimicrobial/antifungal stewardship activities
Information systems specialist	• Provide computer support for surveillance and implementation of recommendations
Microbiologist	• Provide surveillance data on antimicrobial resistance
Infection control professional	• Provide guidance on infection control practices • Provide support on implementation of recommendations • Provide guidance on development of surveillance systems
Hospital epidemiologist	• Provide guidance on the priorities and direction of antimicrobial stewardship

Antimicrobial/antifungal stewardship involves: prospective audits with intervention and feedback; formulary restrictions and pre-authorization; and supplemental activities such as guideline development, de-escalation of empiric therapy, clinical physician order entry, etc.

For a more detailed description of antifungal stewardship, please refer to Appendix B.

Appendix A: Comparative Antimicrobial/Antifungal Usage at City Hospital

[For this appendix, please insert a table of associated data for your organization. Suggest having a table breaking down usage by specific agents, and use cost data (rather than defined daily dosages)]

Appendix B: Antifungal Stewardship Program Outline

Objectives

The goals of an effective antifungal stewardship program vary depending on perspective. From all perspectives, an antifungal stewardship program will maximize effectiveness and safety through the following means:

1. Choosing the most effective antifungal agent/route/dose for each patient
2. Reducing the use and duration of intravenous antifungals
3. Reducing the use and duration of unnecessary antifungals
4. Ensuring appropriate monitoring of antifungals with known safety concerns
5. Facilitating the discharge and follow-up of patients receiving intravenous antifungals

Expected Outcomes

1. Reduced institutional antimicrobial/antifungal resistance
2. Reduced opportunistic infections arising from antimicrobial use (eg, C. difficile, invasive candidiasis, Pseudomonas, and other environmental Gram-negative infections)
3. Reduced venous catheter complications (coagulase-negative staphylococcal bloodstream infections, venous thrombosis)
4. Reduced costs:
    a. Directly from reduced antimicrobial/antifungal use
    b. Indirectly from:
        i. Reduced infection-control costs (eg, isolation bed-days)
        ii. Reduced microbiology laboratory utilization
        iii. Reduced use of PICC lines
        iv. Reduced length of stay

Operationalization

Institution of an effective antimicrobial program is complex for a variety of reasons that lie, primarily, within the following categories: evidence, human factors, and systems.

Evidence

The published evidence surrounding antifungal stewardship is not as robust as with antimicrobial stewardship. However, compelling evidence for stewardship include:

- Changes in antifungal use are paralleled by changes in the prevalence of resistance
- Areas within hospitals that have the highest rates of antifungal resistance also have the highest rates of antifungal use
- Increasing duration of patient exposure to antifungal increases the likelihood of colonization with resistant organisms

Further, many clinical targets of antifungal stewardship are founded on basic principles of infectious diseases and medical microbiology. Therefore, an effective program needs to monitor and disseminate—in an effective and convincing manner—its clinical and microbiological outcomes.

Human Factors

The greatest barrier to an effective antifungal stewardship program is physician uptake. In a teaching hospital, this is even

more complex, as the "physicians" (ie, house staff) change frequently. Many physicians may be reluctant to reduce their own antifungal use primarily because they are fearful that such an approach will expose their patients to increased harm. Dissemination of information by pharmaceutical manufacturers, published clinical practice guidelines, and even personal experience with a patient may strongly influence a physician to adopt a "hit them hard" approach to using antifungals.

Further, physicians may feel that antifungal stewards (who predominantly work from an institutional context, while maintaining a perspective of patient-focused care) work at cross-purposes with their own obligation to the individual patient.

Guiding principles in the development of such a program should include:

- Broad consultation with prescribers, microbiologists and infection control leaders prior to development of policies
- Maximizing physician input and autonomy where possible
- Individualized feedback to "outlying" prescribers (ie, those whose antifungal utilization is outside their peers' practice)
- Escalation of restrictions: early in the program, restrictions must be "milder" to minimize physician "push-back"
- Ongoing feedback to stakeholders regarding patient safety and outcomes

Systems

Below, are the steps that need to be taken, and the systems that need to be put in place in order to operationalize an effective antimicrobial stewardship program.

Decision Support

There is a tremendous amount of data required, especially at the beginning of the program, but then on an ongoing basis as well. Required information includes:

a) Microbiology data (profiling antifungal resistance). This requires both summative information (eg, on a quarterly basis), but also needs to be able to feed to members of the antifungal stewardship team individual culture results where early intervention is needed

b) Infection control data (profiling multidrug-resistant organisms from a clinical perspective, as well as isolation bed-days)

c) Pharmacy (profiling antifungal use, costs, etc.) Such data needs to be in "real time", allowing members of the stewardship team an opportunity to intervene early in the course of treatment

d) Clinical data (profiling patient demographics, adverse events, length of stay, and outcomes)

e) Radiology data (in particular, insertion of PICC lines for antifungal use)

Therefore, an AFS will need appropriate, dedicated decision support.

Development of Antifungal Policies

City Hospital has some guidelines and policies regarding antifungal use in a variety of settings. Nevertheless, they may need revision, modification, or updating. The development of new policies (and modification of old ones) will require input from clinical stakeholders (which may include Emergency Physicians, General Internists, Infection Control, Infectious

Diseases physicians, Intensivists, Microbiologists, Pharmacists, and Surgeons). Because there is (at present) no Antimicrobial/Antifungal Formulary Subcommittee of the Pharmacy & Therapeutics Committee at City Hospital, it is anticipated that such a subcommittee will be formed.

Education and Marketing

After policies have been developed, they will need to start to be implemented. For successful implementation, an education and marketing campaign is necessary, akin to the hand-washing initiatives undertaken by Infection (Prevention and) Control. Slogans such as "Saving Antibiotics Saves Lives" and "Treat Infections not Culture Results" will likely bring antimicrobial/antifungal overuse on the radar of physicians. Coupling marketing with effective reporting of drug-resistance, and education on the appropriate use and the safety issues of antifungal overuse will be necessary to change provider behavior. Implementation will likely be a combination of "forced" policies (eg, restriction of antimicrobials/antifungals) and academic detailing (eg, one-on-one feedback from AFS to prescriber). AFS will need to be visible, knowledgeable, trusted, and available.

An obvious initial target of detailing will be the intensive care units, where roughly half of all antimicrobials/antifungals (on a cost basis) is prescribed (or at least started). Whether antimicrobial stewardship of the intensive care units will involve regular rounding with the ICU team, academic detailing, "forced policies" or a combination thereof will depend on the results of consultation with the intensive care team. The frequency, duration and timing of such meetings would have to be agreed upon.

Information Technology/Physician Order Entry (POE)

An effective AFS program must, at some point, use the electronic medical record and electronic order entry as a tool to control antimicrobial/antifungal use.

Acting on Results

Because all effective AFS programs are effective quality improvement programs, studying results and then acting on them—in a rapid-cycling time frame—is imperative. Therefore, having effective program management, with statistical/actuarial support, is the final necessary piece of an antimicrobial stewardship program.

Appendix C: Job Descriptions of Members of Antimicrobial Stewardship Team

AFS Officer

- 0.3-0.5 FTE
- Infectious Diseases Physician
- Responsible for leading the development, harmonization, implementation and dissemination of antifungal policies at City Hospital
- Responsible for the study of antifungal utilization at City Hospital
- Responsible for reducing antifungal resistance (together with Infection Control)
- Expected to interact regularly (ie, academic detailing) with high antifungal utilizers (either quantity or cost): intensivists, general internists, oncologists, general surgeons

- Will be required to develop an educational program, targeting all levels of learners (medical students, residents, and staff physicians; other allied health providers and nurses)
- Report to the Senior Vice-President, Medical, the Corporate Quality Committee and the Medical Advisory Committee

Antifungal Pharmacist

- 0.5-1.0 FTE
- Pharmacist with expertise/additional training in the use of antifungals
- Responsible for assisting in the development, implementation and dissemination of antifungals policies at base hospital
- Responsible (along with Decision Support personnel) for collecting and processing antifungal utilization data at base hospital
- Responsible, on a regular (daily) basis, for ensuring hospital-wide compliance with antifungal policies (including i.v.-to-p.o. step-down conversions, step-down to targeted therapy, restricted antimicrobial use, safety monitoring, etc.)
- Expected to interact regularly with high antifungal utilizers and their house-staff
- Report to Chief of Pharmacy Practice

Antifungal Information Specialist

- 0.3-0.5 FTE
- Specialist in information technology, with expertise/ understanding of electronic health records, administrative records
- Must have knowledge and expertise with flat (and, preferably, relational) database design and analysis
- Responsible for collecting and analyzing clinical, administrative, registration and microbiological data to support decisions made by the AFS Officer and his/her team
- Responsible for working with antifungal pharmacist to analyze and publish utilization data and tools (eg, antimicrobial/ antifungal handbook)
- Responsible for working with Information Technology to develop on-line tools for use in the electronic health record pertaining to antimicrobial/antifungal utilization/optimization
- Will be required to liaise with the teams working on electronic health records
- Reports to Chief Information Officer

Antifungal Program Manager

- 0.25-0.5 FTE
- Program Manager with expertise/knowledge of change management and quality improvement in healthcare settings
- Responsible for coordinating and administering the effective development and implementation of stewardship at City Hospital
- Will work closely with Antifungal Officer to develop a continuous quality improvement process, based on the model of Plan-Do-Study-Act
- Reports to Senior Vice President, Medical

Appendix D: Assessment of Stakeholder Needs & Requirements

Stakeholder	Role	Needs	Requirements
City Hospital	Healthcare service provider	To demonstrate fiscal responsibility in satisfying its mission as a healthcare service provider	Elimination of inappropriate antimicrobial/antifungal use leading to increased healthcare costs and risk to patients
Infection Control	Monitor, control and counsel on the propagation of infectious agents	To obtain microbiology data and records of infection control practices	Access to data storage and archives of microbiology results
Infectious Diseases	Counsel the management and treatment of infectious agents	To obtain information on microbiology, antifungals, antimicrobials, sensitivities, and utilization patterns	Access to data storage and archives of microbiology results and antimicrobial/ antifungal use per patient
Microbiology	Counsel on microbiological matters and identification of infectious agents	To be provided with appropriate draws and samples for testing	Translation of recommendations to infrastructure, process, and practice to ensure timely results and data
Pharmacy & Therapeutics Committee	Counsels on pharmaceutical services, formulary, policies, and administration related to medications	To be kept up to date of clinical, fiscal, and technological developments associated with medication and associated admin	Translation of recommendations to pharmacy for development of infrastructure, process, and practice
Primary-care nurse	Collect patient information, collect samples, and provide necessary care	To be provided with timely information, instructions, and tools required to assist the physician and maintain care of the patient	Be properly informed of the requirements, tools, and schedule for collecting patient information, drawing lab samples, and administering antifungal treatment
Pharmacists	Counsel and manage the administration and use of medications	To be kept up to date on patient and drug information	Access to information on microbiology, progression of antimicrobial therapy, and innovations/initiatives
Most responsible physician (and delegates)	Diagnosis of patient complications and management of patient	To receive patient information/results and have procedures performed in a timely manner	Have microbiology orders completed and reported in a timely manner; receive appropriate counsel on the treatment
Patient	Recipient of care and medications for identified complications	To have their healthcare needs addressed with as little inconvenience as possible	Receive the right antimicrobial medications at an appropriate duration for a properly diagnosed infection

Appendix E: Business Case Analysis and Forecasting

See sample business case analysis and forecasting at **www.idologist.com/Blog/2009/09/23/business-case-for-anti-microbial-stewardship/**

References for Sample Business Case

1. Williams RJ, Heymann DL. Containment of antibiotic resistance. *Science*. 1998;279:1153-4.
2. Shlaes DM, Gerding DN, John JF, et al. Society for Healthcare Epidemiology of America and Infectious Diseases Society of America Joint Committee on the Prevention of Antimicrobial Resistance: guidelines for the prevention of antimicrobial resistance in hospitals. *Infect Control Hosp Epidemiol*. 1997;18(4):275-91.
3. European Commission Directorate-General XXIV Consumer Policy and Consumer Health Protection Directorate B—Scientific Health Options Unit B3 Management of scientific committees II M, 1999. Opinion of the Scientific Steering Committee on Antimicrobial Resistance. 1999; 1-121.
4. Select Committee on Science and Technology. House of Lords Session 1997–98. 7th Report. Resistance to antibiotics and other antimicrobial agents. SMAC Main Report. Standing Medical Advisory Committee Sub-Group on Antimicrobial Resistance. The path of least resistance. London, Department of Health; 1998.
5. Auditor General O. Special Report on the Prevention and Control of Hospital-acquired Infections. In: Ontario OotAGo, editor. Toronto, ON: Queen's Printer for Ontario; 2008; 42.
6. Dellit TH, Owens RC, McGowan JE, Jr., et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clin Infect Dis*. 2007;44(2):159-77.

References for the Chapter

1. Centers for Disease Control and Prevention. Antibiotic use in the United States, 2017: progress and opportunities. Atlanta, GA: US Department of Health and Human Services, CDC; 2017.

2. Ananda-Rajah MR, Slavin MA, and Thursky KT. The case for antifungal stewardship. *Curr Opin Infect Dis*. 2012; 25:107-115.

3. MacDougall C, Polk R. Antimicrobial stewardship programs in health care systems. *Clin Microbiol Rev.* 2005;18(4):638-56.

4. Barlam TF, Cosgrove SE, Abbo LM, et al. Implementing an antibiotic stewardship program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. *Clin Infect Dis*. 2016;62(10):e51-77.

5. Writing a business case. https://www.skillsyouneed.com/write/business-case.html. Accessed April 27, 2018.

6. Centers for Disease Control and Prevention. The core elements of hospital antibiotic stewardship programs checklist. https://www.cdc.gov/antibiotic-use/healthcare/pdfs/checklist.pdf. Accessed October 31, 2018.

7. Muñoz P, Valerio M, Vena A, et al. Antifungal stewardship in daily practice and health economic implications. *Mycoses*. 2015;58(suppl 2):14-25.

8. Center for Disease Control. Checklist for Core Elements of Hospital Antibiotic Stewardship Program. http://bit.ly/1pgmuw4. Accessed 03-24-2018.

9. The Joint Commission on Hospital Accreditation. Approved: new antimicrobial stewardship standard. *Jt Comm Perspect*. 2016;36(7):1-8.

10. National action plan for combating antibiotic resistant bacteria. https://obamawhitehouse.archives.gov/sites/default/files/docs/national_action_plan_for_combating_antibotic-resistant_bacteria.pdf. Accessed March 24, 2018.

11. Centers for Medicare & Medicaid Services. CMS issues proposed rule that prohibits discrimination, reduces hospital-acquired conditions, and promotes antibiotic stewardship in hospitals [press release]. June 13, 2016. https://www.cms.gov/newsroom/fact-sheets/cms-issues-proposed-rule-prohibits-discrimination-reduces-hospital-acquired-conditions-and-promotes. Accessed October 31, 2018.

12. National Quality Forum. National Quality Partners Playbook: Antibiotic Stewardship in Acute Care. https://www.qualityforum.org/Publications/2016/05/National_Quality_Partners_Playbook__Antibiotic_Stewardship_in_Acute_Care.aspx. Accessed April 12, 2018.

13. World Health Organization. Global action plan on antimicrobial resistance 2015. http://www.who.int/antimicrobial-resistance/publications/global-action-plan/en. Accessed April 12, 2018.

14. Watanabe JH, McInnis, T, and Hirsch JD. Cost of prescription drug-related morbidity and mortality. *Ann Pharmacother.* 2018;52(9):829-837.

15. Schumock GT, Li EC, Wiest MD, et al. National trends in prescription drug expenditures and projections for 2017. *Am J Health Syst Pharm*. 2017; 74(15):1158-73.

16. Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States, 2013. https://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf. Accessed October 31, 2018.

17. Nowak MA, Nelson RE, Breidenbach JL, et al. Clinical and economic outcomes of a prospective antimicrobial stewardship program. *Am J Health Syst Pharm*. 2012;69(17):1500-8.

18. Johannsson B, Beekman SE, Srinivasan A, et al. Improving antimicrobial stewardship: the evolution of programmatic strategies and barriers. *Infect Control Hosp Epidemio*l. 2011;32(4):367-74.

19. Agarwal S, Barnes R, Brüggemann RJ, et al. The role of the multidisciplinary team in antifungal stewardship. *J Antimicrob Chemother*. 2016;71(suppl 2): ii37-ii42.

20. Talbot TR; Joint Commission Resources, Antimicrobial Stewardship Initiative. Module 1: healthcare organization infection prevention and control programs: essential partners of antimicrobial stewardship programs. https://www.azdhs.gov/documents/preparedness/epidemiology-disease-control/healthcare-associated-infection/advisory-committee/antimicrobial-stewardship/joint-commission-r-2012-healthcareo-Infection-prevention.pdf. Published March 2012. Accessed December 5, 2018.

21. Perencevich EN, Stone PW, Wright SB, et al. Raising standards while watching the bottom line: Making a business case for infection control. Infect Control Hosp *Epidemiol*. 2007;28(10):1121-33.

22. Mindtools. How to write a business case: getting approval and funding for a project. https://www.mindtools.com/community/pages/article/newPPM_62.php. Accessed April 30, 2018.

23. Walton M. Generating Buy-In. Mastering the Language of Leadership. New York, NY: AMACOM; 2004.

24. Lipmanowicz H. Buy-in versus ownership. http://static1.1.sqspcdn.com/static/f/1272828/17864115/1335380597587/Buy. Accessed April 30, 2018.

25. Botwinick L, Bisognano M, Haraden C. Leadership guide to patient safety. IHI Innovation Series white paper. Cambridge, MA: Institute for Healthcare Improvement; 2006. http://www.ihi.org/resources/Pages/IHIWhitePapers/LeadershipGuidetoPatientSafetyWhitePaper.aspx. Accessed April 30, 2018.

26. Anderson, DJ, Jenkins TC, Evans SR, et al. The role of stewardship in addressing antibacterial resistance: Stewardship and Infection Control Committee of the Antibacterial Resistance Leadership Group. *Clin Infect Dis*. 2017:64(suppl 1):S36-S40.

27. Dellit T, Owens RC, McGowan JE Jr, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clin Infect Dis*. 2007;44(2):159-77. .

28. Andruszko B, Ashley ED. Antifungal stewardship: an emerging practice in antimicrobial stewardship. *Curr Clin Microbiol Rep*. 2016;3(3):111-9.

29. Miller RA. A case for antifungal stewardship. *Current Fungal Infections Reports*. 2018;12(1):33-43.

CHAPTER 3:

Guidance for Successful Implementation of Antifungal Stewardship

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Introduction and Overview

Antifungal prescribing frequently occurs in immunocompromised oncology and transplant populations or critically ill patients, where prescribing appropriate antifungal treatment or prophylaxis has meaningful impact on survival, length of stay, and hospital readmission.[1] The rate of inappropriate antifungal prescribing is higher than inappropriate antibiotic prescribing according to a large-scale evaluation of antifungal prescribing across 53 countries.[2] Yusef and colleagues demonstrated that antifungals are 1.4 times less likely to have an appropriate indication and 1.3 times less likely to have a planned duration of therapy compared to antibiotics.

Introduction and Overview (cont.)

Additionally, antifungals were less likely to be prescribed in accordance with institutional guidelines and order sets than antibiotics [57% vs 71%, OR 0.6 (0.5-0.6)]. Moreover, the authors of a published case-based survey evaluating 121 European prescribers' responses to antifungal stewardship scenarios noted significant deficiencies, especially in residents and physicians treating critical care patients. Only 69% of prescribers (62.7% of residents and 77.8% of staff physicians) were able to adequately distinguish *Candida* colonization from infection and 52% of prescribers (49.3% of residents and 55.6% of staff physicians) could distinguish *Aspergillus* colonization from infection. Additionally, only 42% of prescribers (36.9% of residents and 48.1% of staff physicians) knew the diagnostic value of galactomannan assay, and 37% (34.8% of residents and 38.9% of staff physicians) knew the recommended duration of therapy for various fungal infections.[3]

These studies demonstrate differences and challenges in antifungal prescribing practices and shouldn't be surprising given the unique challenges associated with assessing and improving prescribing. Some significant differences that differentiate antifungal stewardship (AFS) from antimicrobial stewardship should be noted:

1. Implementing a successful AFS program requires collaboration among all parties involved in the care of patients at risk for invasive fungal infections. Developing a positive and collaborative attitude toward antifungal stewardship within the infectious diseases, oncology, transplant and intensivist divisions, and others are critical for developing a successful AFS program.
2. Prescribing appropriate antifungal prophylaxis or treatment provides unique challenges that are different from traditional antimicrobial stewardship (usually considered antibiotic stewardship), as prescribing overlaps between inpatient and outpatient settings require increased coordination of treatment plans; insurance coverage of medication is often a barrier, which can lead to delays in therapy or non-compliance, and diagnosis and laboratory confirmation of fungal infections is often more challenging than diagnosis of bacterial infections.
3. Implementing evidence-based AFS into practice is challenging, as the quantity and quality of literature is sparse compared to antibiotic stewardship literature. However, the unique challenges should not be used to minimize the need and expected benefits of implementing an AFS program.

This chapter will provide an overview of common areas to focus AFS efforts; discuss accreditation requirements for stewardship programs in hospitals and applying them to antifungal prescribing; and identify AFS best practices. The ultimate goal of this chapter is provide a framework that can be used to improve the structure and day-to-day practices of the AFS program at your institution and facilitate improvements in appropriate antifungal prescribing.

Common Areas of Antifungal Prescribing Requiring Antifungal Stewardship

Overview

Antifungal prescribing occurs more frequently in certain patient populations, including critically ill patients admitted to intensive care units, oncology patients, and bone marrow and solid organ transplant recipients. Each population offers a unique focus and associated challenges with improving antifungal prescribing.

Oncology Patients

Oncology patients represent a significant population at high risk for invasive fungal infections (IFIs), but the risk and implications for AFS varies among oncology patients. Pagano and colleagues reported an overall incidence of IFIs in hematologic malignancies but demonstrated significantly different rates. Acute myeloid leukemia (AML) had the highest incidence of IFIs (12%), followed by acute lymphoid leukemia (6.5%), chronic myeloid leukemia (2.5%), chronic lymphoid leukemia (0.5%), multiple myeloma (0.5% and lymphoma (0.7-1.6%).[4] The incidence of IFIs likely varies due to the severity and duration of immunosuppression as a result of the specific cancer and chemotherapy; treatment of refractory or relapse disease, local fungal ecology, and presence of antifungal prophylaxis. Understanding the differences in epidemiology of IFIs in various oncology populations and associated degree of immunosuppression of chemotherapy can help AFS programs build appropriate measures to prevent the development of IFIs.

Providing antifungal prophylaxis is generally preferred over pre-emptive antifungal treatment in high risk patients, as two multicenter, randomized trials reported lower incidence of IFIs with empiric therapy.[5,6] Additionally, selecting the appropriate antifungal for prophylaxis may reduce the risk for IFI and associated outcomes, and stewardship programs should strongly consider promoting specific agents as first-line therapy when outcomes are improved.[7]

Providing antifungal prophylaxis for patients at high risk for IFIs also requires drug expertise in chemotherapy and antifungal drug-drug interactions.[8] Chemotherapy and antifungal drug-drug interactions can affect chemotherapy concentrations and elimination significantly, as well as affect toxicity and efficacy. Thus, choosing antifungal prophylaxis that does not significantly interact with the chemotherapy regimen is imperative. Unfortunately, there is minimal data quantifying the extent and clinical significance of antifungal-chemotherapy interactions, and it is general practice to avoid giving chemotherapy that undergoes hepatic metabolism at the same time a patient is receiving azole therapy that impacts the same metabolism pathways.

Evaluating the cost of therapy and the ability of the patient to afford care is essential in increasing compliance and efficacy.

Finally, the duration of necessary treatment or prophylaxis should be well defined within institutional guidelines to avoid

unnecessary exposure. For example, patients with uncomplicated candidemia should receive 2 weeks of antifungal therapy from the day of the first negative blood culture. Duration of antifungal prophylaxis will frequently extend beyond the hospitalization, sometimes over a period of 30 days to even months in length. Developing a multidisciplinary process to include antifungal prophylaxis and treatment plans across transitions of care will help ensure unnecessary exposure that can lead to increased risk for adverse effects, increase in cost, and possibly antifungal resistance. Transitions of care are especially important given the cost of antifungal treatment and lack of consistent coverage among third-party payers. Evaluating the cost of therapy and the ability of the patient to afford care is essential in increasing compliance and efficacy.

Critical Care Patients

Critical care intensivists are especially concerned with IFIs in 2 settings: severe sepsis in high-risk patients and complicated intra-abdominal infections, both of which are predominantly caused by *Candida* species. Improving antifungal prescribing among critical care providers should target appropriate *empiric* prescribing of therapy for *Candida* infections in high-risk patients through effective education, implementation of criteria and guidelines or protocols, and prospective audit and feedback. In contrast, oncologists and transplant physicians prescribe antifungal therapy as prophylaxis to prevent IFIs and are more likely to manage *Aspergillus* and other mold infections. Thus, common targets for improvements in antifungal prescribing in critically ill patients includes defining appropriate populations to receive empiric therapy.

Table 1. Risk Factors for Candidiasis and Associated Odds Ratios[9]

Risk Factors (Days of ICU stay)	All *n*=352 (%)	Cases *n*=88 (%)	Control *n*=264 (%)	P-value	OR (95% CI)
Broad spectrum antibiotics (-7 to 0)	80 (22.7)	30 (34.1)	50 (18.9)	0.005	2.21 (1.29-3.79)
Broad spectrum antibiotics (1 to 3)	296 (84.1)	85 (96.6)	211 (79.9)	<0.001	7.12 (2.17-23.4)
Broad spectrum antibiotics (-7 to 3)	298 (84.7)	85 (96.6)	213 (80.7)	<0.001	6.74 (2.06-22.33)
Central venous catheter (1 to 3)	272 (77.3)	81 (92)	191 (72.3)	<0.001	4.42 (1.95-10.02)
Surgery (-7 to 0)	40 (11.4)	11 (12.5)	29 (11)	0.700	1.16 (0.55-2.43)
Surgery (-7 to 3)	224 (63.6)	62 (70.5)	162 (61.4)	0.159	1.50 (0.89-2.53)
Abdominal surgery (-7 to 3)	92 (26.1)	40 (45.5)	52 (19.7)	<0.001	3.40 (2.02-5.70)
Immunosuppressants (-7 to 0)	38 (10.8)	15 (17)	23 (8.7)	0.045	2.15 (1.07-4.34)
Pancreatitis (-7 to 3)	6 (1.7)	2 (2.3)	4 (1.5)	0.642	1.51 (0.27-8.40)
TPN (1 to 3)	69 (19.6)	33 (37.5)	36 (13.6)	<0.001	3.80 (2.18-6.63)
Dialysis (1 to 3)	32 (9.1)	10 (11.4)	22 (8.3)	0.396	1.41 (0.64-3.11)
Systemic corticosteroids (-7 to 3)	134 (38.1)	41 (46.6)	93 (35.2)	0.076	1.60 (0.98-2.62)
Diabetes	101 (28.7)	26 (29.5)	75 (28.4)	0.892	1.06 (0.62-1.80)
Mechanical ventilation (-7 to 3)	210 (59.7)	56 (63.6)	154 (58.3)	0.413	1.23 (0.75-2.03)
Mean APACHE II Score, Day 1 (±SD)	15.9 (9.5)	17.0 (8.8)	15.5 (9.7)	0.195	1.03 (0.99-1.06)
Mean pre-ICU LOS, Days (±SD)	1.7 (0.24)	3 (7.3)	1.3 (3.0)	0.036	1.08 (1.01-1.14)

OR, odds ratio; CI, confidence interval; TPN, total parenteral nutrition; APACHE, Acute Physiology and Chronic Health Evaluation; LOS, length of stay.

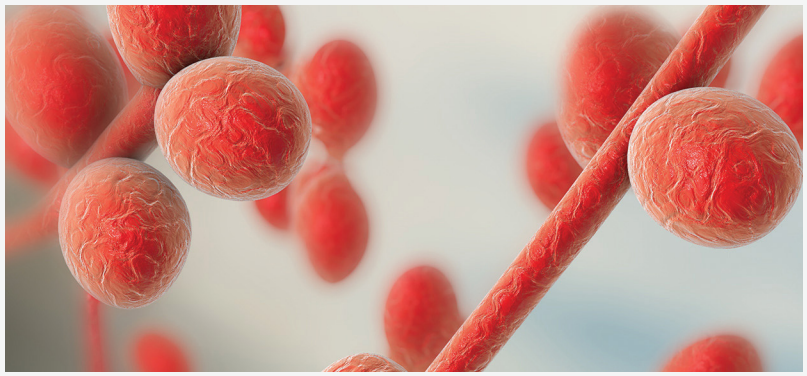
Numerous studies have identified and attempted to validate risk factors for candidiasis in the intensive care unit (ICU). Frequently reported risk factors include total parenteral nutrition, prolonged durations of broad-spectrum antibiotics, abdominal surgery, colonization with *Candida*, presence of central venous catheters, immunosuppression, length of hospitalization, elevated Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) II score, and diabetes.[9] Unfortunately, it appears that the positive predictive value of risk-factor based empiric treatment is relatively low, and not appreciably accurate. However, the negative predictive value is frequently very high and can help identify populations where empiric antifungal therapy is not warranted.

Hermsen and colleagues conducted a retrospective validation study of 4 published risk factors (two Paphitou rules [TPN, hemodialysis, or history of diabetes mellitus with or without broad-spectrum antibiotics], and two Ostrosky-Zeichner rules [central venous catheter and two or more of the following: TPN, hemodialysis, major surgery, pancreatitis, corticosteroids, immunosuppressants and the use of broad-spectrum antibiotics]) and demonstrated a positive predictive value of 41-54% and a negative predictive value of 98-99%.[9]

Utilizing *Candida*–specific rapid diagnostic testing can help with timely diagnosis and initiation of treatment. The negative predictive value of some tests is very high and can help with discontinuation of unnecessary antifungal therapy. These tests include magnetic resonance imaging assay, Multiplex FilmArray for yeast, peptide nucleic acid fluorescent *in situ* hybridization, beta-D-glucan assay, and mass spectrometry time of flight, which are reviewed in more detail in the section of this chapter entitled "Antifungal Diagnostic Testing."

Transplant Patients

Implementing AFS in solid organ transplant recipients and hematologic stem-cell transplant recipients requires a strong collaborative approach with the infectious diseases team, the transplant team, and the antimicrobial stewardship team. Providing solid evidence-based stewardship principles for prevention and treatment of fungal infections in transplant patients may be the most challenging of the different patient groups described in this chapter, given the lack of high-quality epidemiologic studies, comparison studies with different treatment or prophylaxis regimens, and lack of stewardship



The best way to minimize excessive antifungal exposures is to limit the development of fungal infections.

interventional studies.[10,11] Despite the challenges with the transplant population, it's also an essential target for AFS programs when minimizing unnecessary antifungal prescribing. Transplant patients may be at risk for both mold and *Candida* infections (and other opportunistic infections), but the risk varies significantly based on type of transplant, level of immunosuppression, concomitant infections requiring antibiotic, antiviral, or antifungal treatment, and the presence and severity of graft-versus-host disease (GVHD).

The best way to minimize excessive antifungal exposures is to limit the development of fungal infections. Treatment of fungal infections, especially *Aspergillus*, Mucorales, and other mold infections, typically requires prolonged courses of therapy. Developing appropriate antifungal prophylaxis guidelines can help define which transplant patients should receive antifungal therapy (and which patients should not) and standardize the duration of prophylaxis. Institutional guidelines are essential in curbing excessive antifungal prophylaxis.[11] Well-written guidelines help guide initial antifungal options based on transplant type and patient risk factors for fungal infection (see Table 2). However, transplant patients who have acute and chronic GVHD require modification to the immunosuppressive regimen because it increases the risk for fungal infections. Therefore, institutional guidelines should include modifications to antifungal regimens based on development and severity of GVHD and associated alterations to immunosuppressive therapy. Antifungal prophylaxis frequently will be required after hospitalization, and therefore require the AFS program to focus on transitions of care issues. To support a successful antifungal prophylaxis program post discharge, consideration should be given to:

- Assessing the patient's ability to afford continuing antifungal medications
- Evaluating medication compliance
- Minimizing the potential for drug-drug interactions
- Developing a plan for monitoring therapeutic levels of antifungal agents and response of the patient
- Monitoring for and managing adverse effects relating to therapy

Transitions of care issues are more likely to be effectively addressed through strong communication and collaboration with clear accountability among the treatment team, social workers, discharge planners, outpatient providers, primary care providers, and pharmacy.

The ability to accurately differentiate colonization versus infection is essential in providing good AFS in transplant patients, especially lung transplant recipients. Although colonization with *Aspergillus* and other molds frequently occurs in patients with lung transplants, it can occur in other transplant populations—especially those patients with concomitant chronic pulmonary diseases, such as chronic-obstructive pulmonary disease (COPD). *Candida* colonization is also a common issue in some transplant patients that require long hospitalizations or prolonged antifungal treatment courses. Transplants involving intra-abdominal organs—such as liver, pancreas or intestines—are more often associated with *Candida* infections rather than *Aspergillus* and other mold infections. Therefore, developing treatment guidelines for *Candida*, *Aspergillus*, and Mucorales is essential in providing timely and appropriate antifungal therapy. Similar to antifungal prophylaxis guidelines, treatment guidelines should account for the type of transplant and level of immunosuppression when recommending appropriate antifungal treatment and duration (see Table 2).

Table 2. Example Treatment Guideline for Invasive Aspergillosis and Mucormycosis from the University of Michigan Health System

Clinical Setting	Therapy	Duration	Comments
Invasive Aspergillosis (IA) **Categories (see footnote for host and radiology criteria)** **Proven IA** Histopathology demonstrating invasive disease or culture of a sterile site **Probable IA** A susceptible host with suggestive radiology who has either culture, cytopathology/smear, or serum/BAL galactomannan positive. A (+) serum BDG test is supportive of, but not specific for a diagnosis of probable IA **Possible IA** Negative microbiology (culture, pathology, or galactomannan assay), but radiographically suggestive in a susceptible host	Infectious disease consult is *strongly* recommended if aspergillosis is suspected (ie, positive biomarker or culture, radiologic findings) **Preferred** Voriconazole 6 mg/kg IV/ PO q12h x 2 doses, then 4 mg/kg PO/IV q12h (on an empty stomach). During voriconazole load and in severely ill patients, IV therapy is preferred **Preferred alternative in patients intolerant to voriconazole (see comments)** Isavuconazole 372 mg q8h IV or PO x 48 hours, then 372 mg IV or PO daily **Preferred alternative in patients intolerant to voriconazole and isavuconazole or with refractory or breakthrough disease on voriconazole and isavuconazole, or unable to receive azoles due to interaction (see comments)** LAmB (liposomal amphotericin B) 5 mg/kg IV daily **Options for salvage therapy or in patients intolerant to above therapies (see comments)** Posaconazole OR Micafungin OR **Combination therapy** Voriconazole + Micafungin **Micafungin dosing** ***Monotherapy with micafungin should only be considered in possible disease if above options are not feasible. Use is not recommended as monotherapy for primary treatment*** Micafungin 150 mg IV daily **Posaconazole dosing** Posaconazole delayed-release tablets 300 mg PO twice daily on day 1 then 300 mg PO daily starting on day 2 (cannot be crushed or divided)	Minimum of 3-6 months; determined by clinical response, radiological response, and patient's underlying disease or immune status	**Therapeutic drug monitoring** • Therapeutic drug monitoring is strongly encouraged for isavuconazole, posaconazole, and voriconazole. See Figure 1 for timing of therapeutic drug monitoring and dose adjustment recommendations **Drug Interactions** • Numerous significant drug interactions occur with azole antifungals. A comprehensive review of the patient profile should be undertaken when these agents are initiated and discontinued (see footnote for specific notes) **Adverse Reactions** • Posaconazole and voriconazole have been associated with QTc prolongation. Isavuconazole is associated with dose-dependent decreases in QTc interval. As such, isavuconazole may be preferred in some patients experiencing issues with QTc prolongation (>500 msec) • Patients with a prolonged QTc or on select anti-arrythmics such as dofetilide should avoid voriconazole/posaconazole or perform EKG monitoring due to an increase risk of QT-prolongation and torsades • Unlike posaconazole and voriconazole, isavuconazole is water-soluble and thus does not require solubilization by cyclodextrin for an intravenous formulation. There are potential nephrotoxicity concerns with cyclodextrin in patients with pre-existing renal impairment. However, there is no strong clinical evidence suggesting an increased risk of worsening renal function with IV voriconazole use, so use of IV voriconazole may be considered, at the shortest duration possible, if deemed clinically appropriate • Isavuconazole and posaconazole are associated with significantly less visual disturbances, hallucinations, and photosensitivity compared to voriconazole. Isavuconazole may be an option in patients intolerant to voriconazole. Of note, visual hallucinations with voriconazole are usually transient (associated with loading dose) and/or associated with supra-therapeutic levels (>5.5 ug/mL). Visual disturbances, such as photopsia, are not dose dependent, may continue to occur, but have no long-term consequences

Table 2. Example Treatment Guideline for Invasive Aspergillosis and Mucormycosis from the University of Michigan Health System (cont'd)

Clinical Setting	Therapy	Duration	Comments
Proven or Probable Mucormycosis (eg, *Rhizopus* spp., *Mucor* spp., *Rhizomucor* spp., others)	**Posaconazole dosing (cont'd)** • *In patients unable to tolerate whole tablets* – Posaconazole oral suspension 200 mg PO QID (should be given with fatty meals and acidic carbonated beverages to ensure adequate levels and use of acid suppression should be avoided) • *In patients unable to tolerate oral medications* – Posaconazole intravenous solution 300 mg IV twice daily on day 1 then 300 mg IV daily starting on day 2 **Initial combination therapy** (addition of micafungin to voriconazole X 2 weeks) may be considered in patients with *proven* or *probable* disease who meet *any* of the following criteria • Have extensive multi-lobar involvement or disseminated infection • Have increasing oxygen requirements or respiratory distress with impending respiratory failure • Expected long duration of neutropenia (>10 days) or extensive GVHD **Infectious disease (ID) consult is strongly recommended if mucormycosis is suspected** **Primary** Surgical debridement is generally necessary **LAmB** 5 mg/kg IV daily with consideration of escalation to a maximum of 10mg/kg daily in patients with progressive or extensive disease or possible CNS disease Combination therapy should be discussed with ID Consultant Options for step-down therapy, salvage therapy, or in patients unable to take LAmB include isavuconazole or posaconazole. Consultation with ID is highly recommended	Minimum of 3-6 months; determined by clinical response, radiological response, and patient's underlying disease or immune status	**Adverse Reactions (cont'd)** • Isavuconazole was associated with fewer hepatobiliary adverse effects than voriconazole (9% vs. 16%, respectively) in a trial of aspergillosis. However, hepatic adverse effects with voriconazole are generally both reversible and do not require discontinuation in clinical trials. As such, pre-existing hepatic impairment is not a contraindication to voriconazole and mild elevations during therapy are often multi-factorial and do not necessarily mandate a change in therapy. Patients with cirrhosis may have supratherapeutic levels on standard dosages of voriconazole. As such, therapeutic drug monitoring recommendations should be followed and Infectious Diseases Pharmacy (pagers 37689/2938/38272) should be contacted for dosing recommendations in patients with cirrhosis **Breakthrough Infection and Salvage Treatment** • Patients with breakthrough infection on voriconazole/posaconazole prophylaxis may be at risk for azole resistance. If an isolate is available, susceptibilities should be performed • Current and prior azole concentrations during prophylaxis/treatment should be reviewed when assessing potential breakthrough infection or need for salvage therapy **Miscellaneous** • In patients with central nervous system involvement, voriconazole therapy is preferred. Liposomal Amphotericin B therapy is appropriate for patients intolerant or refractory to voriconazole. There is insufficient data regarding preference of other alternatives, and such decisions should be made on a case-by-case basis • In patients with endophthalmitis, voriconazole (concomitant systemic and intravitreal) therapy is preferred **Please note that voriconazole IS NOT ACTIVE against mucormycosis**

Specific Recommendations Regarding Drug Interactions with Azoles:

- Sirolimus, tacrolimus, and cyclosporine levels increase. Drug levels and dose adjustment may be necessary in consultation with transplant pharmacy
- Concomitant use of azoles with certain chemotherapeutic agents (vincristine, tyrosine-kinase inhibitors [eg, imatinib, dasatinib, nilotinib, bosutinib, ponatinib], sorafenib, clofarabine, doxorubicin, or if mandated by clinical trial protocol [eg, quizartinib]) is not recommended if chemotherapy is metabolized by the cytochrome system, and an alternative antifungal should be used (discuss with hematology)
- P-450 inducers (eg, rifampin, phenobarbital, carbamazepine, St. John's wort) may result in subtherapeutic azole levels
- Complex drug interactions with antiretroviral agents exist and may alter serum azole and/or antiretroviral levels

Host and Radiologic Criteria for the Diagnosis of Invasive Fungal Infection[12]

Host factors:

- Recent history of neutropenia (<500 neutrophils/mm^3 for >10 days) temporally related to the onset of fungal disease
- Receipt of an allogeneic stem cell transplant
- Prolonged use of corticosteroids (excluding among patients with allergic bronchopulmonary aspergillosis) at a mean minimum dose of 0.3 mg/kg/day of prednisone equivalent for >3 weeks
- Treatment with other recognized T cell immunosuppressants, such as cyclosporine, TNF-a blockers, specific monoclonal antibodies (such as alemtuzumab), or nucleoside analogues during the past 90 days
- Inherited severe immunodeficiency (such as chronic granulomatous disease or severe combined immunodeficiency)
- Suggestive radiologic/clinical findings:
  - Lower respiratory tract fungal disease
    - The presence of 1 of the following 3 signs on CT:
      - Dense, well-circumscribed lesions(s) with or without a halo sign
      - Air-crescent sign
      - Cavity

Applying CDC Stewardship Core Elements to Antifungal Stewardship

The Centers for Disease Control (CDC) core elements for acute care and ambulatory stewardship provide an excellent framework for developing the structure of a stewardship program,[13] which includes obtaining necessary support and resources from health system leadership, recruiting appropriate members of the antifungal stewardship team that have appropriate expertise, and developing methods to track and report appropriate metrics (see Table 3).

Table 3. CDC Stewardship Core Elements Required for Hospital Accreditation[13]

Stewardship Core Element	Overview
Leadership Commitment	Establish stewardship within the hospital reporting structure and provide appropriate resources
Accountability	Appoint physician and pharmacist leaders responsible for implementing stewardship activities
Drug Expertise	Physicians and pharmacists should have adequate training in antifungal stewardship
Action	Implement processes to promote appropriate antifungal utilization
Tracking	Identify and regularly track key stewardship process and outcomes measures
Reporting	Provide key stewardship metrics to physicians, pharmacists, nurses, clinical lab scientists, microbiologists, administrators, and other key stakeholders
Education	Deliver education to healthcare providers that promotes appropriate antifungal prescribing

The CDC core elements, Infectious Diseases Society of America (IDSA)/Society for Healthcare Epidemiology of America (SHEA) stewardship guidelines, and National Quality Forum (NQF) antibiotic playbook are excellent resources that list potential day-to-day stewardship activities that could be considered when focusing on antifungal prescribing.[13-15]

A good example of day-to-day stewardship activities would be actively promoting appropriate management of candidemia that focuses on a comprehensive bundle approach and meeting quality performances measures listed in IDSA guidelines. The IDSA recommended performance measures include timely initiation of treatment, appropriate antifungal selection, documented clearance of blood cultures, ophthalmology exam with non-neutropenic, removal or debridement of the source of candidemia (including removing infected central lines), assessing for disseminated disease, and recommending appropriate duration of therapy. AFS programs that actively recommend compliance with performance measures have significantly improved overall bundle compliance, optimized therapy, and minimized excessive duration of antifungal therapy.

Additionally, the *Journal of Antimicrobial Therapy* published a dedicated supplemental issue to antifungal stewardship, which provides excellent insight to establishing or optimizing AFS.[16] It's also important to note that, as of January 2017, the Joint Commission requires hospitals, critical access hospitals, and nursing care centers that seek accreditation by the Joint Commission to have an antimicrobial stewardship program and have incorporated aspects of the CDC antimicrobial stewardship core elements as part of its requirements.[13] Due to resource gaps, there may be unique barriers to implementing a successful AFS program that is based on the CDC core elements.[16] Table 4 describes barriers to implementing AFS programs in general.

Table 4. Barriers to Implementing an Antifungal Stewardship Program

Insufficient resources including knowledgeable personnel, funding, time, and technology
Lower specificity and sensitivity of fungal diagnostics
Transplant and oncology patients receive antifungal therapy across various inpatient and outpatient settings, which require increased coordination of efforts among all parties providing care
Populations receiving antifungals tend to be more immunosuppressed or critically ill, resulting in potential opposition from patients and providers in limiting antifungal prescribing
Limitations in the quality and quantity of primary literature to support changes in antifungal prescribing practices
Antifungal medications may not be covered by third-party payers, have unaffordable copays, or often require a prior authorization, which may lead to non-compliance, delays in therapy, or need to modify therapy
National treatment guidelines may provide recommendations that do not emphasis stewardship principles of minimizing unnecessary antifungals, and provide cost-effective care

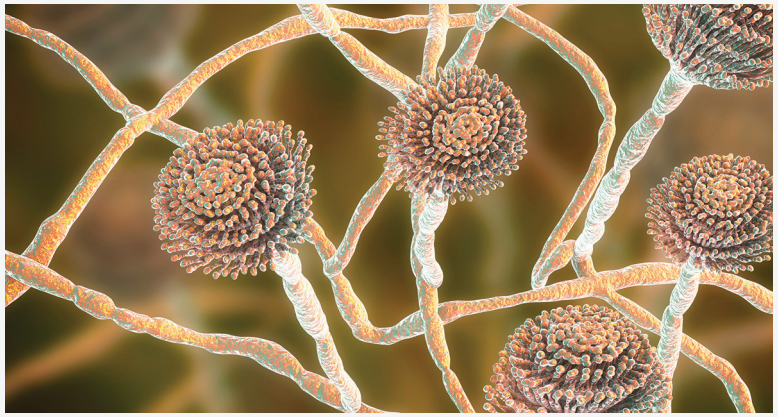
Strategies to meet the CDC core elements can largely be placed into several categories, which include activities that 1) create a structure and culture that promotes appropriate antifungal prescribing; 2) promote appropriate antifungal prescribing as one focus of daily follow-up; and 3) promote appropriate management of specific infectious syndromes as another focus of daily follow-up. There are numerous methods to help promote and guide appropriate antimicrobial therapy, but ongoing daily prospective audit and feedback (with or without prior authorization of antifungal therapy) has been the gold standard, which requires a stewardship pharmacist or physician to review patients on targeted antifungal therapy to promote appropriate prescribing. Other common methods used to promote appropriate antifungal prescribing include prescriber-directed antimicrobial time-outs, developing and promoting compliance with institution-defined antifungal criteria, creating guidelines for the treatment of specific infections, and developing guidelines for prophylaxis in high-risk populations. Prescriber-directed antimicrobial timeouts have been promoted by the CDC as a way to self-evaluate prescribing to ensure appropriate therapy is provided at the correct dose and frequency and provide an appropriate plan for duration of therapy. Table 5 lists categories of AFS activities as basic, intermediate, and advanced. Many hospitals just starting AFS programs will need to start with basic stewardship activities, and then expand into intermediate and advanced activities as their programs mature. Additionally, the advanced activities may require hospitals to utilize resources across departments, such as developing leukemia-specific antibiograms, developing computerized alerts, and developing dashboards for tracking stewardship metrics and associated clinical outcomes. Computerized alerts could provide patient-specific guidance for appropriate testing, starting timely antifungal treatment, promoting other process/performance metrics, or recommending correct duration of therapy. Hospitals should individually evaluate their current problem areas and available resources, then list AFS goals. The levels of basic, intermediate, and advanced stewardship activities (see Table 5) to meet individual hospital needs will vary and should evolve over time as prescribing antifungal patterns change.

Table 5. Basic, Intermediate, and Advanced Antifungal Stewardship Activities

Stewardship Activities	Basic	Intermediate	Advanced
Develop a structure and culture that promote appropriate antifungal prescribing	• Assign pharmacy and physician leads for stewardship programs with specific job descriptions that outline stewardship responsibilities • Meet regulatory and accreditation standards	• Identify key metrics associated with antifungal stewardship activities • Promote collaboration with key stakeholders • Provide stewardship education for healthcare providers	• Develop accountability-based goals that are linked to stewardship activities and metrics • Stewardship activities and metrics are tied to performance evaluations or incentives • Implement stewardship policy that allows discontinuation or modification of inappropriate antifungal prescribing
Promote appropriate antifungal prescribing	• Retrospective review and identification of specific interventions to improve antifungal prescribing	• Prior authorization and/or prospective audit and feedback, to promote appropriate antifungal prescribing (including dose, route, frequency, and duration) based on pre-established criteria and guidelines • Utilize clinical decision support to assist with dose optimization, IV-to-PO, duplicate coverage, and de-escalation • Implement antifungal time-out policy, which promotes prescriber self-evaluation of therapy • Develop unit-specific antibiograms • Establish multi-disciplinary process to manage drug shortages and promote appropriate alternatives • Evaluate patient's ability to afford antifungal therapy upon discharge and assist with third-party prior authorization or patient assistance programs as needed • Include nurses and other healthcare providers in antimicrobial stewardship activities	• Develop ICU-, transplant-, and/or cancer-specific antibiograms use data to help identify populations that require broad spectrum antifungal therapy and those that can use narrower spectrum therapy • Utilize prospective audit and feedback to help identify areas for improvement that results in changes to workflow, antifungal criteria, or guideline modifications • Incorporate rapid diagnostic testing plus real-time stewardship recommendation to improve antifungal timing • Develop communication and follow-up workflow process that ensures appropriate prescribing across transitions of care
Promote appropriate management of infectious syndromes, including empiric and definitive treatment for candidemia, invasive aspergillosis, Mucormorales infection	• Develop institutional treatment guidelines	• Guidelines contain information for management for common drug-drug interactions, toxicities, duration of therapy, therapeutic drug monitoring, and promotion of performance measures • Institutional guidelines are posted on hospital website, and provided as applications for mobile devices • Prospective audit and feedback to promote appropriate antifungal prescribing based on guidelines • Develop guidance for appropriate diagnostic testing, interpretation, and antifungal modification	• Prospective audit and feedback of syndrome specific infections, with stewardship leading efforts to promote appropriate overall multi-disciplinary management of infectious syndrome • Develop decision support tools to facilitate appropriate prescribing • Develop communication and follow-up workflow process that ensures appropriate management across transitions of care • Link process and prescribing measures with associated clinical and financial outcomes

The Significance of Transitions of Care as Part of an Antifungal Stewardship Program

Oncology, solid organ transplant, and hematologic stem-cell transplant recipients frequently require antifungal prophylaxis or treatment that requires prolonged durations of therapy. Thus, patients will be treated in several settings, including within the hospital, at outpatient infusion centers, oncology or transplant specialist offices, at home, and extended care facilities. It is imperative to develop good communication practices to ensure the appropriate antifungal treatment plan and duration is completed. Moreover, changes in non-antibiotic regimens (such as chemotherapy, oral anticoagulation, immunosuppressive therapy, and others) that occur across transitions of care may impact antifungal therapy. Additionally, government and third-party payers may not cover certain antifungal treatments, have unaffordable copays, or require prior authorizations. Thus, continuing an antifungal regimen that is considered first-line in hospital antifungal treatment or prophylaxis guidelines may not be possible. Developing a good transition of care program to address challenges patients encounter as they enter and leave various settings is essential in ensuring successful antifungal treatment. Table 6 lists common areas of concern as patients transition across spectrums of care.[16,17]



Many hospitals just starting AFS programs will need to start with basic antifungal stewardship activities, and then expand into intermediate and advanced activities as their programs mature (see Table 5)

Table 6: Areas of Concern as Patients Transition across Spectrums of Care

Area of Concern	Potential Barriers to Address	Solutions to Potential Barriers
Affordability of antifungal medication	• Patient lacks insurance coverage or insurance coverage is insufficient • Insurance requires prior authorization, which may delay the patient's ability to fill prescription • The inability to afford first-line antifungal therapy may lead to noncompliance or use of medications that are suboptimal or toxic	• Patient's ability to afford antifungal therapy should be addressed during hospitalization or during office visit • Integration of social work into routine discharge planning for patient with antifungal prescriptions • Patient assistance programs may improve affordability and compliance
Suboptimal or excessive duration of antifungal therapy	• Patients often receive care from several prescribers, which increases the likelihood of errors in duration of antifungal therapy	• Clear documentation of intended duration should be documented • Treatment plan should be communicated with all providers, and a single provider should be responsible for management of antifungal regimen
Drug-drug interactions	• Many of the azole antifungals have drug-drug interactions which can impact efficacy and safety • Drug-drug interactions can occur in any setting a patient receives healthcare • The effects of drug-drug interactions can occur when a medication is started, changed, or discontinued	• Patients should maintain an accurate list of medication regimens they are taking, including over-the-counter and nontraditional medications • Prescribers or pharmacists should conduct medication reconciliation during every healthcare setting interaction • Assess drug-food interactions • All prescribers across transitions of care should be responsible for evaluating potential drug-drug interactions when modifying medication therapy (starting, pausing, stopping, or changing)
Compliance with intended antifungal prescription	• Many factors can contribute to poor compliance, including complexity of medication regimens, real or perceived adverse effects, inability to afford medication,	• Assess the patient's ability to take the regimen • Avoid complex regimens, including different tablet or capsule strengths of the same drug, confusing measuring instructions for suspensions or solutions, and the number of total prescriptions per day • Communicate treatment outcomes expectations since many fungal infections take months of therapy before complete resolution • Schedule appropriate follow-up to ensure patient is tolerating antifungal therapy
Adverse effects	• Adverse effects are common with antifungal therapy and may impact overall efficacy	• Communicate potential adverse effects to the patient • Develop a plan to monitor antifungal adverse effects and associated labs, and communicate monitoring plan to all healthcare providers taking care of the patient • Conduct therapeutic drug monitoring when appropriate to minimize adverse effects

Tools and Resources

Therapeutic Drug Monitoring

The correlation of efficacy or toxicity with serum levels of several azole antifungals and flucytosine (5-fluorocytosine) is known. Regardless of which patients undergo therapeutic drug monitoring, a well-conceived plan for when levels will be taken and who makes dose adjustments should be communicated to the patient and all providers at the initiation of antifungal therapy. There are additional antifungal therapeutic drug monitoring resources that could aid hospitals in developing therapeutic drug monitoring recommendations[8,18] (see Figure 1).

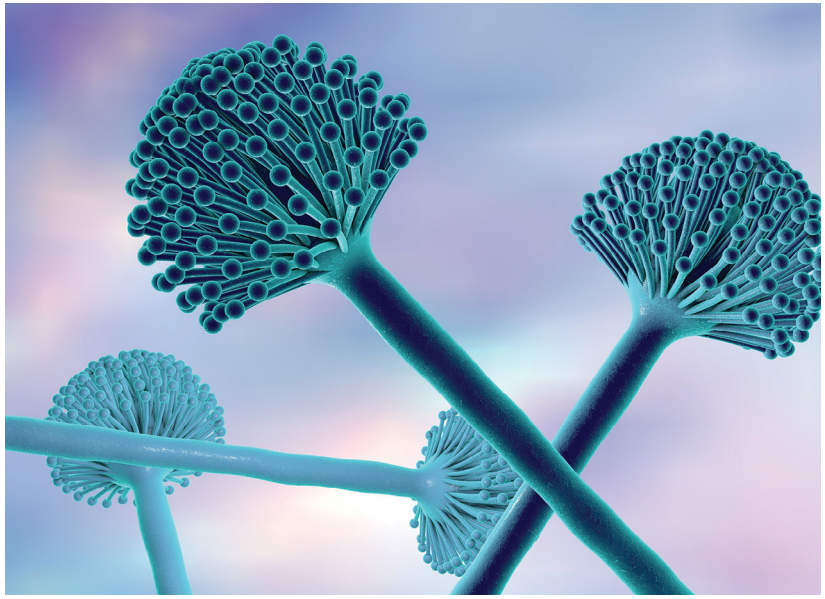


Figure 1. Sample Antifungal Therapeutic Drug Monitoring and Dose Adjustment Guideline from the University of Michigan Health System

VORICONAZOLE

Serum trough goals based on indication:

- Treatment: 1.0 to 5.5 mcg/ml: Routine monitoring recommended in all patients.
- Prophylaxis: 1.0 to 5.5 mcg/ml: A steady-state level is recommended, then a level is needed only if occurrence of persistent diarrhea, GVHD, possible hepatotoxicity or neurotoxicity, or breakthrough infection, once therapeutic

When to Get Trough Levels:

- First level should be drawn at Day 5-7 (steady state)
- Follow-up levels may be performed once monthly

Reasons for checking trough levels more frequently:

- Changes in voriconazole dosing or route, GVHD with diarrhea, addition or withdrawal of interacting medications, diarrhea, or perceived fungal disease progression or toxicity, suspected toxicity or concerns regarding non-adherence

Adult Dose Adjustment*:

- Levels greater than 5.5 mcg/ml should prompt dose reduction to minimize neurotoxicity and hepatotoxicity
- If the level is less than desired, increase daily dose by 50-100 mg and recheck level in 1 week. Make sure the patient is taking the drug on an empty stomach
- If the level is greater than 5.5 decrease daily dose by 100 mg and recheck level in 1 week

Figure 1. Sample Antifungal Therapeutic Drug Monitoring and Dose Adjustment Guideline from the University of Michigan Health System (cont'd)

ISAVUCONAZOLE

Serum trough goals based on indication:

- Treatment: >1,000 ng/mL: Routine monitoring recommended in all patients
- Prophylaxis: >1,000 ng/ml: Routine monitoring recommended in all patients

When to Get Trough Levels:

- First level should be drawn at Day 5-7 (steady state)
- Follow-up levels may be performed once monthly
- Trough levels are preferred; random levels are acceptable

Reasons for checking through levels more frequently:

- Changes in the dosage or formulation delivery, addition or withdrawal of interacting medications, perceived fungal disease progression, toxicity or concerns regarding non-adherence

Adult Dose Adjustment*:

- Although no data are available to inform therapeutic target levels or levels associated with toxicity, therapeutic drug monitoring is recommended to ensure that patients are absorbing drug. Troughs <1,000 ng/mL may warrant a dose increase, depending on the patient's clinical response to therapy. Isavuconazole is available as 186 mg (ie, half-dose) capsules, so doses should be increased or decreased by 186 mg

POSACONAZOLE

Serum trough goals based on indication:

- Treatment: >1,250 ng/ml: Routine monitoring recommended in all patients
- Prophylaxis: >700 ng/ml: No routine monitoring required for posaconazole tablets, except for morbid obesity, diarrhea for >72 hours, possible toxicity or breakthrough fungal infection. Monitoring is recommended for posaconazole suspension

When to Get Trough Levels:

- First level should be drawn at Day 5-7 (steady state)
- Follow-up levels may be performed once monthly
- Trough levels are preferred; random levels are acceptable

Reasons for checking through levels more frequently:

- Changes in the dosage, addition or withdrawal of interacting medications particularly PPIs, perceived fungal disease progression, development of mucositis, diarrhea or vomiting, suspected toxicity, concerns regarding non-adherence

Adult Dose Adjustment*:

- Delayed release tablet: Dose should be increased or decreased by 100mg, and adjustments of 200 mg or more should be avoided
- Oral suspension: Dosing at 200 mg four times daily will result in higher levels than 400 mg BID. Increasing the dose (>200 mg PO four times daily) will not generally result in a linear increase in levels as this drug has saturable absorption. Oral suspension should be taken with a fatty meal and acidic beverage such as cola. Use of acid suppression should be avoided

Figure 1. Sample Antifungal Therapeutic Drug Monitoring and Dose Adjustment Guideline from the University of Michigan Health System (cont'd)

ITRACONAZOLE

Serum trough goals based on indication:

- Treatment: itraconazole plus hydroxyintraconazole level >1-2 mcg/ml.
- Prophylaxis: itraconazole plus hydroxyintraconazole level >0.5 mcg/ml.
- Routine monitoring recommended in all patients.

When to Get Trough Levels:

- First level should be drawn 10-14 days after starting therapy
- Follow-up levels may be performed once monthly
- Random levels are acceptable because of long half-life

Reasons for checking trough levels more frequently:

- Changes in the dosage or delivery of itraconazole, addition or withdrawal of interacting medications, perceived fungal disease progression, suspected toxicity, or concerns regarding non-adherence.

Adult Dose Adjustment*:

- Capsules: Optimal absorption is dependent on administration *with food*. Also, absorption is dependent on gastric acidity, so discontinue unnecessary proton pump inhibitor (PPI) or H-2 antagonist therapy. Absorption can be increased by taking the capsules with an acidic drink, such as Coca-Cola. Avoid capsules in patients requiring PPI therapy. If patient has low levels on capsules despite the above measures, consider changing to solution or increasing the daily dose by 100-200 mg.
- Solution: Absorption is not affected by gastric pH. Optimal absorption dependent on administration in the *fasting* state.

FLUCYTOSINE

Serum peak level goal: between 50-75 mcg/ml.

When to Get Levels:

- First level should be drawn on day 3 after starting therapy, and peak should be obtained 2 hours after oral administration
- Peak levels >100 mcg/ml are associated with myelosuppression and hepatotoxicity
- Follow-up levels may be performed twice weekly

* Goal drug levels and recommendations for monitoring apply to both adult and pediatric patients. Please consult a clinical pharmacy specialist regarding dose adjustments for patients <18 years.

Antifungal Diagnostic Testing

Incorporating diagnostic testing with magnetic resonance, Multiplex FilmArrays, peptide nucleic acid fluorescent *in situ* hybridization, beta-D-glucan, and mass spectrometry time of flight (MALDI-TOF) can aid in the timely diagnosis of invasive *Candida* infections in the intensive care unit. Of these diagnostic test options, beta-D-glucan and MALDI-TOF are more widely available. Each test has unique characteristics and offers advantages in diagnosing *Candida* infections.[19]

The primary advantage of *Candida* magnetic resonance assay is the ability to detect *Candida* in a relatively quick timeframe of 3 to 5 hours, which is currently the quickest method for detecting candidemia. Additionally, *Candida* magnetic resonance assay may be able to detect candidiasis in patients with negative blood cultures. Unfortunately, testing all patients is cost-prohibitive and institutions frequently limit testing to high-risk groups, such as intensive care unit patients with risk factors for candidiasis.

The Multiplex FilmArrays and peptide nucleic acid fluorescent *in situ* hybridization systems can detect specific *Candida* species within a short period of time, after yeast is detected on Gram stain. These platforms allow for rapid *Candida* detection compared to traditional methods and allow selective testing in patients with positive blood cultures, but results are available approximately 16 to 24 hours later than *Candida* magnetic resonance assay.

MALDI-TOF can aid in rapid organism identification, which is also performed after positive blood culture or isolation of organism from plates for non-bacteremia source. MALDI-TOF can identify an organism 1 to 2 days quicker than traditional methods. Finally, beta-D-glucan assay can detect (1,3) beta-D-glucan in the fungal cell wall of several pathogens, including *Candida* spp., *Acremonium, Aspergillus* spp., *Coccidioides immitis, Fusarium* spp., *Histoplasma capsulatum, Trichosporon* spp., *Sporothrix schenckii, Saccharomyces cerevisiae,* and *Pneumocystis jirovecii*. The test is not specific for *Candida*, and appropriate diagnosis requires coordination of test results with patient presentation, risk factors, and other laboratory and diagnostic tests. However, the test is essentially helpful in diagnosing candidiasis infection without candidemia, especially when cultures cannot be obtained from the suspected site of infection. See Table 7 for differences in available diagnostic tests for *Candida* and candidemia.[19] Galactomannan is an *Aspergillus* antigen test with very good positive predictive value, but poor negative predictive value. Thus, it's helpful in diagnosing invasive *Aspergillus*, but doesn't help in AFS in discontinuing therapy when results are negative.

Table 7. Diagnostic Tests for *Candida*

Technology	**Magnetic resonance imaging**	**Mass spectrometry**	**Polymerase chain reaction or Multiplex FilmArray**	**Peptide nucleic acid fluorescent *in situ* hybridization**	**Beta-d-glucan assay (modified *Limulus* assay)**
Substrate	Direct from blood	Requires growth from any specimen	Requires growth from blood culture	Requires growth from blood culture	Direct from blood
Turnaround time	180-300 minutes	5-10 minutes	60 minutes	90 minutes	8-12 hours
Site of *Candida* infection	Blood*	Any Site	Blood	Blood	Any Site
Published studies utilizing diagnostic technology within AFS program	No	Yes	Yes	Yes	No

*Able to detect some *Candida* infections outside blood stream, but current FDA indication is for diagnosis of candidemia.
Information is current as of August 2018.

Treatment and Prophylaxis Guidelines

National guidelines for treatment and prophylaxis of fungal infections frequently provide solid evidence-based recommendations but may not provide recommendations from a stewardship perspective. Guidelines frequently list multiple FDA–approved options for treatment or prophylaxis, and institutions should review guidelines and discuss the best option for their patients. Additionally, institutional antifungal criteria and treatment guidelines should take care to minimize excessive and unnecessary antifungal duration of therapy. Table 8 contains links to commonly used antifungal treatment and prophylaxis guidelines.

Table 8. Common Antifungal Treatment and Prophylaxis Guidelines

IDSA Treatment Guidelines for Coccidioidomycosis
IDSA Treatment Guidelines for Aspergillosis
IDSA Treatment Guidelines for Candidiasis
IDSA Treatment Guidelines for Blastomycosis
IDSA Treatment Guidelines for Sporotrichosis
IDSA Treatment Guidelines for Histoplasmosis
NCCN Guideline for Prevention and Treatment of Cancer-Related Infections

Chemotherapy-Antifungal Drug-Drug Interactions

Drug-drug interactions with antifungal therapy and chemotherapy are common, but the appropriate management of these interactions is complex. Most antifungal-chemotherapy interactions are not listed in national datasets used by Electronic Health Records, which creates a scenario where significant interactions are not identified upon entry of a chemotherapy or antifungal order.[8] A common practice oncology clinicians use is to evaluate any potential interaction by evaluating if either regimen undergoes or influences cytochrome metabolism, then avoiding the antifungal if a potential interaction is identified. Some of these interactions are likely insignificant and do not require any medication or dose modifications, but studies that describe the extent of the interaction are frequently lacking. Thus, prescribers err on the side of avoiding any potential interaction, which creates a scenario where a second-line antifungal therapy is prescribed, which may alter efficacy or toxicity. Regardless of a clinician's preference to hold interacting antifungal therapy while patients receive chemotherapy, the AFS program should help build processes to identify and address drug-drug and drug-food interactions. This is essential to minimize unnecessary adverse effects. Chau and colleagues published a consensus guideline which includes a review of antifungal drug-drug interactions.[8]

Summary of Recommendations for Readers

The following recommendations for effective AFS are provided as guidance for oncology, transplant, and critical care patients, which typically comprise the majority of antifungal prescribing at hospitals.

Oncology and Transplant Patients

- Starting timely antifungal prophylaxis and treatment in oncology and transplant patients is as important as stopping inappropriate therapy
- Develop an institutional guideline for antifungal prophylaxis that provides appropriate drug selection, dosing, and duration based on underlying cancer and chemotherapy (for oncology patients), and transplant type and risk for infection (for transplant patients). The guideline should include recommendations for avoidance of significant drug-drug interactions, management of toxicities associated with antifungal therapy, and should provide recommendations for therapeutic drug monitoring, when appropriate
- Understand local epidemiology for invasive *Candida, Aspergillus*, and *Mucor* infections and local antifungal antibiogram
- Develop antifungal treatment guidelines for appropriate diagnosis and treatment of *Candida, Aspergillus*, and *Mucor* infections. Guidelines should include appropriate drug selection, dosing, and duration of therapy. Guidance for therapeutic drug monitoring, management of drug-drug interactions, and toxicities associated with antifungal therapy should be included in the treatment guideline
- Establish a transition of care program that helps patients navigate third-party payers and patient assistance programs to increase affordability and compliance. Additionally, plans for appropriate antifungal duration of therapy should be developed to limit unnecessary antifungal exposure

Critical Care Patients

- Empiric therapy targeting invasive *Candida* infections should be an AFS focus. Development of an empiric treatment guideline is essential to minimize unnecessary antifungal prescribing, which should include data from local epidemiology, local resistance patterns, and incorporate risk factor-based therapy with or without *Candida* diagnostics
- Risk factor–based scoring tools offer low positive predictive value and good negative predictive value
- Several diagnostic technologies can improve timely diagnosis of candidemia, fluorescence *in situ* hybridization, and magnetic resonance imaging assay for *Candida* has a strong negative predictive value
- Education and/or infectious diseases consults should be provided to help intensivists differentiate fungal colonization vs infection
- Guidelines for the comprehensive treatment of invasive fungal infections should be developed to promote compliance with the IDSA performance measures, including timely appropriate therapy, ophthalmology exams, removal of infected sources of infection, appropriate duration of therapy, and appropriate work-up for disseminated candidiasis. Stewardship team prospective audit with feedback and/or infectious diseases consult for patients with candidemia significantly improves compliance with performance measures

Below are practical recommendations for establishing an effective AFS program

- Build a business case for AFS and obtain support from hospital administration (Chapter 2)
- Establish a core antifungal stewardship group with an infectious diseases physician and infectious diseases pharmacist leaders who are appropriately trained, and have experience in treating oncology, transplant, and critically ill patients
- Create a multi-disciplinary group with key stakeholders from infection prevention, microbiology, infectious diseases,

pharmacy, nursing, informatics, quality improvement, oncology, solid organ transplant, bone marrow transplant, and intensive care

- Identity key metrics and outcomes that reflect an effective AFS, and which could point to opportunities for improvement (Chapter 4). Align daily responsibilities to track and improve corresponding metrics and outcomes
- Create a reporting structure to provide routine updates of successes and challenges to stakeholders and hospital administrators
- Develop tools and structure to address AFS across transitions of care that promote appropriate initiation and discontinuation of antifungal therapy and appropriate monitoring; assess affordability and compliance; and provide multidisciplinary involvement in the inpatient and outpatient settings

Conclusion

Developing good AFS practices should follow the recommended outline provided by the CDC core elements for antimicrobial stewardship in acute care and ambulatory care settings. However, the actions taken to help promote AFS will vary based on hospital needs and identified problems. Evaluating antifungal prescribing in critical care, oncology, and transplant patients is essential to building a successful AFS program. Building a strong collaborative approach across transitions of care with key stakeholders is required to minimize unnecessary antifungal therapy and adverse effects, and to optimize outcomes.

Implementing AFS requires a long-term commitment, with a desire to progress from basic to advanced stewardship activities outlined in this chapter.

References

1. Muñoz P, Bouza E; COMIC (Collaboration Group on Mycosis) study group. The current treatment landscape: the need for antifungal stewardship programmes. *J Antimicrob Chemother.* 2016;71(suppl 2):ii5-ii12.
2. Yusuf E, Versporten A, Goossens H. Is there any difference in quality of prescribing between antibacterials and antifungals? Results from the first global point prevalence study (Global PPS) of antimicrobial consumption and resistance from 53 countries. *J Antimicrob Chemother.* 2017;72(10):2906-2909.
3. Valerio M, Vena A, Bouza E, et al.; COMIC study group (Collaborative group on Mycosis). How much European prescribing physicians know about invasive fungal infections management? *BMC Infect Dis.* 2015;15:80.
4. Pagano L, Caira M, Candoni A, et al. The epidemiology of fungal infections in patients with hematologic malignancies: the SEIFEM-2004 study. *Haematologica.* 2006;91(8):1068-1075.
5. Cordonnier C, Pautas C, Maury S, et al. Empirical versus preemptive antifungal therapy for high-risk, febrile, neutropenic patients: a randomized, controlled trial. *Clin Infect Dis.* 2009;48(8):1042-1051.
6. Morrissey CO, Chen SC, Sorrell TC, et al. Australasian Leukaemia Lymphoma Group and the Australia and New Zealand Mycology Interest Group. Galactomannan and PCR versus culture and histology for directing use of antifungal treatment for invasive aspergillosis in high-risk haematology patients: a randomised controlled trial. *Lancet Infect Dis.* 2013 Jun;13(6):519-528.
7. Cornely OA, Maertens J, Winston DJ, et al. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. *N Engl J Med.* 2007;356(4):348-359.

8. Chau MM, Kong DC, van Hal SJ, et al. Consensus guidelines for optimizing antifungal drug delivery and monitoring to avoid toxicity and improve outcomes in patients with haematological malignancy, 2014. *Intern Med J*. 2014;44(12b):1364-1388.

9. Hermsen ED, Zapapas MK, Maiefski M, Rupp ME, Freifeld AG, Kalil AC. Validation and comparison of clinical prediction rules for invasive candidiasis in intensive care unit patients: a matched case-control study. *Crit Care*. 2011;15(4):R198.

10. Seo SK, Lo K, Abbo LM. Current state of antimicrobial stewardship at solid organ and hematopoietic cell transplant centers in the United States. *Infect Control Hosp Epidemiol*. 2016 Oct;37(10):1195-1200.

11. So M, Yang DY, Bell C, Humar A, Morris A, Husain S. Solid organ transplant patients: are there opportunities for antimicrobial stewardship? *Clin Transplant*. 2016;30(6):659-668.

12. De Pauw B, Walsh TJ, Donnelly P, et al. Revised Definitions of Invasive Fungal Disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clin Infect Dis*. 2008;46:1813-21.

13. Center for Disease Control and Prevention. Antibiotic Prescribing and Use in Hospitals and Long-Term Care. Core Elements of Hospital Antibiotic Stewardship Programs. www.cdc.gov/antibiotic-use/healthcare/implementation/core-elements.html. Accessed 10-1-2018.

14. Barlam TF, Cosgrove SE, Abbo LM, et al. Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. *Clin Infect Dis*. 2016;62(10):e51-77.

15. National Quality Partners Playbook™: Antibiotic Stewardship in Acute Care. (Epub). National Quality Forum. 2016.

16. Antifungal stewardship: existing framework and future perspectives. *J Antimicrob Chemother*. 2016;71(suppl 2).

17. Jones JM, Leedahl ND, Losing A, Carson PJ, Leedahl DD. A pilot study for antimicrobial stewardship post-discharge: avoiding pitfalls at the transitions of care. *J Pharm Pract*. 2018;31(2):140-144.

18. Ashbee HR, Barnes RA, Johnson EM, Richardson MD, Gorton R, Hope WW. Therapeutic drug monitoring (TDM) of antifungal agents: guidelines from the British Society for Medical Mycology. *J Antimicrob Chemother*. 2014;69(5):1162-1176.

19. Hamdy RF, Zaoutis TE, Seo SK. Antifungal stewardship considerations for adults and pediatrics. Virulence. 2017;8(6):658-672.

CHAPTER 4:

Antifungal Stewardship Outcome and Evaluation Strategies

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Introduction/Overview

Antifungal drug use often accounts for a significant component of an institutional pharmaceutical budget. Data that examined antifungal drug use during an 11-year period from 2005 through 2015 demonstrate that almost half of the use of these agents—totaling nearly a billion dollars annually in the United States—occurs in the hospital setting.[1]

The primary goals of antimicrobial and antifungal stewardship programs are to optimize drug use while minimizing unintended consequences.[2] However, measuring the impact of these programs is often overlooked beyond traditional financial metrics. This chapter discusses the key concepts of measuring antifungal stewardship initiatives and provides practical guidance on how to best assess efforts directed at optimizing use of these agents.

Quality Frameworks

It is important to define your measurement ideally before—but certainly as you are beginning to design your stewardship program and targeted interventions. Given that stewardship operates in the realm of patient safety and quality, any metrics selected need to align with measurement concepts within the quality domain. There are 3 main quality of care frameworks that have been validated in practice and are used to guide decision making in health systems. These include the Donabedian model,[3] which takes a healthcare system perspective; the World Health Organization (WHO) model, which focuses on universal right to healthcare guiding decisions[4]; and the Bamako Initiative,[5] a more economic perspective implemented in African counties, which focuses on situations that may already be suboptimal or where systems are already failing. Each of these has relevant aspects that can be employed when assessing antifungal stewardship efforts (Table 1). In order to ensure the most success for the local stewardship program, stewardship leadership should consult the

Table 1: Key Elements of Quality Assessment Frameworks[6]

Framework	Element for Evaluation	Potential Antifungal Stewardship Applications
Donabedian	Structure	• Are all Centers for Disease Control Core Elements for Stewardship met and include antifungal use?[7] • Are fungal pathogens included in hospital antibiogram? • Do routine data extracts include data on antifungal drug use?
	Process	• Are antifungal agents included in prior authorization (restriction) protocols? • Do guidelines for use include most common fungal infections encountered at the facility? • Do empiric treatment guidelines address when empiric antifungal therapy should be administered?
	Outcomes	• What is the rate of fungal infection among patients in whom antifungal prophylaxis is routinely administered? • What is the mortality rate for invasive aspergillosis at your facility
World Health Organization (WHO)	Optimal health for all	• Is antifungal drug use appropriate (as determined by local, national, or international treatment guidelines)?
	Responsiveness	• Are guidelines for antifungal use up to date
	Fairness in financing	• Are appropriate patient assistance programs in place to ensure all patients receive consistent care? • What percentage of at-risk patients receive first-line antifungal prophylaxis agents?
Bamako	Effectiveness	• Do available antifungal agents have susceptibility for the most common pathogens in my facility?
	Efficiency	• Does drug availability limit our ability to keep patients on antifungal prophylaxis regimens both in and out of the hospital?
	Sustainability	• Are there measures in place to support patients who cannot continue antifungal treatment regimens when they leave the hospital (either due to cost or other factors)?
	Equity	• When guidelines for antifungal use are not followed, are the deviations warranted based on best practices or unique patient circumstances? • Do we routinely review the need to update local treatment guidelines?

local quality and safety experts about systematic approaches to quality data. Knowing what this group considers the key determinants of success before finalizing any assessment plan for stewardship or other activities will lead to more successful integration of these reports into existing quality reporting.

Antifungal Stewardship

Following the principles of the Donabedian quality framework,[3] successfully optimizing antifungal therapy will depend on the ability to measure several aspects of an antifungal stewardship program. The structure of the program will fall under the same rubrics that are in place to assess the overall stewardship program at the institution and follow the Centers for Disease Control and Prevention (CDC) Core Elements model.[7] There are, however, specific areas targeting antifungal drug use that should be added under certain core element areas to ensure there is a comprehensive program for addressing antifungal drug use in place. For the elements of leadership, accountability and drug expertise, there will likely not be dedicated resources for the antifungal component of the program. For the tracking and reporting core elements, it will be important to assess whether or not antifungal drug use is included in the measurement of overall drug use. Under the action element, ensuring there are guidelines in place for appropriate and relevant areas of antifungal drug use should also be considered. Examples of this might include assessing whether specific guidelines for use of antifungal drug use are included, as well as whether or not antifungal agents are included in other stewardship interventions such as prior authorization (or approval) programs or other interventions that cover both antibacterial and antifungal areas of use. Similarly, educational offerings specifically targeting areas of common antifungal drug overuse—such as treatment of funguria in asymptomatic catheterized patients and routine prophylaxis of intensive care unit (ICU) patients with antifungal agents—should be included in educational offerings of the stewardship program.

Measuring the process of stewardship will also resemble measurements of the rest of the stewardship program, assessing what the stewardship team is doing and the actual implementation of the interventions. Activities such as cases reviewed, whether or not guidelines are followed, and changes in antifungal drug use will be included in these assessments. The quantity of antifungal drug use will also be tracked as an outcome of an antifungal stewardship program and, as such, will be a main focus of the stewardship team in antifungal stewardship activities.

Measuring Antifungal Drug Use

Sources of Data and Strategies for Obtaining Data

Obtaining reliable data on drug use is a challenge for any medication class. Like antibacterial agents, drug use for hospitalized patients can be assessed using different data sources, each with advantages and disadvantages. The 3 main sources of data are financial data (quantity purchased); dispensing data (amount released from the pharmacy with intent to use); and administration data (what was actually given to the patient).

When selecting the data source(s), it is important to weigh factors associated with the quality of the data versus the relative effort required to obtain the data. As outlined in Table 2, many stewardship metrics rely on administration data that provides very granular comparisons of data, but these often require a data source at the level of the medication administration

record (MAR). Obtaining these data relies on the availability of a good electronic medication administration record (eMAR) and programming capabilities to readily extract the data. Even if an eMAR is in place at an institution, if stewards do not have access to local programming expertise or centralized reporting that can quickly and easily obtain the data, using these sources of data will not be adequate to meet the ongoing needs of the stewardship team. It is preferable to use patient-specific measures of drug use instead of purchasing data that provides no patient-level detail. However, if this is the most reliable data source for a facility, it may be more useful for the stewardship assessments than infrequent or unreliable reports on patient-level use metrics.

Table 2: Numerators and Denominator Metrics for Stewardship*

Metric	Definition	How is it calculated?	Advantages	Disadvantages	Data Source
Numerators					
Costs[8]	• The amount paid for antifungal agents	• Sum of all expenditures for antimicrobial class	• Easy to obtain • Often tracked by administration and can be used to justify programs	• Not sensitive to what is given to patients (there are many other reasons for purchasing antifungal drugs that may never reach inpatients) • Often cannot track where drugs are used based on purchasing data • Cost data greatly influenced by different purchasing patterns and contracting that can change frequently	• Pharmacy purchasing software, but be sure to include all sources as often products (such as frozen products) are obtained from outside sources. • If antifungal agents are used rarely, may be difficult to track as supplies may be purchased and not used for a long period of time
Charges[8]	• The amount a facility charges for antifungal agents. Most institutions use a standard cost: charge ratio for this[9]	• Sum of all charges through the hospital billing system[8]	• Should be relatively easy to obtain • Obtained at the individual patient level[8] • Does not run the risk of revealing contract pricing	• Like cost data, often subject to changes in pricing depending on the local charge practices[8]	• Hospital billing department data
Defined daily doses (DDD)[10]	• Assumed average maintenance dose per day for a drug used for its main indication in adults	• A total quantity of drug (in grams) is tallied; this total is divided by the reference standard published by the World Health Organization (WHO)[10]	• Can be calculated from any data source (purchasing, dispensing, administration) • Using the international reference standard makes data comparable between facilities	• Reference standards not valid in pediatric patients • May underestimate use in patients with renal failure • Limited by the quality of data source	• Various sources: can be calculated from pharmacy purchasing data dispensing data or administration data (all of these need to be converted to grams of drug)

*Adapted from: Dodds Ashley E, Stenehjem E. Measurement in Antibiotic Stewardship. In: Barlam TF, Neuhauser MM, Tamma P, Trivedi KK, eds. Practical Implementation of an Antibiotic Stewardship Program. New York, NY: Cambridge University Press; 2018:131-154.

Table 2: Numerators and Denominator Metrics for Stewardship (cont.)

Metric	Definition	How is it calculated?	Advantages	Disadvantages	Data Source
Numerators					
Days of therapy (DOT)/ antimicrobial days[11]	• The number of days that an agent is given	• Counted as each calendar day in which a patient received a given antimicrobial	• Reflects actual drug administration data • Difficult (if not impossible) to measure without electronic medication administration records • Standard adopted by the Centers for Disease Control (CDC) for the National Healthcare Safety Network Antimicrobial Use Option	• A DOT does not necessarily reflect a full effective day of treatment • Combination therapy can result in higher DOT estimates when data are totaled between agents	• Electronic medication administration record (eMAR)
Antimicrobial starts[7]	• The sum of all new orders/ prescriptions during a given time period	• All new orders are compiled and each therapy is counted as a new start	• May be easier to calculate without eMAR data • Recommended as a measure of antibiotic use for long-term care facilities	• Does not measure overall exposure (length of therapy); therefore, chronic/prophylactic therapy and single dose prophylaxis regimens are counted the same • Have to develop a method for tracking formulation changes that may result in a new "order" without changes in therapy	• Pharmacy dispensing data; eMAR data
Doses dispensed[11]	• Sum of all individual doses dispensed from the pharmacy department	• Total of all individual doses dispensed	• Does not require eMAR data; most pharmacy software programs capture doses dispenses per each order • Can be used to estimate DOT data if needed	• Subject to variations in pharmacy dispensing model • Between 30-50% of all dispensed doses are never administered to patients so may overestimate use	• Pharmacy dispensing data; eMAR data
Length of therapy[11]	• Duration of antifungal use	• Sum of DOT for a given treatment course in a given patient care setting (inpatient)	• Looks at total duration for a treatment course and not just for a given agent	• Can be difficult to combine step-down therapy (either through de-escalation or IV to oral conversion) without counting overlap day	• Agent-specific eMAR data
Overall length of therapy[11]	• Overall duration of both inpatient and outpatient antifungal treatment for a given infection/treatment course	• Sum of DOT for inpatient treatment and planned outpatient duration	• Better descriptor of overall exposure	• Inpatient use is measured in DOT so captures drug actually administered to patients • There is no verification of outpatient medication administration and therefore, this portion of calculation is simply an estimate	• eMAR data in addition to discharge prescription data

Table 2: Numerators and Denominator Metrics for Stewardship (cont.)

Metric	Definition	How is it calculated?	Advantages	Disadvantages	Data Source
Denominators					
Patient Days[11]	• The number of occupied patient bed days; calculated at a single time each day	• At a given time each day • A count is made of each patient in a given location	• Same measure that is used for healthcare associated infections (HAI) data • Readily available in most facilities	• May not count patients who are actually receiving antimicrobials if use is started after transfer/admission • As encounters shorten in length, just a measure of patient days may not adequately reflect patient volumes	• Administrative databases and/or manual calculation
Days present[12]	• Time period during which a given patient is at risk for antifungal[12] exposure for a given patient location	• Count of the number of patients who were present for any portion of day in a given location	• Quantifies risk of exposure accurately for each unit • Allows a more granular description of patient movement	• New metric that relies on electronic data capture, so validation is needed	• Hospital admission, discharge, transfer (ADT) data
Inpatient admission[13]	• An encounter when a patient is admitted to a facility[13]	• Count of the number of patients with inpatient status	• Readily available • In theory captures patient areas most influenced by antimicrobial stewardship team	• Does not count emergency department and observation patients who may be large consumers of antimicrobials • May be inflated by certain patient populations such as inpatient psychiatry and rehabilitation not likely to use antimicrobials	• Administrative databases
Patient encounter[13]	• An interaction between a patient and healthcare provider for the purpose of providing services[13]	• Count of all patient interactions with the health system. Can be limited to type (inpatient encounter)	• Denominator that captures inpatient and outpatient visits. • Used by NHSN for laboratory ID events thus data is readily available for many areas	• Not very specific for type of encounter	• Billing data
Inhabitants	• The census of a given region under study	• Captured through census data	• Easily obtained for most reasons	• Not specific to healthcare setting	• Government census data

One of the most significant challenges to measuring antifungal drug use is that unlike antibacterial agents that are given to at least half of the inpatient population resulting in thousands, if not tens of thousands of administrations each month, antifungal drug use is rarer, even in the largest of facilities. The result for measurement is that it can be much harder to detect errors of omission in the data. Errors of omission in drug data are common and have many causes, including change in product due to drug shortages, purchases outside of traditional supply chains,

The need for antifungal drugs will vary greatly among peer institutions depending on the case load contribution from high-risk patients with hematologic malignancy, hematopoietic stem cell transplantation, and solid organ transplantation.

and use of non-formulary agents that are not appropriately tagged as anti-infective agents in information systems, to name a few. In order to ensure the most accurate data are being used reliably, it is best to adopt routine data validation practices as part of the stewardship program. Stewardship programs may develop internal data validation protocols. A recommended data validation method is also available from the CDC as part of the National Healthcare Safety Network (NHSN) Antimicrobial Use (AU) module.[12] Data regarding antifungal drug use are currently not part of benchmarking calculations; however, these data validation approaches apply to both antibacterial and antifungal agents and will help to ensure data integrity.

Drug Use Metrics

There are several metrics that have been successfully employed to describe antibacterial drug use that easily translate into use with antifungal agents. The 2 most commonly used measures of drug use are the days of therapy (DOT) and defined daily dose (DDD). The DDD is the older of the 2 metrics and was developed by the WHO.[10] Data from any source that provides a total sum of drug in grams/milligrams can be easily converted to the DDD metric using a published conversion factor.[10] The result is total drug use converted into the number of typical daily doses but does not reflect use in actual patients. This is in contrast to DOT, where a single dose of an agent actually administered to a patient on a calendar day is counted as a day of therapy. DOT measures the number of days a patient receives an antimicrobial agent, regardless of the dose. Unlike DDD, DOT can only be measured on data from the eMAR. DOT is the standard metric adopted by the CDC in the NHSN AU module. The current DDD correction indexes for antifungal agents is found in Table 3 and a calculation example using pharmacy purchase data is found in Table 4. Additional metric descriptions and advantages and disadvantages of each of these metrics are discussed in greater detail in Table 2.

Denominators

In order to standardize use among different facilities, an estimate of patient volume is needed to normalize the data. This is very similar to the process used for infection prevention activities, but there are notable differences in some of the metrics adopted for use in antifungal stewardship. The various denominators typically employed in antimicrobial stewardship are summarized in Table 2. Each of these would be appropriate for monitoring antifungal drug use as well.

Table 3: WHO DDD Definitions and Dosing Considerations[10]

Agent	Current DDD Index	Usual Daily Dose*	Dosing Considerations					Comments
			Loading Dose?	Weight-based?	Renally-adjusted?	Indication-specific?	Formulation-specific?	
Amphotericin (IV)	35 mg	350 mg		Yes	Yes	Yes	Yes	Information is not available for lipid-based products
Anidulafungin	0.1 g	0.1 g	Yes			Yes		
Caspofungin	50 mg	50 mg	Yes			Yes		
Fluconazole (IV/Oral)	0.2 g	0.4 g	Yes	Yes	Yes	Yes		
Flucytosine (IV/Oral)	10 g	7 g		Yes	Yes			
Isavuconazole (IV/Oral)	0.2 g	0.2 g	Yes					
Itraconazole (IV/Oral)	0.2 g	0.2 g	Yes			Yes	Yes	
Micafungin	0.1 g	0.1 g				Yes		
Posaconazole (IV/Oral)	0.3 g	0.3 g	Yes			Yes	Yes	
Voriconazole (IV/Oral)	0.4 g	0.56 g	Yes	Yes	Yes	Yes	Yes	

*Usual dose is based on 70kg patient with normal renal function.

Table 4: Sample Hospital Purchasing Data and Demonstration of DDD Calculations[10]

Drug	Product size	Form	Unit	Grams per package	Number purchased	Total grams	DDD
Fluconazole	400 mg	Vial	10x 1 vial	(0.4g x 10)= 4 g	15	(4 g x 15 packages purchased)=60 g	60 g purchased/0.2 (DDD correction factor)=300 DDD
Fluconazole	200 mg	Tabs	1x 50 tabs	(0.2g x 50 tabs)= 10 g	5	(10 g x 5 packages purchased)=50 g	50 g purchased/0.2 (DDD correction factor)=250 DDD
							Total fluconazole DDD=550
Voriconazole	50 mg	Tabs	1x 30 tabs	(0.05g x 30)=1.5 g	20	(1.5g X 20 packages purchased)=30g	60 g purchased/0.4 (DDD correction factor)=75 DDD

Benchmarks

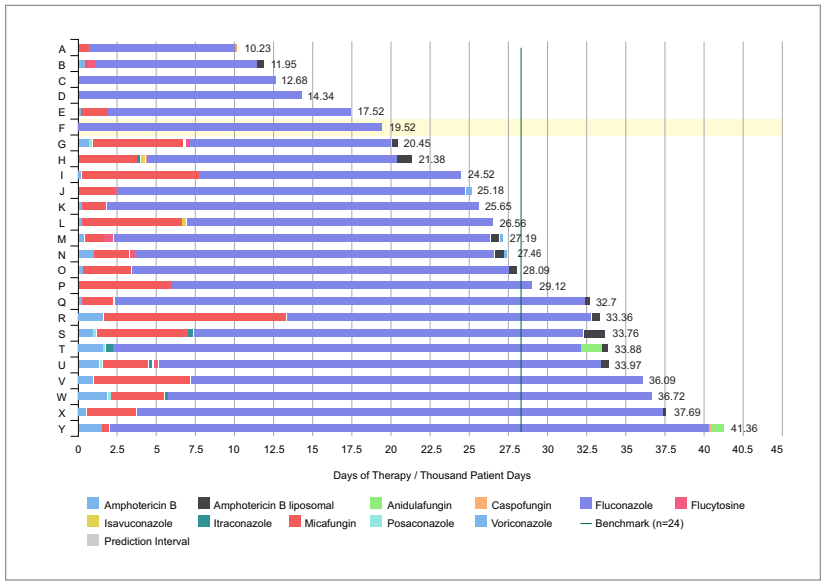
Once appropriate data regarding antifungal drug use has been obtained and normalized to patient volumes using one of the available denominators, the next logical step is to find data with which to compare this use. A key consideration in this process is the overall burden of fungal disease and presence of high-risk patient populations within your institutions. High-risk populations have been discussed in other sections of this manual but quantifying the at-risk population at your institution is an essential part of measurement for assessing your stewardship program. The need for antifungal drugs will vary greatly among peer institutions depending on the case load contribution from high-risk patients with hematologic malignancy, hematopoietic stem cell transplantation, and solid organ transplantation.

External sources of antifungal drug use data may be difficult to identify at first, but there are several suggestions for potential sources with which to compare your data. One initial place to begin is through your pharmaceutical purchasing group. Often, there are comparative data sources that can be readily obtained. The NHSN AU option does facilitate capture of antifungal drug use. For antibacterial agents, a standardized antibiotic administration ratio (SAAR), a risk adjusted tool for comparing antimicrobial use is calculated for key targeted agents in the most common types of hospital units.[14] There is currently not a SAAR calculation available for antifungal drug use within acute care hospitals, but this is something being considered for future releases through NHSN.

Figure 1 is a representative sample of community hospitals and individual facility antifungal use normalized to 1,000 patient days. Figure 1 demonstrates great variability among these facilities as well as great differences in patient care areas. In this example, only 5 of the representative hospitals have a dedicated oncology unit as defined by NHSN.[12] The hospitals with dedicated oncology units cluster toward the high areas of antifungal use

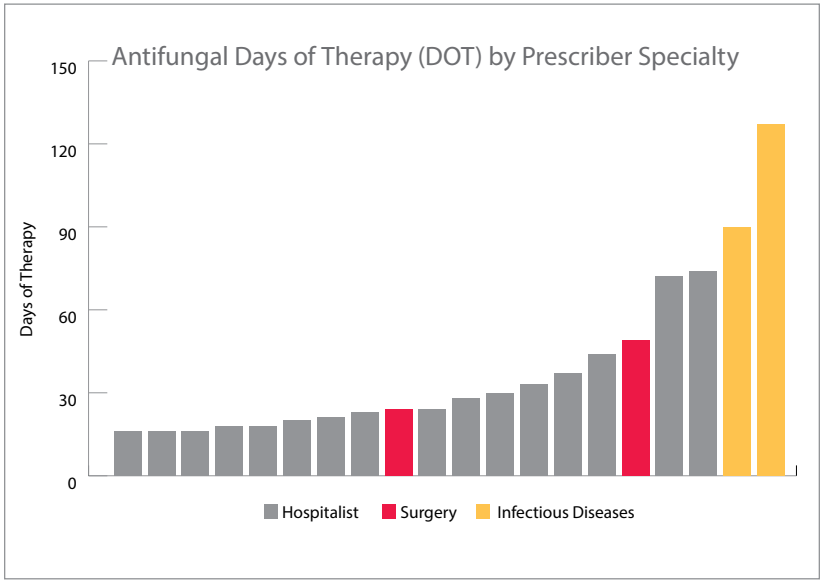
and include facilities labeled X, W, T, Q, and G. Similar trends would be expected for facilities where there are large transplant populations.

Figure 1: Example of Summary Antifungal Use Data by Individual Hospital (indicated as A through Y)



Stratifying use by hospital certainly gives some external perspective to overall drug use, but in some cases, internal benchmarks may be the most appropriate comparator to employ. Tracking use of overall antifungal drugs as well as individual agents over time is a tool employed by most antifungal stewardship programs. Stewardship programs also find value in stratifying antifungal use by unit in order to identify areas of high use where to target efforts. Reporting antifungal drug use by prescriber is a newer approach and is also helpful in identifying key individuals with whom the stewardship program should target antifungal stewardship planning and education. Figure 2 provides an example of prescriber-specific reports by specialty as well as individual blinded provider, and another example of further stratification by route selection within a specific hospitalist service. There is variability among members of this team caring for somewhat similar patient populations. In this example, targeted discussions with provider S and T to assess reason for this variation in practice may be warranted.

Figure 2: Example of Antifungal Drug Days of Therapy Stratified by Prescriber



Appropriateness

One of the main goals of antifungal stewardship is to drive more appropriate antifungal drug use. However, the definition of appropriate drug use remains a challenge. Currently approved drug indications often do not represent true areas of use for drugs, and even with sufficient evidence of efficacy to treat a fungal disease of interest, there may be local reasons limiting use of an agents for concerns for resistance and or safety. Therefore,

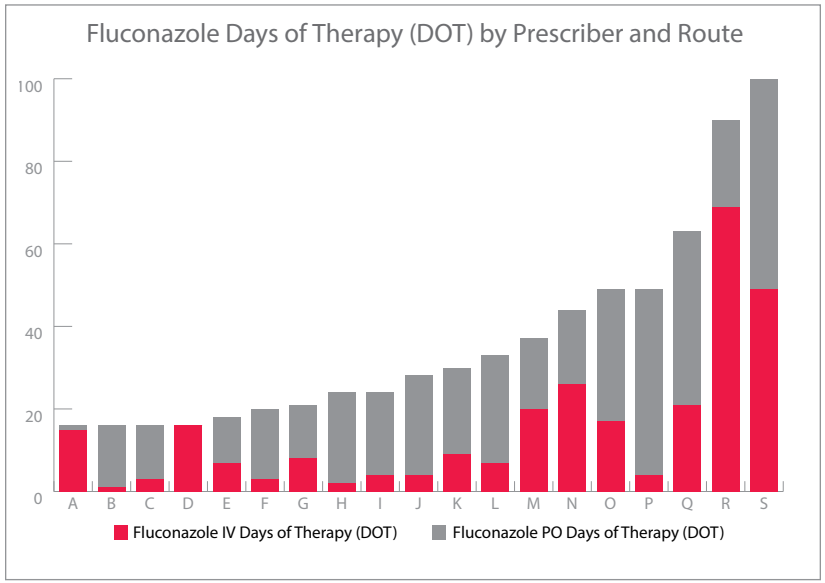
for the local stewardship team, assessing appropriateness of is best done when comparing actual antifungal drug use to locally developed and approved guidelines for use.

Outcomes

Sources of Data

One of the most commonly employed methods to capture data on patient outcomes is through traditional medication use evaluations (MUEs) which can also be performed as disease state–specific reviews. A detailed review of the overall process for conducting an MUE is included in the appendix in Figure 3. These reviews have been conducted for decades but are often limited in scope due to the time required to review all of the individual patient records in order to assess true outcomes.

Figure 3: MUE Process



In order to minimize the workload of traditional MUEs, groups have turned efforts to mining the electronic health record to assess outcomes of patients receiving antifungal therapy. The most successful example of this is work done at Veterans Administration medical centers. Their work has validated hand collected data with electronic data extracts of the same outcomes and have shown that electronic data sources can be adequate.[15] Electronic data sources have many outcomes data that may be of interest. This includes patient disposition, including mortality, disposition at discharge, and the need for escalated care (eg, if an intensive care unit or surgery is required. In addition, many safety metrics can be gleaned from the electronic health record, including occurrence of medication-related adverse events, which, if coded correctly, have been shown to be effectively found in queries of the electronic record.[16] More sophisticated technology can use data recognition approaches to scan computerized notes using natural language processing; however, that is a very resource-intensive approach and is used more in the research setting than for routine quality improvement work.

Financial Outcomes

Cost savings have been associated with stewardship programs since the very first reports of successful stewardship and antifungal agents were included often, given the high cost of these medications. Most often, financial outcomes have been limited to cost savings on individual drugs. These types of analyses can be very useful for justifying ongoing or expanded support for the stewardship program at the institutional level, but do not provide a comprehensive review of outcomes that may be associated with stewardship activities targeting antifungal agents. It has been well documented that sometimes

the least expensive option for one hospital department may end up resulting in significantly increased charges to other departments that may not be appreciated.

An example of this is the debate regarding use of conventional versus the more expensive lipid formulations of amphotericin B. Clearly, from the pharmacy perspective, the conventional amphotericin B product will result in lowest pharmacy costs, but with a 30% incidence of renal failure resulting in a cost of approximately $30,000 per case, the additional pharmacy cost of the lipid formulations could easily be justified.[17] This is just one example of the importance of including all cost aspects in assessing antifungal stewardship interventions. In the realm of antifungal therapy, the role and costs of diagnostic testing have a significant part in determining the overall impact of a program. Many of the new and more rapid diagnostic strategies can help ensure that patients receive appropriate therapy earlier and may delay the need for costly and toxic antifungal therapy in some patients due to better pathogen detection and identification.

Similar to the disconnect between drug cost and toxicity with amphotericin B, these newer tests can certainly decrease pharmacy costs but have very real cost and personnel requirements for the laboratory. It is important to include these estimates in any economic impact assessment.[18] For some of the newer diagnostic tests, a comprehensive economic review has found that the newer technologies do not always result in improved care or lower overall costs,[19,20] further highlighting the importance of assessing overall costs—including diagnostics—after implementing antifungal stewardship interventions.

Financial outcomes are slightly more difficult to assess when determining the efficacy of antifungal prophylaxis strategies. In this case, the drug is being administered, often for long times at significant costs to prevent events that may be relatively rare to begin with. These avoided costs are important to include but often more difficult to quantify given the challenge of measuring what does not happen. A way to help determine the overall economic impact of these strategies is to estimate the number of cases prevented. This can be done by literature estimates or, in the case of a newly implemented intervention, the actual change in case rate seen. Once an estimated number of cases is determined, estimated disease treatment costs can be applied to the cases to determine the overall estimated savings. Table 5 includes estimated treatment costs for various invasive fungal infections based on 2005 dollars.[14] There is a high cost to the diagnostic workup for any invasive fungal infection. Having to do so in the setting of prophylaxis would be included as a cost of that prophylaxis as it would be seen as a clinical failure. Therefore, in some instances it is appropriate to determine the change in patients undergoing diagnostic workup whether or not fungal infection was found. Working with stewardship champions in the laboratory, infection prevention and control, and within hospital administration will facilitate access to these more nontraditional economic data.

Table 5: Estimated Inpatient Cost of Invasive Fungal Infections[14]

Metric	Data Source
Invasive candidiasis	$35,140
Aspergillosis	$23,550
Cryptococcosis	$2,918
Zygomycosis	$60,486

Clinical outcomes

Treatment

The ultimate outcome in treating any infection is successful cure of disease without significant toxicity; however, the applicability of this metric in antifungal stewardship efforts is challenging as the work of the steward may not necessarily change overall success if only unnecessary drug use is being eliminated. Many stewardship programs use overall mortality as a balancing measure to ensure that efforts to drive more appropriate antifungal use are not causing patient harm. Other similar balancing metrics are commonly suggested as good measures to document the impact of stewardship programs, including

- Drug toxicity
- Need for escalation of care
- Measures of treatment failure
  - escalating antifungal treatment due to lack of clinical response
  - undergoing additional diagnostic work up as part of antifungal prophylaxis regimens

For absolute effect of the stewardship program, measuring clinical outcomes alone to determine the ultimate success of any stewardship intervention remains challenging for both bacterial- and fungal-based efforts. In fact, in a recent consensus panel activity that assessed 90 candidate metrics for routine tracking and reporting of stewardship interventions, none of the 20 proposed clinical outcomes were determined to be meaningful for stewardship, associated with improved prescribing, or feasible in facilities with electronic health records.[21] Therefore, any assessment of antifungal stewardship interventions targeting infection treatment will likely include a combination of use metrics and balancing clinical outcomes, as discussed above.

As previously mentioned, one aspect of antifungal therapy that differs greatly from the majority of antibacterial drug use is long-term prophylaxis regimens. In clinical trials of these regimens, a well-accepted convention is to use a composite endpoint to measure success. One of the most common examples of this comes from the literature regarding prophylaxis for fungal infections in patients with hematologic malignancy. The most commonly employed composite endpoint includes 5 components: survival, resolution of fever, successful treatment of any fungal infection (if present), no breakthrough infection while on empiric therapy, and no toxicity from the drug requiring a change in therapy. A similar approach to assessing stewardship interventions at the local level is certainly reasonable. To implement this, you need to have an agreed upon definition of success, which may include elements such as no need to start empiric antifungal therapy for suspected or proven infection, need for hospitalization or transfer to a higher level of care, and additional measures of toxicity. Using the composite endpoint approach tries to combine all of the various competing priorities of a stewardship program into dichotomous outcomes that are easier to summarize and provide an overall assessment of success.

For absolute effect of the stewardship program, measuring clinical outcomes alone to determine the ultimate success of any stewardship intervention remains challenging for both bacterial- and fungal-based efforts.

Conclusions

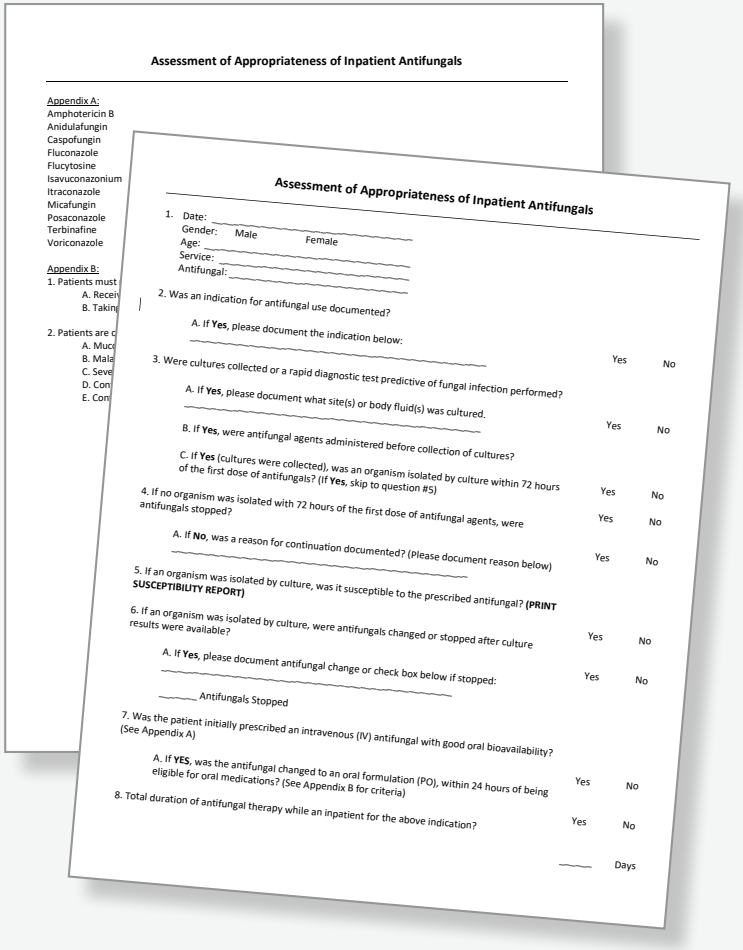
Measuring antifungal drug use has many similarities to antibacterial drug use, although often the scale will differ greatly from the latter drugs that are used more commonly in the acute care setting. Being able to measure antifungal drug use and compare this use within individual institutions over time and between institutions caring for similar at-risk patient populations are key aspects to implementing meaningful stewardship and tracking the outcomes of your stewardship program. These data alone, however, will not change use, so having strategies to interpret and share these measurements with key stakeholders are essential elements to stewardship success.

Appendix/Tools

1. **Data collection method:** Traditionally, MUEs have included long hours of manual data collection. However, with the advent of more comprehensive electronic health records, it is now possible to conduct much of the MUE process using electronic data capture. An all-electronic MUE process has been proven effective within the VA health system.[15] Of course, this requires appropriate IT resources to abstract the data. Using a combined electronic and manual data capture is another process that is frequently used. In this process, case forms are populated as much as possible with data from easily retrievable electronic systems and then supplemented by manual data capture. If data collection is being performed manually, it is important that a data dictionary is developed to ensure consistency among reviewers and that expectations are clear for all involved in the process.
2. **Patient identification method:** It probably seems intuitive that you will be looking for patients who received a targeted antifungal of interest, and this can be generated from hospital electronic data sources whether it is a pharmacy dispensing system or a more comprehensive electronic health record. Although the title implies these reviews are drug-focused, there are also disease state–focused reviews that can be conducted in a similar manner. These disease state reviews use alternate data sources such as microbiology laboratory report for all patients with a pathogen of interest (such as *Candida* spp., for example) in order to identify targeted patients. Others use more manual, real-time patient lists. This might be rounding sheets kept by a clinical pharmacist or kinetics service that might be reviewing patients who had therapeutic drug monitoring of an antifungal regimen.
3. **Select the sample size:** Unlike clinical trials that rely on statistical methods to determine sample size, MUEs typically aim to capture enough data from which to guide program activities. Often, the sample size required is based on many factors, including how many patients had the targeted agent or infection of interest during a reasonable time and the resources available for data collection. In our experience in our stewardship network, starting with a target sample size of around 30 patients provides sufficient data to identify trends in antifungal use and better inform stewardship decisions. There are certainly examples of other approaches, as well. One strategy that has been used is a point prevalence approach that identifies a period of time (day, week, month) during which all patients are reviewed to give a snapshot of use. In this case, sample size is driven by the number of eligible patients during the pre-identified period of time.

4. **Prepare the data collection instrument:** This step deserves the most thought, preparation, and review. It is important to ensure all necessary data are captured so additional data retrieval steps are not required. It is important for many people to review the design during this phase. The CDC has prepared and distributed validated assessment tools that can be deployed easily to capture data as part of an MUE. Assessment tools like an MUE are excellent for measuring more aspects regarding drug use in a targeted fashion. An example of this form, with modifications for antifungal drug use, can be found in Figure 4.
5. **Collect the data:** This can be one of the most time-consuming parts of the process. Key factors to success are setting data collection deadlines that are reasonable for all involved and then routinely checking in with everyone who is collecting data to be sure there are no questions regarding data collection and that progress is being achieved as planned.
6. **Analyze the data:** Data summaries should be comprehensive but brief and digestible for the end user. Typically, graphic and tabular summaries of key elements (demographics, outcomes of interest) and summaries of key points/next steps work best to ensure the data are useful in guiding stewardship activities.
7. **Use the data for change:** Once collected, the data should be used to inform the best next steps for guiding appropriate antifungal drug use. In order for the data to be most useful, the results of the MUE should be shared widely with key stakeholders for antifungal drug use.

Figure 4: Example MUE from the CDC[22]



Assessment of Appropriateness of Inpatient Antifungals

Appendix A:
Amphotericin B
Anidulafungin
Caspofungin
Fluconazole
Flucytosine
Isavuconazonium
Itraconazole
Micafungin
Posaconazole
Terbinafine
Voriconazole

Appendix B:
1. Patients must
A. Recei
B. Takin

2. Patients are c
A. Muc
B. Mala
C. Seve
D. Con
E. Con

Assessment of Appropriateness of Inpatient Antifungals

1. Date: _____
Gender: Male Female
Age: _____
Service: _____
Antifungal: _____

2. Was an indication for antifungal use documented? Yes No

A. If **Yes**, please document the indication below:
_____

3. Were cultures collected or a rapid diagnostic test predictive of fungal infection performed? Yes No

A. If **Yes**, please document what site(s) or body fluid(s) was cultured.
_____

B. If **Yes**, were antifungal agents administered before collection of cultures? Yes No

C. If **Yes** (cultures were collected), was an organism isolated by culture within 72 hours of the first dose of antifungals? (If **Yes**, skip to question #5) Yes No

4. If no organism was isolated with 72 hours of the first dose of antifungal agents, were antifungals stopped? Yes No

A. If **No**, was a reason for continuation documented? (Please document reason below) Yes No
_____

5. If an organism was isolated by culture, was it susceptible to the prescribed antifungal? **(PRINT SUSCEPTIBILITY REPORT)** Yes No

6. If an organism was isolated by culture, were antifungals changed or stopped after culture results were available? Yes No

A. If **Yes**, please document antifungal change or check box below if stopped: Yes No
_____

_____ Antifungals Stopped

7. Was the patient initially prescribed an intravenous (IV) antifungal with good oral bioavailability? (See Appendix A) Yes No

A. If **YES**, was the antifungal changed to an oral formulation (PO), within 24 hours of being eligible for oral medications? (See Appendix B for criteria) Yes No

8. Total duration of antifungal therapy while an inpatient for the above indication? _____ Days

References

1. Fitzpatrick MA, Suda KJ, Evans CT, Hunkler RJ, Weaver F, Schumock GT. Influence of drug class and healthcare setting on systemic antifungal expenditures in the United States, 2005-15. *Am J Health Syst Pharm*. 2017;74:1076-1083.

2. Barlam TF, Cosgrove SE, Abbo LM, et al. Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. *Clin Infect Dis*. 2016;62:e51-77.

3. Donabedian A. Evaluating the Quality of Medical Care. *Milbank Mem Fund Q*. 1966;44:Suppl:166-206.

4. World Health Organization. Quality of Care: A Process for Making Strategic Choices in Health Systems. Geneva: WHO, 2006.

5. Bamako Initiative Management Unit, UNICEF. The Bamako Initiative. Reaching Health Goals Through Strengthened Services Delivery. New York: UNICEF, 1990 (Mimeo).

6. Dodds Ashley E, Stenehjem E. Measurement in Antibiotic Stewardship. In: Barlam TF, Neuhauser MM, Tamma P, Trivedi KK, eds. Practical Implementation of an Antibiotic Stewardship Program. New York, NY: Cambridge University Press; 2018:131-154.

7. CDC. Core Elements of Hospital Antibiotic Stewardship Programs. Atlanta, GA: US Department of Health and Human Services, CDC; 2014. http://www.cdc.gov/getsmart/healthcare/implementation/core-elements.html. Accessed July 8, 2018.

8. Finkler SA. The distinction between cost and charges. *Ann Intern Med*. 1982;96:102-109.

9. Cost-to-Charge Ratio Files. Healthcare Cost and Utilization Project (HCUP). Agency for Healthcare Research and Quality, Rockville, MD. www.hcup-us.ahrq.gov/db/state/costtocharge.jsp. Accessed July 1, 2018.

10. Defined Daily Dose (DDD). http://www.who.int/medicines/regulation/medicines-safety/toolkit_ddd/en/. Accessed December 3, 2018.

11. Schwartz DN, Evans RS, Camins BC, et al. Deriving measures of intensive care unit antimicrobial use from computerized pharmacy data: methods, validation, and overcoming barriers. *Infect Control Hosp Epidemiol*. 2011;32:472-480.

12. AU Option Implementation Data Validation. https://www.cdc.gov/nhsn/pdfs/ps-analysis-resources/aur/AU-Option-Implementation-Data-Validation-P.pdf; Accessed July 3, 2018.

13. 8.11 Resource Encounter-Content. https://www.hl7.org/fhir/encounter.html. Accessed December 3, 2018..

14. Dodds Ashley E, Drew R, Johnson M, et al. Cost of invasive fungal infections in the era of new diagnostics and expanded treatment options. *Pharmacotherapy*. 2012;32:890-901.

15. Jones B, Haroldsen C, Madaras-Kelly K, et al. In Data We Trust? Comparison of Electronic Versus Manual Abstraction of Antimicrobial Prescribing Quality Metrics for Hospitalized Veterans With Pneumonia. *Med Care*. 2018;56:626-633.

16. Wang X, Chase H, Markatou M, Hripcsak G, Friedman C. Selecting information in electronic health records for knowledge acquisition. *J Biomed Inform*. 2010;43:595-601.

17. Bates DW, Su L, Yu DT, et al. Mortality and costs of acute renal failure associated with amphotericin B therapy. *Clin Infect Dis*. 2001;32:686-693.

18. Forrest GN, Mankes K, Jabra-Rizk MA, et al. Peptide nucleic acid fluorescence *in situ* hybridization-based identification of *Candida albicans* and its impact on mortality and antifungal therapy costs. *J Clin Microbiol*. 2006;44:3381-3383.

19. Prasad P, Fishman JA. Impact and cost of the serum galactomannan assay at a tertiary care facility. *Transplantation* 2014;98:773-780.

20. Bertz H, Drognitz K, Finke J. Analysis of the efficiency and costs of antifungal prophylaxis and mycological diagnostics in patients undergoing allogeneic haematopoietic cell transplantation: "real life" evaluation. *Ann Hematol*. 2016;95:457-463.

21. Moehring RW, Anderson DJ, Cochran RL, et al. Expert Consensus on Metrics to Assess the Impact of Patient-Level Antimicrobial Stewardship Interventions in Acute-Care Settings. *Clin Infect Dis*. 2017;64:377-383.

22. Centers for Disease Control. CDC implementation resources. https://www.cdc.gov/antibiotic-use/healthcare/implementation.html. Accessed December 21, 2018.

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