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Proceedings From a Consensus Panel

Antifungal Stewardship as a Means of Optimizing the Management of Invasive Fungal Infection

This guide is intended to provide an overview of selected topics in the management of patients with fungal infections. Although this information may provide guidance to clinicians, it is not intended to serve as a substitute for fungal infection treatment guidelines (Infectious Diseases Society of America [IDSA]), sound clinical judgment or decision-making, and professional experience.

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Introduction

The combination of factors that exist within the arena of invasive fungal infections (IFI) make the principles of antifungal stewardship important for institutions to consider.[1-4] Contributing factors include the challenges in diagnosing fungal infections and resulting treatment delays, inappropriate antifungal use in some patients, and increasing costs related to such use. There is a desire to maintain current best standards of care and address requirements from various influential bodies.[3]

Importantly, stewardship may provide optimization opportunities to an institution, regardless of size or type. These examples below were provided by faculty members at the consensus panel:

- The large, **800-bed community hospital** that is struggling with antifungal costs and use. Stewardship may align the hospital staff toward creating guidelines for the appropriate use of treatment, which eventually may help rein in costs.

- The **tertiary care center** with high-risk populations in its transplant program and medical and surgical intensive care units (ICUs) may assess and change its protocol through stewardship, by generating local epidemiology data, tracking antifungal susceptibility patterns, and adapting established guidelines.

- The **300-bed suburban teaching hospital** that is dealing with inappropriate empiric treatment of IFI and a growing concern about emerging species that are less susceptible to treatment may use stewardship to evaluate prescriptions for antifungals, decrease inappropriate use, and track patient outcomes.

- The **long-term acute-care facility** facing recurrent infections and periodic outbreaks in patients may employ stewardship principles to not only reduce infection events but also to educate staff on risk factors.

To help support institutions and their plans for stewardship, this guide has been developed with leading experts in the field of infectious disease. It will examine the rationale, potential benefits, and possible elements of an antifungal stewardship program. It will present guideposts—a practical approach from a systems perspective—for establishing a program. This guide is not a "recipe" or "cookbook" for implementing antifungal stewardship and is not intended to create new treatment guidelines. Instead, this guide intends to help create an understanding of how to be a steward of good treatment practices for the management of IFI.

The Rationale for Antifungal Stewardship

In their policy statement, the IDSA and the Society for Healthcare Epidemiology of America (SHEA) define antimicrobial stewardship as a way to achieve the best clinical outcomes while minimizing adverse events and limiting selective pressures that drive the emergence of resistance.[5]

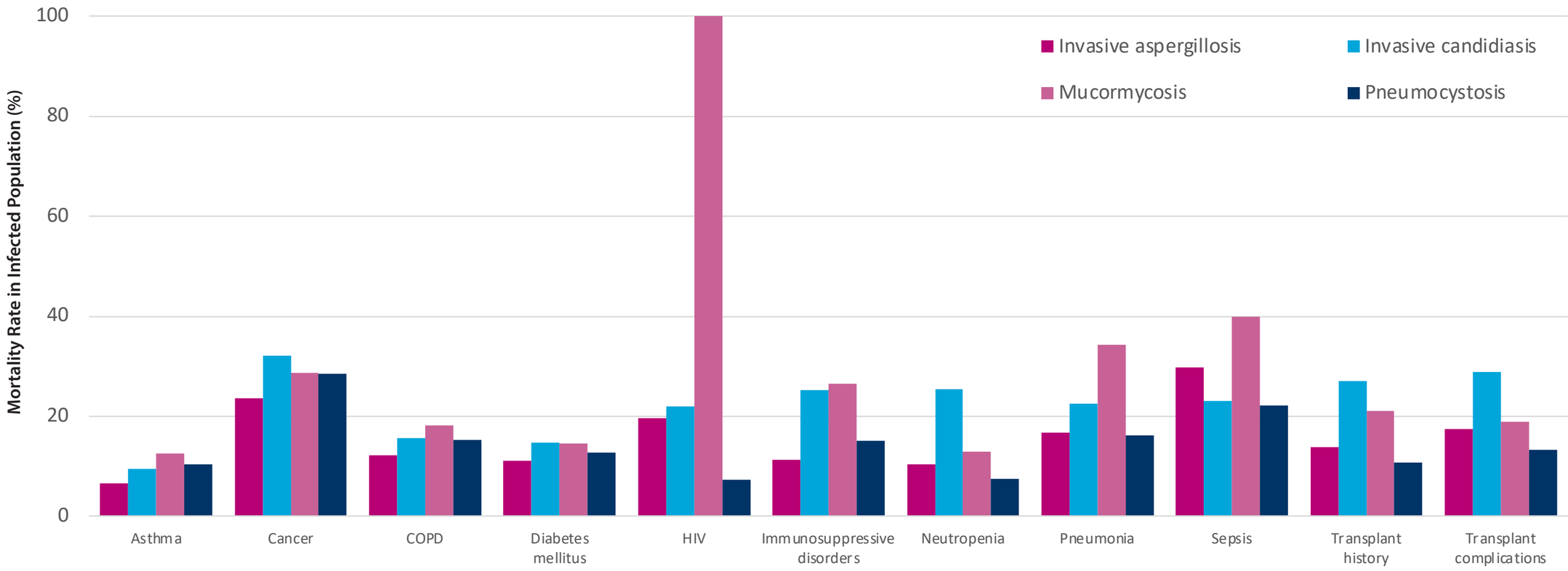
According to the statement, such programs "may also reduce excessive costs attributable to suboptimal antimicrobial use."[5] The objectives outlined in this definition apply to antifungal stewardship as well[3]; that is, optimize clinical outcomes while minimizing unintended consequences of antifungal use, such as toxicity, treatment selection, and the emergence of resistance. The Mycoses Study Group Education and Research Consortium (MSGERC) states that the core principles of antimicrobial stewardship are essential to antifungal stewardship; however, there are challenges unique to antifungal stewardship with regard to the patient population at risk for invasive fungal disease and diagnostic approaches.[3]

Costs of antifungal agents along with their recognized toxicities are principal justifications for antifungal stewardship.[3] Antifungal agents are considered one of the most expensive anti-infective agents on hospital formularies. A recent study reported that antifungal agents accounted for $376.1 million of total drug expenditures in nonfederal hospitals in 2019.[6] Another study found that antifungal agent expenditures exceeded $9.37 billion across all health care sectors in the United States for the years 2005 to 2015.[7]

Early and appropriate antifungal therapy given to patients who need it can reduce inappropriate use of antifungal drugs.[3] In a retrospective cohort study of 90 ICU patients who developed candidemia within 14 days of hospital admission, 88.9% received inappropriate therapy.[2] Mean hospital length of stay was significantly longer and associated hospital costs were significantly higher in the group that received inappropriate therapy. Antifungal stewardship may help promote the appropriate use of antifungal therapy by helping to ensure the right drug is prescribed for the right patient for the right amount of time.[3]

The mortality associated with IFIs and diagnostic uncertainty are two of the challenges that can potentially be aided by antifungal stewardship.[8] The overall mortality rate of hospitalized patients diagnosed with fungal infections was approximately 5% in the United States in 2018. However, the mortality rate may vary depending on the type of fungal pathogen and the presence of a risk condition.

Mortality in Patients With Fungal Disease Diagnosed During Inpatient Visits, by Risk Condition in the 2018 Healthcare Cost and Utilization Project, United States[9]



COPD=chronic obstructive pulmonary disease; HIV=human immunodeficiency virus.

Antifungal resistance is an emerging treatment issue that may also be addressed in an antifungal stewardship program.[3,10-12] Influential bodies, such as the IDSA, SHEA, Pediatric Infectious Diseases Society (PIDS), The Joint Commission, and the Centers for Disease Control and Prevention (CDC) support antimicrobial stewardship, which includes antifungal stewardship.[5,13,14] For example, The Joint Commission has an antimicrobial stewardship standard for hospitals, critical access hospitals, and nursing care centers.[13] The MSGERC has published a set of evidence-based recommendations for best practices in antifungal stewardship.[3]
The CDC recommends antifungal stewardship as a way to reduce antifungal resistance, and the Centers for Medicare and Medicaid Services has a standard for antibiotic stewardship programs for hospitals and critical access hospitals.[14,15]

Potential Benefits of Antifungal Stewardship

The clinical and nonclinical benefits of antimicrobial stewardship have been widely documented.[16-21] Meanwhile, data on the benefits of antifungal stewardship are accumulating. Implementation of stewardship-related actions have been shown to improve the selection of appropriate antifungal therapy and compliance with therapy duration; decrease the time to receipt of effective antifungal therapy; result in early initiation of therapy and improved outcomes, with infectious disease consultation; promote cost-effective therapy; reduce the risk of developing antifungal resistance; reduce adverse events and drug-drug interactions, therefore improving patient safety; and improve timely therapeutic drug monitoring.[3,22-28]

Elements of Antifungal Stewardship

The essential elements of a stewardship program are well described for antimicrobial stewardship[29] and may be applied to antifungal stewardship.[3] While the principles of antimicrobial stewardship are essential to antifungal stewardship, substantial differences exist in diagnostic approaches for the patient population at risk for IFI.[3]

- **Core elements.** In its antimicrobial stewardship standard, The Joint Commission outlines core elements for stewardship programs that include leadership commitment; accountability; drug expertise; implementing recommended actions; monitoring the program, which may include tracking information on antibiotic prescribing and resistance patterns; regular reporting of information on the program to relevant staff; and educating practitioners, staff, and patients.[13] These core elements are aligned with a set of evidence-based recommendations for best practices in antifungal stewardship published by the MSGERC in 2020.[3]

- **Multidisciplinary approach.** An orchestrated effort is needed in antifungal stewardship programs with engagement of a multidisciplinary team and consensus building with individual users.[3] Core members of a stewardship program may include the ID physician, infection preventionist(s), pharmacist(s), practitioner, and nursing lead, according to The Joint Commission.[13] Depending on the site, the multidisciplinary team may also include an oncologist or critical care specialist.[3] The Joint Commission also requires the use of organizational-approved multidisciplinary protocols for stewardship programs.[13] Recommended protocols from the IDSA and SHEA include preauthorization and/or prospective audit and feedback; facility-specific clinical practice guidelines for common infectious diseases; interventions to improve antimicrobial use and outcomes in specific infectious diseases; intravenous to oral conversions; and strategies to encourage prescriber-led reviews.[29]

- **Implementation of antifungal guidelines.** Guidelines need to be applicable to the setting where the patient is being treated.[3] The MSGERC describes educating prescribers and developing local guidelines as the first steps in establishing antifungal stewardship.

- **Translate data into action.** The Joint Commission includes data as an element of performance for its antimicrobial stewardship standard. The standard recommends that facilities collect, analyze, and report data related to antimicrobial stewardship, such as antimicrobial use and resistance patterns. Facilities can then implement improvements based on that data.[13] Electronic health records and clinical decision support systems help to track resistant pathogens, antimicrobial use, data on patient-specific microbiology cultures and susceptibilities, patient-specific factors, adverse drug reactions, and drug-drug interactions.[28] The MSGERC recommends using data-driven strategies to optimize antifungal stewardship interventions.[3] Guidelines from the IDSA and SHEA suggest specific measurements for stewardship programs,

including days of therapy, cost of therapy, and measurements applicable to the specific intervention.[29]

- **Education.** The Joint Commission and the MSGERC suggest that institutions provide education on antimicrobial resistance and opportunities for improving antimicrobial use for physicians and other health care practitioners.[3,13] IDSA/SHEA guidelines stress that lectures, pamphlets, and other types of so-called "passive" education should be combined with other strategies such as prospective audit and feedback.[29]

Multidisciplinary Guidelines

Antifungal stewardship programs should be supported by the current scientific literature.[13] Guidelines need to be applicable to the setting where the patient is being treated. Adapting practice guidelines to the local setting is an important element of antifungal stewardship.[3] For example, the National Comprehensive Cancer Network published guidelines on the prevention and treatment of infections in patients with cancer.[30] Management of IFI is supported by guidelines from the MSGERC, the IDSA, and other organizations, which are designed to assist clinicians in providing appropriate evidence-based care.[3,31-33] In addition to guiding IFI therapy, the IDSA has published guidelines regarding catheter care in patients with IFI.[34]

Adapting practice guidelines to the local setting is an important element of antifungal stewardship[3]

- Core recommendations for antifungal stewardship include offering clinical care pathways or treatment bundles at the point of care

NCCN Clinical Practice Guidelines in Oncology: Prevention and Treatment of Cancer-Related Infections Version 1.2021[30]

Core Recommendations for Antifungal Stewardship: A Statement of the Mycoses Study Group Education and Research Consortium[3]

Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America[31]

Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America[32]

Updated Guidelines of the Infectious Diseases Working Party of the German Society of Hematology and Medical Oncology[33]

Clinical Practice Guidelines for the Diagnosis and Management of Intravascular Catheter-Related Infection: 2009 Update by the Infectious Diseases Society of America[34]

NCCN=National Comprehensive Cancer Network.

Evidence-based guidelines are playing an increasingly prominent role, due in part to availability of different classes of antifungal agents (polyenes, triazoles, and echinocandins) and the complexity of treatment selection.[31]

IDSA publications provide guidance for prophylaxis (use of antifungal in a patient with no evidence of infection), preemptive therapy, empirical therapy (use of antifungal in the presence of persistent and refractory fever in patients at high risk for fungal infection), and culture-based treatment of candidiasis and aspergillosis.[31,32]

Guideposts and Considerations: Establishing an Antifungal Stewardship Program

This section describes guideposts that came out of the Antifungal Stewardship Consensus Panel based on general guidelines and published references. Collectively these steps encompass the principles of antifungal stewardship. But they are not intended to serve as new guidelines or as a substitute for your own clinical judgment and professional experience.

BECOME FAMILIAR WITH PUBLISHED GUIDELINES: Published standards for stewardship (e.g., The Joint Commission) and guidelines (e.g., IDSA) are available.[13,29] In general, the concepts and components of antimicrobial stewardship are relevant to antifungal stewardship.[3]

In addition to general guidelines, the MSGERC suggests assessing the needs of the specific institution to determine how guidelines can be adapted to the institution (the local setting) based on their available resources and expertise. The Joint Commission and the MSGERC agree that the core strategies of antifungal stewardship can be implemented most successfully based on a close understanding of risk factors, local epidemiology, outcomes, and available resources, which will differ among institutions.[3,13] Published studies recommend that antifungal stewardship programs also reflect the needs of high-risk populations and adopt a standard policy for risk factors such as catheter care.[35,36]

RECOGNIZE RISK FACTORS FOR IFI: Understanding and recognizing the risk factors for IFI may help to implement a successful antifungal stewardship program.[3]

Risk factors for invasive candidiasis are diverse and include[32]:

- *Candida* colonization
- Severity of illness
- Exposure to broad-spectrum antibiotics
- Recent major surgery, especially abdominal surgery
- Necrotizing pancreatitis
- Hemodialysis
- Parenteral nutrition
- Corticosteroids
- Use of central venous catheters

Risk factors for invasive aspergillosis include[37]:

- Severe immunosuppression (due to hematologic malignancy, hematopoietic stem cell transplant, solid organ transplant) combined with:
  - Neutropenia
  - Prolonged immunosuppressive therapy, and/or
  - Graft-versus-host disease

TRACK SUSCEPTIBILITY PATTERNS: The MSGERC notes the importance of understanding local/institutional fungal epidemiology and antifungal susceptibility patterns.[3] It also recommends stewardship programs have access to timely antifungal susceptibility testing and involvement of knowledgeable ID experts to identify patterns in resistance. According to the IDSA, species-level identification and antifungal susceptibility testing are key.[32]

ASSESS DIAGNOSIS AND TREATMENT PRACTICES: (Diagnostic challenges for fungal infections are discussed in the Appendix.) Species-specific diagnoses are ideal, and it needs to be determined if effective, timely treatment is being achieved.[3] Fundamentally, an antifungal stewardship program aims to promote early diagnosis and utilization of the most appropriate and effective therapy in a timely manner, according to the MSGERC. The MSGERC also notes that diagnosis and appropriate intervention require a multidisciplinary approach, suggesting that necessary next steps may include instituting a team approach, identifying team members, and outlining responsibilities at the outset of the program.

ADDRESS PROCESS ISSUES: According to the MSGERC, identifying potential obstacles (e.g., delays in diagnostic testing) and strategies to support earlier intervention (e.g., administration of appropriate antifungal prophylaxis) is crucial.[3] To support timely intervention, the MSGERC recommends ensuring that diagnostic tests are performed as quickly as possible and that test results are reported in a timely manner. From the perspective of the MSGERC, questions that need to be addressed about the process may include: Is appropriate diagnostic testing available? What is the testing time frame? Are there barriers to timely diagnosis?

INCREASE AWARENESS OF IFI: According to the consensus panel as well as published reviews, awareness of IFI is critical to establishing an antifungal stewardship program. To support increasing awareness, the MSGERC recommends acquiring data from global, national, and local perspectives.[3] While global data are useful, local data from the regional, state, and institutional level are key. If practical, determining the local epidemiology and microbiology of IFI may also be helpful. Of the isolates collected from 66 medical centers worldwide from 2017 to 2019 in the

SENTRY Antifungal Surveillance Program, 80.5% were *Candida* spp., 13.2% were *Aspergillus* spp., 1.8% were *Cryptococcus* spp., 1.5% were other non-*Candida* yeast, 0.8% were species within the Mucorales, 0.6% were *Scedosporium* spp., 0.5% were *Fusarium* spp., and 1.0% were other moulds.[38] The MSGERC also emphasizes the importance of becoming aware of the local, pathogen-specific risk factors; sensitivity; and antifungal utilization patterns and trends.[3]

ASSESS CAPABILITIES AND RESOURCES: Some institutions may already have resources that are useful in developing, implementing, and operating an antifungal stewardship program. For example, The Joint Commission notes that an institution's leaders, who are committed to antifungal stewardship, dedicate necessary resources (human, financial, information technology) to an antifungal stewardship program.[13] Staff members with experience in managing various aspects of IFI, including epidemiology and susceptibility, laboratory diagnosis, and pharmacokinetics of antifungal drugs, are also key resources, according to the MSGERC.[3]

PROMOTE BUY-IN: According to The Joint Commission and the MSGERC, promoting institutional buy-in is key to establishing successful antifungal stewardship as is identifying stakeholders and potential champions to collaborate with institutional leaders.[3,13] Both these groups also note the importance of involving the institution's administration from the beginning. When developing an antifungal stewardship program, The Joint Commission highlights the importance of educating practitioners, staff, and patients on antimicrobial resistance and antimicrobial stewardship practices.[13] The MSGERC notes the importance of developing educational programs and identifying knowledge gaps for practitioners.[3]

MAKE A PLAN TO IMPLEMENT THE PROGRAM: From the perspective of the MSGERC, implementing the antifungal stewardship program should be tailored to the institution.[3] The program may be implemented using critical care pathways or treatment "bundles," which include a series of steps taken throughout treatment to monitor patient response. The MSGERC also suggests that initiatives to optimize continuity of care and discharge planning (inpatient to outpatient transition) should be considered.

ASSESS PROGRAM PERFORMANCE INDICATORS: To demonstrate any changes resulting from an antifungal stewardship program within a facility, the MSGERC suggests a reporting system that includes metrics on antifungal drug use, assessment of patient outcomes, and sharing data findings directly with practitioners.[3] For the process of collecting, analyzing, and reporting outcome data, The Joint Commission provides guidelines.[13] Following the program assessment, the institution may take action to improve the program if needed.

Summary and Conclusion

Antifungal stewardship may be justified by the cost and health and economic burdens of IFI.[3] Influential bodies, such as the IDSA, SHEA, PIDS, The Joint Commission, and CDC support antimicrobial stewardship, the elements of which can also be applied to antifungal stewardship.[5,13,14] The implementation of multidisciplinary stewardship encompasses diagnosis, treatment, and management of infection.[3] It involves health care personnel of all specialties and disciplines, and it can align clinical and administrative staff in achieving the institution's goals. Importantly, guideposts and considerations are available to help institutions move toward establishing antifungal stewardship.

Appendix

Table. Diagnostic Challenges[1-5]

Diagnostic Test		
Microscopy/Culture	**Imaging (X-ray, CT, MRI)**	**Other Diagnostic Methods**
• Blood cultures may be negative • Appropriate sample collection is needed • Careful tissue handling is needed • Fungal growth is slow	• Findings may be variable, nonspecific • Characteristic signs not diagnostic	• False-positive, false-negative cultures may occur • Sensitivity, specificity may vary • Some are not available/ standardized (e.g., polymerase chain reaction)
Each of the techniques for diagnosing IFI has its own set of challenges that can influence timely, accurate diagnosis, according to clinical guidelines.[1-5]		
Challenges: Obtaining appropriate samples for analysis may be challenging. Blood samples can be of limited value because they may yield negative results. Clinical specimens should be obtained from affected areas, typically using invasive procedures, but this may be impractical in some patients. Once clinical specimens are obtained, they must be handled with care. With some delicate filamentous fungi, such as Mucorales, culture yield may be low or negative if specimens are aggressively processed before plating. Another factor to consider is that the slow growth of many filamentous fungi poses a challenge to the timely diagnosis of infection.	*Challenges:* When using imaging in patients with suspected infection, findings can be highly variable in select patients, ranging from nonspecific signs to more specific features. Although specific radiographic features like the halo sign may be suggestive of a particular type of infection, such as invasive aspergillosis, these signs are not diagnostic for invasive aspergillosis.	*Challenges:* Depending on the diagnostic methods, sensitivity and specificity may vary, or false positives or false negatives may occur. Some assays, such as polymerase chain reaction, might not be available for certain types of infections or standardized for clinical use.

CT= computed tomography; IFI=invasive fungal infection; MRI=magnetic resonance imaging.

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