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

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Title

International perspective on the new 2019 ATS/IDSA CAP guideline – a critical appraisal by a global expert panel

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Conflicts of Interest:

MWP reports grants and personal fees from Pfizer, MSD, Novartis, Bayer, Roche, Angelini, Thermofisher and Becton Dickinson.
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DS has received research grants from the Swiss National Foundation, AstraZeneca AG, Pan Gas AG, Weinmann AG, Curetis AG, Boston Scientific AG, Circassia Pharmaceuticals and Lungenliga Switzerland; received payment for lectures, advisory panels or sponsorship to attend scientific meetings from Novartis AG, AstraZeneca AG, GSK AG, Roche AG, Zambon, Pfizer and Schwabe Pharma AG. DS is the current education council chair of the European Respiratory Society and immediate past president of the European Board of Accreditation in Pneumology, and is the current GOLD representative for Switzerland.
BW has received received speaker's honorarium from BioFire (BioMerieux).
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SA reports personal fees from Bayer Healthcare, personal fees from Grifols, personal fees from Astra Zeneca, personal fees from Zambon, grants and personal fees from Chiesi, grants and personal fees from INSMED, personal fees from GlaxoSmithKline, personal fees from Menarini, personal fees from ZetaCube Srl, grants from Fisher & Paykel, outside the submitted work.

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Abstract

In 2019, the American Thoracic Society (ATS) / Infectious Diseases Society of America (IDSA) issued a substantial revision of the 2007 guideline on community-acquired pneumonia (CAP). Despite generalization of infectious disease guidelines is limited due substantial geographic differences in microbiological etiology and antimicrobial resistance, the ATS/IDSA guidelines are frequently applied outside the USA. Therefore, this project aimed to give a perspective on the ATS/IDSA CAP recommendations related to the management of CAP outside of the USA. For this, an expert panel comprised of 14 international key opinion leaders in the field of CAP from 10 countries across 5 continents, who were not involved in the 2019 guideline, was asked to subjectively name the five most useful, the most critical and the recommendation that can not be applied to their respective region. There was no formal consensus process and the paper reflects different opinions. Recommendations welcomed by the vast majority of the international pneumonia experts included the abandonment of the concept of “health-care associated pneumonia” (HCAP), the more restrictive indication for empiric macrolide treatment in outpatients, the increased emphasis on microbiological 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.

INTRODUCTION

Treatment recommendations for infectious diseases are usually more complex and particular sophisticated than those for other human diseases. In non-infectious 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 changed over time in light of a relatively slow pace of human evolution. Among infectious diseases, the main goal is to identify and kill the pathogen, and protect the host from both early and long-term complications. The evolution of most of the microorganisms is – compared to humans – usually extremely rapid causing substantial spatio-temporal differences. The CoVID-2019 virus is a current example for 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].

After more than 10 years since the last American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) CAP guideline, a substantial revision has been 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 clinicians. Furthermore, the strictly followed structure of "summary of evidence", "rationalization of recommendation" and "research needed in this area" is very useful for both clinicians -who recognize where 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 sixteen PICO questions now reflects the current state of the art for guidelines. However, as for all guidelines -since 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 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 focus on immunocompetent patients in the United States of America (USA).

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, healthcare systems, and standard operating procedures related to the management of CAP outside of the USA.

METHODS

An expert panel comprised of 14 international key opinion leaders in the field of CAP from 10 countries across 5 continents who were not involved in the 2019 ATS/IDSA CAP guideline, has been developed. All experts were asked to answer 3 specific questions:

1. *What are for you – compared to 2007 – the up to 5 most important useful changes in the* 2019 ATS/IDSA CAP *guidelines?*

2. *What is the recommendation in the* 2019 ATS/IDSA CAP *guidelines you do in general not agree with or that you see most critical?*
3. *Are there recommendations in the* 2019 ATS/IDSA CAP *guidelines 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 who made the same or similar statement on a certain guideline recommendation. Some agreed in general, but mentioned important exceptions that we also considered in the text. Due to the kind of questions asked the displayed number does not always mean that the remaining experts had an opposing opinion but sometimes did just not comment on this particular recommendation. For details please see the original blinded comments in the supplement. There was no formal consensus process and the paper reflects different opinions. The expert number of 14 revealed on the one hand some interesting agreement and uncovered or rather confirmed on the other hand areas of uncertainty.

RESULTS

The most important changes in new 2019 ATS/IDSA CAP Guidelines

This section compresses the answers to question #1 and #2.

1) Abandoning the categorization of health-care associated pneumonia

For most of the experts (13 out of 14; 92.9 %), the abandoning the category "health-care associated pneumonia" (HCAP) was the most useful change in the new 2019 ATS/IDSA CAP Guidelines. There was broad consensus that the positive predictive value of the HCAP definition was far too low to justify empiric antibiotic regimens covering Multi-Drug Resistant (MDR) bacteria, and data clearly demonstrates that this classification resulted in overtreatment of CAP patients, and may be associated with adverse outcomes including increased mortality [5-9].

The alternative concept of "strong risk factors", e.g. known colonization of Methicillin-resistant *Staphylococcus aureus* (MRSA) or *Pseudomonas aeruginosa*, have been recently suggested by international experiences 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 ESBL-containing *Enterobacteriaceae* as a cause of CAP [11]. Since 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 6 out of 14 (42.9 %) experts (see below) [12].

2) Recommendation against the use of corticosteroids

Prior meta-analyses suggesting a benefit to corticosteroids may have triggered a increased usage corticosteroid use[13]. The guideline committee recognized that differences across healthcare systems worldwide, not accounted for in the meta-analyses, may have a marked influence on the benefit of corticosteroids on length of stay (LOS) and, therefore, advised against the routine use in CAP. Specifically, the dominant use of β-lactam monotherapy and longer baseline LOS in the control group of these European studies that was almost twice as long as standard in the USA, raising concerns about the generalizability of these results in the US-population[14]. For most of the experts (11 out 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 clinicians.

However, whereas nine out of 14 (64.3 %) of experts 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 benefit ratio of use should be distinguished between moderate and severe CAP could have been discussed more, where mortality is high and the risk-benefit ratio may be different compared to moderate severity. This position was rationalized by referring to a study that has shown a benefit in terms of treatment failure measured by radiological improvement in selected patients with high inflammation, as reflected by a C-reactive protein >150mg/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 and qSOFA) [17]. Sepsis studies may, therefore, provide some insights in this issue of debate. Although the question of which corticosteroid and at what dose and duration was 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 the 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 the expert panel. Two experts rated the recommendation against using procalcitonin to initiate or withhold empiric antibiotics among the top 5 useful recommendations of the novel guideline; they particularly agreed that completely withholding antibiotics might underestimate the burden of bacterial super-infections, which are associated with a particularly high mortality. In contrast, for two other experts, that recommendation was the most critical in the guideline. They argued that the recommendation against the use of procalcitonin for initial antibiotic treatment has ignored important studies, and was mainly based on a single study which excluded patients with radiological evidence of CAP[19]. They also argued that procalcitonin should be used as one among many pieces of diagnostic data to help a clinician justify early discontinuation of antibiotics when other evidence strongly supports a primary viral 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 patients' safety *versus* the aim to decrease unnecessary antibiotic usage[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 the 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 cut off of 25% of macrolide resistance in pneumococci, above which macrolides should not be used. However, half of the experts opposed to the 25% cut off, stating that this was too liberal and that a cut off 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 co-morbidities (bronchiectasis, COPD, asthma), who are especially prone to CAP, may increase the risk for macrolide-resistant pneumococci in these patients.

5) Recommendation on sputum and blood culture to be obtained in patients with severe CAP, as well as in all inpatients empirically treated for MRSA or *P. aeruginosa*

Testing practices of adults hospitalized with CAP varied significantly by geography and disease severity and there is a wide discordance between real-life testing practices and international guideline recommendations[25]. Compared to the 2007 CAP guideline, in which the cost versus impact on treatment decisions of diagnostic testing was emphasized, the new 2019 ATS/IDSA CAP guidelines place greater value on microbiological diagnostics. The indication for blood and sputum culture was expanded from severe diseases to all inpatients that are empirically treated including coverage to non-core pathogens such as MRSA or *P. aeruginosa*. This is a logical necessity, since the recommendation to de-escalate requires the identification of the underlying pathogen.

The increased value of diagnostics was seen as an improvement by most of the experts (9 out of 14; 64.3 %). However, some critical comments have been made; 7 out of 14 (50.0 %) experts suggested that this recommendation did not go far enough, compared to usual practice in other countries, such as UK [26], Germany[27] or Japan [28], where blood and sputum cultures are required for all in-patients. Furthermore, the limitation mentioned above was seen critical by some experts since the "strong" recommendation implies that is appropriate for quality assessment and public reporting. This will be a major change in emergency department workflow and there was concern among the panel that it may result in poor quality specimens. In addition, there was concern that decisions about which diagnostic tests to order are often made prior to antibiotic and ICU admission decisions, making these recommendations logistically impractical due to the conditional nature on these other management decisions.

6) Other areas considered as substantial change by individual experts

Other changes of recommendation that were mentioned favorably by some experts included recommendation against using anaerobic coverage for suspected aspiration (2 out of 14; 14.3 %) recommendation for urinary antigen testing (1 out of 14; 7.1 %) and the stronger evidence in favor of beta-lactam/macrolide combination for severe CAP (1 out of 14; 7.1 %).

Other various items that experts viewed as omissions or inadequately addressed included the recommendation to use antibiotics with antivirals for influenza in the outpatient setting (3 out of 14; 21.4 %) the overall lack of emphasis on the role of antibiotic stewardship (1 out of 14; 7,1 %) or on CAP prevention by vaccination and smoking cessation (1 out of 14; 7.1 %). Furthermore, (1 out of 14; 7.1 %) experts doubted that the general recommendation to use beta-lactam/macrolide combination in all inpatients is not justified by the current evidence.

Recommendations that are difficult to implement in a context outside of the USA

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

Epidemiology and empiric treatment. Several experts from Northern and Central European countries, as well as those from South Africa stated that due to the low incidence of CA-MRSA , this organism should not be covered empirically (5 out of 14; 35.7 %)[10]. In contrast, the rate of macrolide (e.g. in Japan, Spain) - and to a lesser degree doxycycline (South Africa) - resistant pneumococci 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 for the recommendation of fluoroquinolones even as an alternative for outpatients in their countries and other regions with high tuberculosis incidence (6 out of 14; 42.9 %) due to concern for obscuring the diagnosis of underlying tuberculosis or NTM infection. Indeed, there are some studies suggesting that fluoroquinolones can delay the diagnosis for tuberculosis by several months. Vice-versa, the widespread use of fluoroquinolones in MDR-tuberculosis was linked to an increase in fluoroquinolone-resistant pneumococci in a report from South Africa[29]. Two experts (2 out 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 (e.g. influenza PCR and MRSA-PCR from nasal swabs) is not widely available in their countries (2 out of 14; 14.3 %). However, several experts referred to their national guidelines that valued sputum samples higher, and would not restrict them to patients with risk for MRSA and/or *P. aeruginosa* (4 out of 14, 28,6 %).

Discussion

Although most physicians are aware of limitations to the generalization of guidelines in infectious disease, the ATS/IDSA Guidelines for the management of CAP in adults nevertheless remain influential, globally and are 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 MDRO 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 geographic-specific *caveats* of the guidelines.

In summary, additions to the updated CAP guidelines that were welcomed by international pneumonia experts included the abandonment of the concept of HCAP, to rate more restrictive indications for empiric macrolide treatment in outpatients, increased emphasis on microbiological diagnostics in an expanded populations, and addressing the use of corticosteroids. Main criticisms included the somewhat arbitrary choice of a 25% resistance threshold for outpatient macrolide monotherapy, recommendation of 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 acknowledgement of a possible benefit in selected populations with severe CAP. Finally, we recognized that the 2019 ATS/IDSA CAP Guidelines were not developed for the management of immunocompromised patients, despite the fact that these patients may comprise as many as 18% of CAP admissions worldwide[30]. An international position paper of the management of CAP in immunocompromised paper is anticipated soon.

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TABLES

Table 1. Major changes in recommendations from the 2007 to the 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 healthcare-associated pneumonia category	Accepted as introduced in the 2005 ATS/IDSA hospital-acquired and ventilator-associated pneumonia guidelines	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 combi-nations 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

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