COMMENTARY

Inconsistencies in the Indian Guidelines for the Prescription of Antibiotics for Critically Ill Patients

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Abstract

The recently formulated guidelines by Khilnani GC et al. for the prescription of antibiotics for critically ill patients present an extensive compilation of evidence and recommendations. Despite their comprehensive nature, several inconsistencies need addressing. In this commentary, we delve into some of these discrepancies in the order in which they appeared in the guidelines, starting with the misrepresentation of "nonbronchoscopic bronchoalveolar lavage (BAL)" and "mini BAL" as different techniques when they are, in fact, identical. Secondly, the Centers for Disease Control and Prevention (CDC) in the year 2013 replaced the older, unreliable ventilator-associated pneumonia (VAP) definition with ventilator-associated events (VAE). This new VAE definition eliminates subjectivity in pneumonia diagnosis by focusing on objective criteria for ventilator support changes, avoiding dependence on potentially inaccurate chest X-rays and inconsistent medical record keeping. Thus, using the term VAP in the Indian guidelines seems regressive. Furthermore, the recommendation for routine anaerobic coverage in aspiration pneumonia is outdated and unsupported by current evidence. Lastly, while endorsing multiplex polymerase chain reaction (PCR) for pathogen identification, the guidelines fail to adequately address its limitations and the risk of overdiagnosis.

Keywords: Antibiotic guidelines, Critically ill patients, Diagnostic accuracy, Inhaled antibiotics, Respiratory infections.

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Highlights

- This commentary critically evaluates the recently published guidelines for antibiotic prescription in critically ill patients, identifying significant inconsistencies, and gaps in evidence, particularly regarding respiratory specimen collection, ventilator-associated pneumonia (VAP) definition, anaerobic coverage, and the role of multiplex polymerase chain reaction (PCR).

Introduction

The guidelines for the prescription of antibiotics for the critically ill were formulated by Khilnani G et al. recently.[1] There is no iota of doubt that it summoned herculean effort on the part of the authors to compile more than 100 pages of evidence and recommendations encompassing a wide variety of infections encountered among the critically ill. While sincere applause is due, so is the need to bare the inconsistencies and the thin ground on which several recommendations stand. In the subsequent paragraphs, we will delve into some of these discrepancies in the order in which they appeared in the guidelines.[1]

Respiratory Specimen Collection for the Diagnosis of Ventilator-associated Pneumonia (VAP)

In the said article, the terms "Nonbronchoscopic bronchoalveolar lavage (BAL)" and "mini BAL" were used, which implies that these are different techniques, whereas in reality, they are the same, that is, protected, blind, alveolar lavage fluid. So, it would have been prudent to use either of these two terms throughout the guidelines. Additionally, a culture of respiratory specimens, such as sputum, nonbronchoscopic BAL, bronchoscopic BAL, and protected specimen brush (PSB) have been discussed collectively for diagnosing infections of the lung which again gives the impression that their yield and diagnostic accuracy are similar and one can choose any of them. For diagnosing VAP, studies indicate that nonbronchoscopic BAL is an effective and less invasive alternative to bronchoscopic methods. Khilnani GC et al. in their study found that nonbronchoscopic BAL matches the effectiveness of bronchoscopic BAL and is inexpensive, easy to perform, requires less expertise, and shows good microbiologic concordance with bronchoscopic BAL.[2] Khilnani GC et al. compared the bronchoscopic and nonbronchoscopic protected BAL and bronchial brush techniques and endotracheal tube aspirate (ETA) and reported that the yield was lowest with ETA, followed by nonbronchoscopic protected BAL (68%), bronchoscopic BAL (64%), and highest with bronchial brush.[2] Similarly, the sensitivity of ETA

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was quite low (55.6%), followed by nonbronchoscopic protected bronchoalveolar lavage (NPBAL) (83.3%) and BAL (64%), while with a bronchial brush, it was highest (94.9%).[2]

Among the two studies mentioned in the guideline, the one by Fernando SM et al. was a meta-analysis of the diagnostic ability of various respiratory specimens.[3] According to their findings, ETA demonstrated a 67.9% specificity and a 75.7% sensitivity. With regard to bronchoscopic procedures for sampling, BAL had a sensitivity and specificity of 71.1 and 79.6%, respectively, whereas PSB demonstrated a sensitivity and a specificity of 61.4 and 76.5%, respectively. They did not examine the utility of nonbronchoscopic methods of sampling respiratory specimens Although bronchoscopy does not reduce short-term mortality for VAP diagnosis, its therapeutic applications, such as aiding in sputum suction, can reduce short-term mortality in VAP patients.[4] Thus, it is imperative to highlight which respiratory specimen to collect to have the best sensitivity and specificity to identify the pathogen in lower respiratory infections.

Ventilator-associated Events (VAE) and VAP

The Centers for Disease Control and Prevention (CDC) working group created the VAE surveillance definition algorithm in 2013, and it has undergone many revisions. The group identified various conditions and complications in mechanically ventilated adult patients and devised three distinct levels within the composite term, VAE. These tiers were: 1. Ventilator-associated conditions (VACs), 2—infection-related ventilator-associated complications (IVAC), and possible ventilator-associated pneumonia (PVAP).[5] Ventilator associated condition are commonly caused by pneumonia but also by atelectasis, adult respiratory distress syndrome (ARDS), and pulmonary edema. The erstwhile definition of VAP had no valid, reliable definition; the criteria used for diagnosis were neither sensitive nor specific and required radiologic findings of pneumonia. The technique of obtaining radiographic imaging and its interpretation was marred by subjectivity and variability. Further, the definition of VAP was based on clinical signs and symptoms, which were subjective and often inconsistently documented in the medical records. Thus, using the term VAP in the Indian guidelines seems regressive.[5]

Diagnosis of Tuberculosis in Recipients of Solid Organ Transplants (SOT)

In patients of SOT recipients, microbiologic examination of bronchoscopy or BAL samples, or histopathological examination (HPE) from the involved site have been recommended. We want to add that the World Health Organization recommends cartridge-based nucleic acid amplification (CB-NAAT) test of the BAL fluid, which would help in detecting not only *Mycobacterium tuberculosis* but also resistance to rifampicin within two hours, and this could have been incorporated.[6]

Nebulized Antibiotics in VAP

As the authors correctly pointed out, there was no mortality advantage observed in VAP patients after amikacin nebulization. Tang R et al., in a meta-analysis compared intravenous (IV) alone or with adjunctive inhaled antibiotics, reported that while the latter led to improved rates of clinical recovery and microbial eradication in VAP, it failed in demonstrating any mortality benefits.[7] They opined that there was insufficient data to justify the usual therapeutic use of nebulized antibiotics for VAP. Moreover, the appropriate device and dosage for nebulized antibiotics, particularly in the treatment of VAP caused by multidrug-resistant organisms are yet to be determined. Currently, the range of antibiotics approved for nebulized administration is limited, and IV formulations are often administered via the airway. Nevertheless, the unsuitable pH as well as osmolarity of IV preparations could cause airway irritation, as demonstrated by bronchospasms reported in numerous studies.[7,8] The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) cautioned against using aerosolized antibiotics because there was inadequate evidence of their efficacy and risks of side effects.[9] The type of nebulizer used is also important as a jet nebulizer retains a sizeable quantity of drugs at the end of nebulization, and the heat produced by the ultrasonic nebulizers risks denaturation of the drug. So, only vibrating mesh nebulizers are suitable for the nebulization of antibiotics. Currently, the Food and Drug Administration (FDA) has recommended only nebulized tobramycin and aztreonam in cystic fibrosis and amikacin for *Mycobacterium avium complex* lung disease.[10] Thus, it was bewildering to see that the Indian guidelines recommend the use of nebulized antibiotics like colistin and aminoglycosides as an adjunct to systemic therapy for the empirical management of VAP (3A) more so as the authors failed to produce any evidence supporting the use of nebulized antibiotics.

Anaerobic Coverage in Aspiration Pneumonia

The guidelines by Khilnani GC et al. recommend supplementing anaerobic cover to patients suspected of community-acquired pneumonia (CAP) due to aspiration.[1] Of the studies quoted, one, almost two decades old, mentioned that in adult CAP leading to lung abscesses, *Klebsiella pneumoniae* was a more common cause than anerobes.[11] The other study by Yamasaki K et al. mentioned that the incidence of anaerobes and oral bacteria identified as pathogens in CAP was 15.6% each, particularly among patients with milder pneumonia severity index (PSI).[12] In the 1970s, research revealed that anaerobes were a key cause of aspiration pneumonia, leading to the development of new antibiotic against them. This highlighted the significant role of anaerobic bacteria in aspiration pneumonia. The findings led to the widespread usage of antibiotics with anaerobic cover for patients with clinical suspicion of aspiration pneumonia. However, recent evidence suggests that incorporating anaerobic coverage might not necessarily lead to favorable outcomes. There has been a shift in the pathogenic organisms commonly associated with hospital-acquired pneumonia (HAP) and CAP, with a decrease in the number of anaerobes involved. The recent guidelines have considered these findings and do not recommend the routine coverage of anaerobic pathogens in the treatment of aspiration pneumonia.[13] Due to these changes, anaerobic cover should not be included in the ideal empirical therapy for aspiration pneumonia. Evidence suggests that routine anaerobic coverage may be not only ineffective but also potentially harmful. Avoiding unnecessary broad-spectrum antibiotics for anaerobes is crucial to prevent potential resistance, adverse effects, and increased healthcare costs.[14] In patients on mechanical ventilation, aspiration does not result in an increase of obligate anaerobes in the lower respiratory tract (LRT). Instead, critically ill individuals tend to experience a reduction in anaerobic commensals originating from the oral cavity.[15]

Microbiologic Analysis in Hospital-acquired Pneumonia (HAP) and VAP

For patients suffering from HAP and VAP, the guidelines recommend that the intensivist consider the use of traditional culture and

Table 1: Critical analysis of current guidelines with author-suggested improvements

Serial no.	*Issue*	*Published guideline*	*Authors' suggestions*
1	Terminology consistency	Uses "nonbronchoscopic BAL" and "mini BAL" interchangeably	Use consistent terminology throughout
2	Diagnostic accuracy of respiratory specimens	Groups different methods together without differentiating accuracy: "invasive sampling (nonbronchoscopic BAL or bronchoscopic BAL, protected specimen brushing) should be performed in VAP for microbiologic diagnosis and definitive antibiotic therapy"	Specify the best methods based on evidence: Nonbronchoscopic BAL is a less invasive and effective alternative to bronchoscopic methods, showing good microbiologic concordance
3	VAE and VAP definitions	Uses the term "VAP"	Align with CDC's VAE definitions, which categorize ventilator-associated event into VAC, IVAC, and PVAP. The use of the term "VAP" seems regressive, as the criteria for its diagnosis is neither sensitive nor specific
4	Tuberculosis in solid organ transplant recipients	Recommends that SOT patients require an invasive procedure, such as bronchoscopy with BAL or lung biopsy for diagnosis of tuberculosis	Include CB-NAAT testing for TB and rifampicin resistance
5	Nebulized antibiotics	Recommends that adjunct nebulized antibiotics (colistin, aminoglycosides) can be used in combination with systemic therapy for empiric treatment of VAP on case-to-case basis of microbiologic sensitivity	Caution against routine use of nebulized antibiotics without strong evidence as nebulized antibiotics fail to demonstrate any mortality benefits. The optimal device and dosage for inhaled antibiotics remain unknown
6	Anaerobic coverage in aspiration pneumonia	Recommends that empirical antibiotics with anaerobic coverage should be considered for treatment of CAP in ICU in presence of witnessed aspiration, lung abscess, empyema, or necrotizing pneumonia	Reconsider routine anaerobic coverage, as it may not improve clinical outcomes. The shift in pathogens associated with CAP and HAP indicates that fewer anaerobes are involved. Unnecessary broad-spectrum antibiotic use should be avoided to prevent resistance, adverse effects, and increased healthcare costs
7	Microbiologic analysis in HAP/VAP	Recommends that microbiologic analysis of blood, respiratory specimen (nonbronchoscopic or bronchoscopic BAL) and other samples like pleural fluid should be performed using conventional culture and molecular methods for identification of pathogens in non-responding HAP and VAP	Emphasize multiplex PCR for detecting atypical pathogens and viral agents, which are often missed in conventional cultures or take longer to grow. Multiplex PCR has a high sensitivity and specificity and can detect fastidious bacteria and viruses that are usually considered too late for diagnosis, leading to inappropriate antibiotic use

BAL, bronchoalveolar lavage; CAP, community-acquired pneumonia; CB-NAAT, cartridge-based nucleic acid amplification test; HAP, hospital-acquired pneumonia; IVAC, infection-ventilator-associated conditions; PCR, polymerase chain reaction; PVAP, possible ventilator-associated pneumonia; SOT, solid organ transplant; TB, tuberculosis; VAC, ventilator-associated conditions; VAE, ventilator-associated events; VAP, ventilator-associated pneumonia

molecular techniques for identifying microorganisms in blood, respiratory specimens (nonbronchoscopic or bronchoscopic BAL), and other samples such as pleural fluid (3A). The authors of the guideline aptly pointed out that multiplex polymerase chain reaction (PCR) has a short turn-around time, increased diagnostic accuracy for the detection of GNBs and also the detection of extended-spectrum beta-lactamases (ESBL) and carbapenemase genes in 75% of cases, we would like to highlight that multiplex PCR helps in identifying agents causing atypical pneumonia-like *Mycoplasma*, *Chlamydia,* and *Legionella* which are easily missed in routine culture media or takes longer time to grow. Also bacteria such as *H. influenzae* which challenging to culture and susceptible to being outgrown by normal microbiota can be detected using multiplex PCR. Moreover, many viral agents, such as influenza, rhinovirus, enterovirus, and adenovirus are usually considered very late for diagnosis, and during that time, injudicious use of antibiotics affects the patient's health. The role of multiplex PCR becomes crucial in such scenarios. Multiplex PCR enables the concurrent detection of several pathogens in a single assay, facilitating rapid and accurate diagnosis. Multiplex PCR not only helps in identifying the specific viral agent responsible for the infection but also plays a significant role in detecting coinfections, where more than one pathogen is present. Many studies have recognized the impact of multiplex PCR on sputum or BAL samples in correctly diagnosing the agents and with prompt, specific, and guided treatment that can save patients' lives.[16,17] Nevertheless, like all tools, it also suffers from its share of cons, like the risk of inappropriate antibiotic therapy because of overdiagnosis of resistance gene detection.

The critical analysis of current guidelines along with author-suggested improvements are summarized in Table 1. Thus, we hope that the authors of the guidelines for the prescription of antibiotics in the critically ill will consider the points raised in this article and update the guidelines accordingly.

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