ferritin, erythrocyte sedimentation rate, platelet count, albumin, and fibrinogen, also play significant roles in the inflammatory process associated with COPD.

Although we agree that including comprehensive inflammatory indices such as the systemic immune inflammation index (2) and the neutrophil-lymphocyte ratio (3, 4) is advisable, we would like to emphasize the practicality and clinical relevance of using white blood cell count and neutrophil percentage. These markers are widely used in clinical practice because of their accessibility and cost-effectiveness. They are routinely measured in standard blood tests, making them readily available for clinicians to assess systemic inflammation without the need for additional specialized tests.

In conclusion, although the integration of comprehensive inflammatory indicators such as the systemic immune inflammation index and the neutrophil-lymphocyte ratio can enhance our understanding of COPD-related inflammation, the use of white blood cell count and neutrophil percentage remains a practical and effective approach in clinical practice. These markers provide essential information that is both accessible and actionable, supporting their continued use in the evaluation of systemic inflammation. We agree that future studies should aim to include a broader range of inflammatory markers to better capture the complexity of systemic inflammation in COPD. This approach could lead to more precise assessments and potentially identify novel therapeutic targets for managing COPD. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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Clinical Guidelines: Asking the Right Questions to Guide Fungal Infection Management

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To the Editor:

The American Thoracic Society's clinical practice guideline "Treatment of Invasive Pulmonary Aspergillosis and Preventive and Empirical Therapy for Invasive Candidiasis in Adult Pulmonary and Critical Care Patients" provides essential recommendations for managing fungal infections in critically ill patients (1). However, certain aspects of the guideline require sharper focus to better align with current evidence and clinical realities, ensuring its applicability in diverse healthcare settings.

One significant concern is the guideline's reliance on studies evaluating amphotericin B deoxycholate, a formulation largely abandoned in contemporary clinical practice because of its high toxicity. Current care protocols prioritize liposomal amphotericin B, demonstrating superior safety profiles, particularly in preserving renal function in critically ill patients (2). This transition reflects both clinical advancements and patient safety considerations; the guideline risks presenting an outdated view of current antifungal practices by continuing to emphasize amphotericin B deoxycholate (3). The distinction between amphotericin B formulations should be clearly articulated to ensure recommendations align with real-world practice and encourage safer, more effective treatment strategies (4).

Although the guideline recommends voriconazole as the primary treatment for invasive pulmonary aspergillosis (IPA) over amphotericin B deoxycholate, this conclusion is based on its efficacy established in randomized controlled trials. However, the guideline fails to address direct comparisons between voriconazole and liposomal amphotericin B. Evidence from a 2020 Cochrane review demonstrates that liposomal amphotericin B is significantly more effective than voriconazole for empirical therapy in neutropenic cancer patients and should be preferred in such contexts (5). Furthermore, no randomized controlled trials directly compared voriconazole and liposomal amphotericin B under optimal conditions for IPA treatment. This gap in evidence undermines the robustness of the guideline's conclusions regarding voriconazole's efficacy and leaves clinicians without a comprehensive analysis of all available therapeutic options.

Similarly, the guideline discusses combination therapy using a mold-active triazole and echinocandin for IPA but omits

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comparisons with liposomal amphotericin B. This omission further limits the utility of the guideline in helping clinicians navigate complex treatment decisions. A more holistic discussion incorporating head-to-head comparisons among all viable treatment options would significantly strengthen the guideline, offering a broader evidence-based framework.

The section on prophylactic and empirical antifungal therapy targeting *Candida* species also requires critical refinement. Prophylaxis and empirical treatment are distinct strategies with unique indications and clinical objectives. The aim of prophylaxis is to prevent fungal infections in high-risk populations. At the same time, empirical treatment is initiated on the basis of clinical suspicion and severity of illness, such as organ failure, septic shock, or multiple organ failure. Previous guidelines have highlighted that prophylaxis is generally unnecessary for critically ill patients, whereas the complexity of clinical presentations must guide empirical therapy (2). By conflating these two approaches into a single recommendation, the guideline risks causing confusion and reducing clinical applicability. A stratified approach that distinctly addresses prophylaxis and empirical therapy would enhance clarity, usability, and alignment with evidence-based practice.

Robust methodology is indispensable for developing clinical guidelines but must be complemented by practical clinical insight. Not all clinical questions can be addressed by existing evidence, and overly rigid recommendations may fail to reflect real-world complexities. Effective guidelines require domain experts' contributions to ensure the recommendations are relevant and applicable. For instance, expertise in methodology only translates seamlessly into addressing complex questions in clinical practice recommendations. Ensuring multidisciplinary collaboration and clinical context is crucial to creating well-rounded, impactful guidelines.

The authors should be commended for their efforts in tackling such a critical topic in pulmonary and critical care medicine. Their work provides a foundation for improving the management of fungal infections in critically ill patients. However, refinements in key areas—such as combination therapy, amphotericin B formulations, voriconazole efficacy, and the distinction between prophylaxis and empirical therapy—would significantly enhance the guideline's relevance and utility.

A balanced approach that integrates rigorous methodology with practical clinical insights will ensure the guideline's recommendations are both evidence based and applicable in real-world practice (6). By addressing these limitations, the guideline can become an even more valuable resource for clinicians, ultimately improving patient outcomes in this challenging and high-stakes area of care. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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Reply to Martin-Loeches and Rodriguez: Clinical Guidelines: Asking the Right Questions to Guide Fungal Infection Management

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From the Authors:

We thank Martin-Loeches and Rodriguez for their insightful critique of certain aspects of our clinical practice guideline (CPG) on the management of fungal infections (1). The first part of their letter laments the fact that question 1 regarding combination therapy for invasive pulmonary aspergillosis (IPA) did not address the role of liposomal amphotericin B (LAmB). The letter writers imply that voriconazole must have been chosen as the backbone of this question to the exclusion of LAmB because our expert panel decided that voriconazole has been proved to be more effective than LAmB for the treatment of IPA. No assumption regarding the comparative efficacy

The authors include the cochairs of the subcommittee of the American Thoracic Society Assembly on Pulmonary Infections and Tuberculosis.

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