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CHEST

International Perspective on the New 2019 American Thoracic Society/Infectious Diseases Society of America Community-Acquired Pneumonia Guideline

A Critical Appraisal by a Global Expert Panel

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In 2019, the American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA) issued a substantial revision of the 2007 guideline on community-acquired pneumonia (CAP). Despite the fact that generalization of infectious disease guidelines is limited because of substantial geographic differences in microbiologic etiology and antimicrobial resistance, the ATS/IDSA guideline is frequently applied outside the United States. Therefore, this project aimed to give a perspective on the ATS/IDSA CAP recommendations related to the management of CAP outside the United States. For this, an expert panel composed of 14 international key opinion leaders in the field of CAP from 10 countries across five continents, who were not involved in producing the 2019 guideline, was asked to subjectively name the five most useful changes, the recommendation viewed most critically, and the recommendation that cannot be applied to their respective region. There was no formal consensus process, and the article reflects different opinions. Recommendations welcomed by most of the international pneumonia experts included the abandonment of the concept of "health-care-associated pneumonia," the more restrictive indication for empiric macrolide treatment in outpatients, the increased emphasis on microbiologic diagnostics, and addressing the use of corticosteroids. Main criticisms included the somewhat arbitrary choice of a 25% resistance threshold for outpatient macrolide monotherapy. Experts from areas with elevated mycobacterial prevalence particularly opposed the recommendation of fluoroquinolones, even as an alternative.

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FOR RELATED ARTICLE, SEE PAGE 1896

ABBREVIATIONS: ATS = American Thoracic Society; CAP = community-acquired pneumonia; HCAP = health-care-associated pneumonia; IDSA = Infectious Diseases Society of America; MDR = multidrug resistant; MRSA = methicillin-resistant *Staphylococcus aureus*

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Treatment recommendations for infectious diseases are usually more complex and, in particular, more sophisticated than those for other human diseases. In noninfectious diseases, such as cardiovascular or neoplastic diseases, different aspects of their pathogenesis are usually similar among patients worldwide, and have not (and will not) substantially change over time in light of the relatively slow pace of human evolution. In infectious diseases, the main goal is to identify and kill the pathogen, and to protect the host from both early and long-term complications. The evolution of most microorganisms is—compared with humans—usually extremely rapid, causing substantial spatiotemporal differences. The virus causing coronavirus disease-2019 (COVID-2019) is a current example of that.[1] Therefore, guidelines for the management of infectious diseases need frequent updates, and may not be easily generalized from country to country or even across different regions in the same country. This holds particularly true for community-acquired pneumonia (CAP), which represents a major global clinical and public health issue.[2]

A substantial revision of the 2007 American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) CAP guideline was published in 2019.[3,4] Some major changes were made in the methodology, including use of the Patient/Population, Intervention, Comparison, and Outcome (PICO) framework and the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) format. On a personal note, structure and readability of the guideline are excellent. Despite an extensive body of literature that has been covered (216 references), the guideline committee managed to limit content to 15 pages—an extent that fits well into the busy daily life of physicians. Furthermore, the strictly followed structure of "summary of evidence," "rationalization of recommendation," and "research needed in this area" is very useful for both physicians, who recognize where there is still uncertainty regarding state-of-the-art treatment, and researchers, who can develop ideas for future clinical studies. Major changes in the recommendation were also nicely highlighted for quick review (Table 1). The highly formalized GRADE procedure with answers to the selected 16 PICO questions now reflects the current state of the art for guidelines. However, as for all guidelines—because for many questions no specific evidence is available—most of the final recommendations tend to reflect a consensus of those experts who have been involved in producing these guidelines. This is demonstrated by different conclusions that are sometimes drawn by different researchers on the same study. Finally, the committee clearly stated that the 2019 ATS/IDSA CAP guideline specifically focuses on immunocompetent patients in the United States.

The aim of the present project was to give the scientific community an international perspective on the 2019 ATS/IDSA CAP guideline recommendations according to pathogen epidemiology, populations, health-care systems, and standard operating procedures related to the management of CAP outside of the United States.

Methods

An expert panel composed of 14 international key opinion leaders in the field of CAP from 10 countries across five continents, who were not involved in producing the 2019 ATS/IDSA CAP guideline, was assembled. All experts were asked to answer three specific questions:

1. In comparison with the 2007 guideline, what are, for you, the (up to) five most important useful changes in the 2019 ATS/IDSA CAP guideline?
2. What recommendation in the 2019 ATS/IDSA CAP guideline do you not agree with, in general; that is, which do you view most critically?
3. Are there recommendations in the 2019 ATS/IDSA CAP guideline that—from your perspective—make sense in the context of the US landscape but cannot be transferred to your own continent/country?

The following commentary summarizes these statements. We weighed the comments made by displaying the number of experts

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TABLE 1] Major Changes in Recommendations From 2007 to 2019 American Thoracic Society/Infectious Diseases Society of America Community-Acquired Pneumonia Guidelines

Recommendation	2007 ATS/IDSA Guideline	2019 ATS/IDSA Guideline
Sputum culture	Primarily recommended in patients with severe disease	Now recommended in patients with severe disease as well as in all inpatients empirically treated for MRSA or *Pseudomonas aeruginosa*
Blood culture	Primarily recommended in patients with severe disease	Now recommended in patients with severe disease as well as in all inpatients empirically treated for MRSA or *P aeruginosa*
Macrolide monotherapy	Strong recommendation for outpatients	Conditional recommendation for outpatients, based on resistance levels
Use of procalcitonin	Not covered	Not recommended to determine need for initial antibacterial therapy
Use of corticosteroids	Not covered	Recommended not to use. May be considered in patients with refractory septic shock
Use of health-care-associated pneumonia category	Accepted as introduced in the 2005 ATS/IDSA hospital-acquired and ventilator-associated pneumonia guidelines[a]	Recommend abandoning this categorization. Emphasis on local epidemiology and validated risk factors to determine need for MRSA or *P aeruginosa* coverage. Increased emphasis on deescalation of treatment if cultures are negative
Standard empiric therapy for severe CAP	β-Lactam/macrolide and β-lactam/fluoroquinolone combinations given equal weighting	Both accepted but stronger evidence in favor of β-lactam/macrolide combination
Routine use of follow-up chest imaging	Not addressed	Recommended not to obtain. Patients may be eligible for lung cancer screening, which should be performed as clinically indicated

ATS = American Thoracic Society; CAP = community-acquired pneumonia; IDSA = Infectious Diseases Society of America; MRSA = methicillin-resistant *Staphylococcus aureus*.

[a]American Thoracic Society; Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med*. 2005;171(4):388-416.[31]

who made the same or similar statement concerning a certain guideline recommendation. Some agreed in general, but mentioned important exceptions that we also considered in the text. Because of the kind of questions asked the displayed number does not always mean that the remaining experts had an opposing opinion; sometimes they just did not comment on this particular recommendation. For details please see the original blinded comments in e-Table 1. There was no formal consensus process and the article reflects different opinions. The 14 experts revealed on the one hand some interesting agreements and uncovered, or rather confirmed, on the other hand areas of uncertainty.

Results

Most Important Changes in the New 2019 ATS/IDSA CAP Guideline

This section compresses the answers to questions 1 and 2.

1. Abandoning the Categorization of Health-Care-Associated Pneumonia: For most of the experts (13 of 14; 92.9%), abandoning the category "health-care-associated pneumonia" (HCAP) was the most useful change in the 2019 ATS/IDSA CAP guideline. There was broad consensus that the positive predictive value of the HCAP definition was far too low to justify empiric antibiotic regimens covering multidrug-resistant (MDR) bacteria, and data clearly demonstrate that this classification resulted in overtreatment of patients with CAP, and may be associated with adverse outcomes including increased mortality.[5-9]

The alternative concept of "strong risk factors," for example, known colonization of methicillin-resistant *Staphylococcus aureus* (MRSA) or *Pseudomonas aeruginosa*, has been suggested by international experience and was well received by the present expert panel.[10] However, an overemphasis on these two specific pathogens—MRSA and *P aeruginosa*—misses emerging data on extended-spectrum β-lactamase-containing Enterobacteriaceae as a cause of CAP.[11] Because empirical broader therapy based on risk factors will always result in overtreatment, a stronger recommendation for more extensive diagnostic testing would be desirable to support appropriate antibiotic

stewardship according to six of the 14 experts (42.9%) (see below).[12]

2. Recommendation Against Use of Corticosteroids: Prior meta-analyses suggesting a benefit to corticosteroids may have triggered increased corticosteroid use.[13] The guideline committee recognized that differences across health-care systems worldwide, not accounted for in the meta-analyses, may have a marked influence on the benefit of corticosteroids on length of stay and, therefore, advised against their routine use in CAP. Specifically, the dominant use of β-lactam monotherapy and longer baseline length of stay for the control groups in these European studies, the latter almost twice as long as standard in the United States, raised concerns about the generalizability of these results in the US population.[14] For most of the experts (11 of 14; 78.6%), addressing the controversy of corticosteroids in CAP is a major benefit of this guideline per se, as this has been a confusing area for physicians.

However, whereas nine of 14 experts (64.3%) strongly agreed with the wording of the recommendation, four experts (of 14; 28.6%) opposed the guideline recommendation against corticosteroids, citing concerns that it limits the treatment options in severe CAP and may increase mortality in these patients. Three of those four explicitly criticized the guideline summary of corticosteroid treatment as overly simplistic, suggesting that the specific indications and risk-to-benefit ratio of use should be distinguished between moderate and severe CAP and could have been discussed more, where severe CAP mortality is high and the risk-to-benefit ratio may be different compared with moderate CAP. This position was rationalized by referring to a study that has shown a benefit in terms of treatment failure measured by radiologic improvement in selected patients with high inflammation, as reflected by C-reactive protein $>$ 150 mg/L on admission with CAP.[15] As pneumonia is the leading cause of sepsis, substantial overlap exists between community-acquired sepsis and severe CAP,[16] as evidenced by overlapping parameters in sepsis and CAP severity scores (CRB [confusion, respiratory rate, BP] and qSOFA [quick Sepsis-Related Organ Failure Assessment]).[17] Sepsis studies may, therefore, provide some insights in this issue of debate. Although questions concerning which corticosteroid and at what dose and duration were not clearly resolved, the stress-dose steroid recommendations of the Surviving Sepsis Campaign were endorsed by the CAP guideline committee for patients with refractory septic shock.[18]

3. Recommendation Against Use of Procalcitonin to Determine Need for Initial Antibacterial Therapy: The use of procalcitonin has always been an issue of debate, and this was also reflected among members of the expert panel. Two experts rated the recommendation against using procalcitonin to initiate or withhold empiric antibiotics among the top five useful recommendations of the novel guideline; they particularly agreed that completely withholding antibiotics might underestimate the burden of bacterial superinfections, which are associated with particularly high mortality. In contrast, for two other experts, that recommendation was the one viewed most critically in the guideline. They argued that the recommendation against the use of procalcitonin to determine initial antibiotic treatment has ignored important studies, and was based mainly on a single study that excluded patients with radiologic evidence of CAP.[19] They also argued that procalcitonin should be used as one among many pieces of diagnostic data to help a physician justify early discontinuation of antibiotics when other evidence strongly supports a primary virus-only etiology. One expert suggested that procalcitonin might have been recommended at least for shortening antibiotic duration, citing critical care evidence that a strategy of early antibiotic discontinuation based on downward procalcitonin trend may be an approach that balances patient safety vs the aim to decrease unnecessary antibiotic use,[20] which is in fact mentioned in the guidelines as likely to be useful primarily in settings where the average duration of treatment for patients with CAP exceeds normal practice.

4. Recommendation for Conditional Use of Macrolide Monotherapy in Outpatients, Based on Local Resistance Levels: For most experts this represents a major improvement in the updated guideline. The rationale is that outpatients often have a similar pathogen spectrum as inpatients, with the exception perhaps of Gram-negative bacilli and *Legionella*. In outpatients, pneumococci and *Haemophilus influenzae* are often the leading pathogens and are not well targeted with a macrolide. *H influenzae* exhibits intrinsic resistance to macrolides, and macrolide use in patients with *H influenzae* has been associated with treatment failure.[21] Most importantly, pneumococcal resistance to macrolides varies by region and is high in some areas worldwide. The guideline suggests a cutoff of 25% of macrolide resistance in pneumococci, above which macrolides should not be used. However, one-half of the experts opposed the 25% cutoff, stating that this was too liberal and that a

cutoff of 25% reflects a "dangerous" approach that "could demand lives," given the clear association between macrolide resistance and treatment failure. Indeed, the definition of "inadequate spectrum" and an acceptable "gap" of the empiric antibiotic treatment has always been a matter of debate. It is reasonable to aim for a small "gap" in patients with high severity of disease such as those with sepsis—in light of the fact that numerous studies have shown that failing to cover the etiologic pathogen with initial antibiotics is associated with an increased risk of death.[22] In contrast, the consequences of an inadequate spectrum in patients with mild CAP may not be as dramatic, especially considering that a substantial proportion may have a primary viral etiology.[23] In addition, given the roughly one-third of pneumococcal etiology, a margin of 25% would result in an "overall gap" of much less than 25% and seems reasonable in an outpatient population with an overall very low risk of death.[24] Nevertheless, the justification for the 25% threshold was not provided by the guideline committee and seems therefore arbitrary. In contrast, experts were supportive of high-dose amoxicillin treatment, which is successful even in most penicillin-resistant pneumococci. Furthermore, the increasing use of long-term macrolides in patients with chronic comorbidities (bronchiectasis, COPD, asthma), who are especially prone to CAP, may increase the risk for macrolide-resistant pneumococci in these patients.

5. Recommendation That Sputum and Blood Cultures Be Obtained in Patients With Severe CAP, as Well as in All Inpatients Empirically Treated for MRSA or *P aeruginosa*: Testing practices for adults hospitalized with CAP varied significantly by geography and disease severity, and there is wide discordance between real-life testing practices and international guideline recommendations.[25] Compared with the 2007 CAP guideline, in which the cost vs impact on treatment decisions of diagnostic testing was emphasized, the new 2019 ATS/IDSA CAP guideline places greater value on microbiologic diagnostics. The indication for blood and sputum cultures was expanded from severe diseases to all inpatients who are empirically treated including coverage of noncore pathogens such as MRSA or *P aeruginosa*. This is a logical necessity, because the recommendation to deescalate requires the identification of the underlying pathogen.

The increased value of diagnostics was seen as an improvement by most of the experts (nine of 14; 64.3%). However, some critical comments have been made: seven of 14 experts (50.0%) suggested that this recommendation did not go far enough, compared with usual practice in other countries, such as the UK,[26] Germany,[27] or Japan,[28] where blood and sputum cultures are required for all inpatients. Furthermore, the limitation mentioned above was viewed critically by some experts because the "strong" recommendation implies that it is appropriate for quality assessment and public reporting. This will be a major change in ED workflow, and there was concern among the panel members that it may result in poor-quality specimens. In addition, there was concern that decisions about which diagnostic tests to order are often made before antibiotic and ICU admission decisions, making these recommendations logistically impractical because of the conditional nature on these other management decisions.

6. Other Areas Considered by Individual Experts as Monotherapy in Outpatients, Based on Local Resistance Substantial Changes: Other changes in recommendation that were mentioned favorably by some experts included the recommendation against using anaerobic coverage for suspected aspiration (two of 14; 14.3%), the recommendation for urinary antigen testing (one of 14; 7.1%), and the stronger evidence in favor of a β-lactam/macrolide combination for severe CAP (one of 14; 7.1%).

Various other items that experts viewed as omissions or inadequately addressed included the recommendation to use antibiotics with antivirals for influenza in the outpatient setting (three of 14; 21.4%) and the overall lack of emphasis on the role of antibiotic stewardship (one of 14; 7.1%) or on CAP prevention by vaccination and smoking cessation (one of 14; 7.1%). Furthermore, one of 14 experts (7.1%) doubted that the general recommendation to use a β-lactam/macrolide combination in all inpatients is not justified by the current evidence.

Recommendations Difficult to Implement in a Context Outside the United States

This section reflects the answers to question 3, which regarded three issues: epidemiology and subsequent treatment recommendations, as well as availability and use of diagnostic methods.

Epidemiology and Empiric Treatment: Several experts from northern and Central European countries, as well as those from South Africa, stated that because of the low incidence of community-associated MRSA, this organism should not be covered empirically (five of 14; 35.7%).[10] In contrast, the rate of macrolide-resistant

pneumococci (eg, in Japan, Spain), and to a lesser degree doxycycline-resistant pneumococci (South Africa), was mentioned as a significant problem with subsequently opposing macrolide (and doxycycline) monotherapy in outpatients. Experts from Africa and South America were not in favor of the recommendation for fluoroquinolones even as an alternative for outpatients in their countries and other regions with high TB incidence (6 of 14; 42.9%), because of concern for obscuring the diagnosis of underlying TB or nontuberculous mycobacterial infection. Indeed, there are some studies suggesting that fluoroquinolones can delay the diagnosis of TB by several months. Vice versa, the widespread use of fluoroquinolones in MDR TB was linked to an increase in fluoroquinolone-resistant pneumococci in a report from South Africa.[29] Two experts (of 14; 14.3%) did not agree with the recommendation against follow-up chest imaging but did not elaborate why.

Diagnostics: Experts from some countries mentioned that molecular diagnostics (eg, influenza polymerase chain reaction [PCR] and MRSA-PCR from nasal swabs) are not widely available in their countries (two of 14; 14.3%). However, several experts referred to their national guidelines that valued sputum samples more highly, and would not restrict them to patients with risk for MRSA and/or *P aeruginosa* (four of 14; 28.6%).

Discussion

Although most physicians are aware of limitations to the generalization of guidelines in infectious disease, the ATS/IDSA guideline for the management of CAP in adults nevertheless remains influential, and is globally and frequently applied for better or worse outside the United States. This issue is well highlighted by the consequences of the "HCAP" concept leading to significant overestimation of MDR organism incidence and therefore overtreatment, complicated by possible antibiotic resistance and adverse outcomes. Therefore, these observations by a panel of international experts may draw the attention of the international readership to limitations and geographically specific caveats of the guideline.

In summary, additions to the updated CAP guideline that were welcomed by international pneumonia experts included the abandonment of the concept of HCAP, the more restrictive indications for empiric macrolide treatment in outpatients, the increased emphasis on microbiologic diagnostics in expanded populations, and addressing the use of corticosteroids. The main criticisms included the somewhat arbitrary choice of a 25% resistance threshold for outpatient macrolide monotherapy, and the recommendation for fluoroquinolones as an alternative option in areas with elevated mycobacterial prevalence. In addition, a minority of experts was strictly against the categorical and simplistic rejection of adjunct corticosteroids without acknowledgment of a possible benefit in selected populations with severe CAP. Finally, we recognized that the 2019 ATS/IDSA CAP guideline was not developed for the treatment of immunocompromised patients, despite the fact that these patients may represent as much as 18% of CAP admissions worldwide.[30] An international position paper on the management of CAP in immunocompromised patients is anticipated soon.

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Additional information: The e-Table can be found in the Supplemental Materials section of the online article.

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