CHEST Online Supplement

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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e-Table 1.

What are for you - compared to 2007 - the up to 5 most important useful changes in the new CAP guidelines and why?	What is the recommendation you do in general not agree with or that you see most critical?	Are there recommendations, that -from your perspective- make sense in context for the US landscape but cannot be transferred to your country
• Defining risk factors for MDR bacteria according to the positive predictive value of the risk factor. • Why: I like the concept of classifying a risk factors with a high "positive predictive value" as a "strong" risk factor. A strong risk factor will have a high positive predictive value for the presence of MDR-CAP. Due to the strong association, the presence of the risk factor is enough to start empiric therapy. Prior colonization or infection with MRSA or Pseudomonas are consider "strong" risk factors. HCAP is not a strong risk factor for MDR-CAP.	• Selection of outpatient antibiotics based on S. pneumoniae resistant level below 25% ○ The document continued using a resistance level of 25% to define if a macrolide or doxycycline can be selected for empiric therapy of S pneumoniae. This magic 25% resistance level originated from prior guidelines, and was based on expert opinion. From my point of view, 25% resistance implies that one in four patients will fail empiric therapy, and this would be unacceptable. Even 20% resistance, that would produce a failure of 1 in 5 patients, would be unacceptable. But the most important consideration is: Do we have an empiric therapy for S. pneumoniae with less possibility of failure? Why use an antibiotic with 20% resistance to S. pneumoniae when I can have another antibiotic, such as amoxicillin, with less than 5% resistance? I do not agree with the recommendation that outpatient therapy can be performed with a macrolide or doxycycline in areas with 20% resistance to a S. pneumoniae. • Monotherapy with amoxicillin for outpatients without comorbidities. ○ The new guidelines severely downplay the potential role of atypical pathogens in outpatients with CAP. They recognized that there is a "paucity of RTC data in the outpatient setting" and recommend atypical coverage for patients with comorbidities, because they are "more vulnerable to poor outcomes", and no atypical coverage for patients without comorbidities. As the use of	N/A

	PCR for viruses and atypical pathogens is used more frequently, we can clearly recognize poor outcomes in patients without comorbidities presenting with atypical pathogens, such as patients requiring hospitalization due to a progression of an atypical pneumonia. If I have to treat a 25-year-old patient without comorbidities with CAP, I will always treat with a backbone of a beta-lactam (amoxicillin) plus a macrolide or doxycycline. • **Areas of disagreement with all CAP Guidelines.** These guidelines, as so many other CAP guidelines, give recommendations regarding microbiological workup at the time that the patient is having the first contact with healthcare. In questions 1 and 2 the guidelines discuss the need for sputum cultures and gram stains, as well as blood cultures, at the time of diagnosis. The problem with this approach is that during the initial evaluation of a patient with fever and leukocytosis in the emergency department, I do not know why the patient had fever. Pneumonia is just one of my differential diagnosis. During the "fever workup" or "sepsis workup" I would obtain at least urine analysis, urine cultures, chest x-rays, blood cultures, as well as sputum if the patient is coughing. After my initial evaluation is completed, I may have a working diagnosis of CAP, or I may have a working diagnosis of UTI, or If the patient has positive blood cultures, and a follow-up echo is positive, then the working diagnosis may be endocarditis. • At the end of the day, if I am doing research in CAP, only the patient with a final diagnosis of CAP will be in my database. Analyzing my "only CAP" database to define how useful are blood cultures during the initial evaluation of the patient is misleading. During my initial evaluation of a patient most of the time I do not know what will be the final diagnosis.	

• Removal of the HCAP category as this has created a decade more of unnecessary broad spectrum antibiotic usage • Empirical coverage for MRSA or Pseudomonas for those with risk factors. This is based on better data and for selective use of antibiotics based on individual risks and local resistance profiles. The focus on making sure who is a risk of these infections is an improvement from previous guidelines. This is likely more important in certain parts of the world than others based on local profiles. • Coverage of procalcitonin and not recommending for its reliance for initial antibiotics therapy. • The use of combination beta lactam and macrolide for severe CAP showing improved outcomes having macrolides. • The inclusion on the use of corticosteroids has been an important change as this has been a confusing area for clinicians although their possible use in severe CAP could have been discussed more. Also the generic comment on their possible role for patients with refractory septic shock leaves it opens to multiple interpretations.	• The recommendation for antibiotic use with antiviral of influenza positive patients in the outpatient setting could be problematic as this will foster continued inappropriate use of antibiotics. • The use of macrolide alone for outpatients. • The use of quinolones alone for outpatient as an option without discussion of possible avoiding this class of antibiotics in areas where TB is prevalent or when NTM is a concern for the patient to prevent driving resistance to this class.	• We need to highlight in the commentary that the guideline is really for the US and maybe US only unless the etiological profile and resistance patterns are the similar which is usually not the case. In addition, many of the testing are not available or affordable for routine use in other parts of the world making their use impossible.
• Probably the most surprising recommendation was that against basing the initial decision to start antibiotics on a single PCT level. This nuanced but appropriate decision recognizes both subtleties in the clinical trials and practical differences in healthcare systems (early antibiotic administration in the Emergency Department, admitting without antibiotics), in addition to emerging data on correlation of PCT level with etiology. This recommendation does not exclude the possibility of	• A subtle but important phrase included in the recommendation for Question 1 regarding respiratory tract Gram stain and culture – “pretreatment” – will likely result in very low compliance with this recommendation. The strong recommendation implies that this is appropriate for quality assessment and public reporting. Since successful incorporation into clinical practice of the strong recommendation of previous guidelines that the first dose of antibiotics be given in the Emergency Department (ED), complying with this recommendation would fall in ED practitioners. This will be a major change in their	N/A

• Elimination of the HCAP designation is the most important conceptual change in the new CAP guidelines. Unfortunately, practitioners are still left with inadequate recommendations for the appropriate patients who need antibiotics other than the recommended therapy. An overemphasis on specific pathogens – MRSA and Pseudomonas – misses emerging data on ESBL-containing Enterobacteriaceae as a cause of CAP. A better recommendation for more extensive diagnostic testing would be anytime use of antibiotics other than recommended therapy, rather than just suspected MRSA or Pseudomonas. Empirical broader therapy based on risk factors will always result in overtreatment and therefore more extensive diagnostic testing is needed for appropriate antibiotic stewardship. • Probably the most dramatic change to clinical practice is the recommendation against routine use of corticosteroids. A published meta-analysis suggesting a benefit to corticosteroids has resulted in a mini-epidemic of corticosteroid use. The committee recognized that differences in in healthcare systems, not accounted for in meta-analyses, had a marked influence on the benefit of corticosteroids on length of stay (LOS). The dominant use of β-lactam monotherapy and baseline LOS in the control group of these European studies that was almost twice as long as standard in the US make these results inapplicable to our population. The long-awaited VA study is likely to confirm this recommendation.	workflow and likely to be met with resistance and when done, result in poor quality specimens. In addition, antibiotic choices and an ICU admission decision may not be made before the first dose of antibiotic is given in the ED.	
• The inclusion of patients previously defined as HCAP among those patients with	• The preferentially use of the PSI over the CURB-65 to determine the need for hospitalization CAP. (conditional recommendation, low quality of evidence).	• The use of nasal PCR for MRSA is not available in more than 95% of hospitals in our country.

• CAP, including the suspicion of MRSA or P. aeruginosa. • The recommendation of only one antipseudomonal antimicrobial (instead of two) for • the coverage of P. aeruginosa. • The recommendation of testing for influenza with a rapid influenza molecular assay to patients with CAP, when influenza viruses are circulating in the community. • The recognition of the risk of treating with azithromycin alone to outpatients with CAP who do not have risk factors for other than the core pathogens • The way in which the recommendation to treat anaerobes in the case of aspiration has been devalued..	• The lack of consideration of the role of corticosteroids in reducing treatment failure in patients with a level of C-reactive protein greater than 150mg/L at admission. • In adults with CAP whose symptoms have resolved within 5 to 7 days, we suggest not routinely obtaining follow-up chest imaging.	• Molecular assay could not be widely available to diagnose influenza in our country. • Some colleagues in our country are reluctant to use fluoroquinolones in patients who might have tuberculosis as a cause of their CAP.
• Going back to the use of the “penicillins”, and in particular the use of Amoxicillin in high dose, for outpatient use, which was not in the previous guideline because of concerns about penicillin resistance at that time. Penicillin resistance among pneumococci has not been seen to impact on outcome of CAP, even with discordant therapy (use of “penicillins” in patients with penicillin-resistant pneumococcal infections), provided that “appropriate” penicillins are used in “appropriate” doses. • Increased use of routine microbiological testing for a greater number of patients in order to recognize infections with antibiotic resistant pathogens, but also, in particular, to exclude excessive empiric treatment for MRSA and Pseudomonas. • Abandoning the use of the term HCAP, this had resulted in empiric overtreatment of CAP patients and restricting, in the new guideline, the use of additional agents for drug-resistant pathogens only for those patients with risk factors for drug-resistant pathogens.	• I am concerned about the recommendation for use of macrolide monotherapy for outpatients as long as the prevalence of pneumococcal macrolide resistance is less than 25%. I think that level is too high for a condition as significant as CAP. I have seen figures many years ago that suggest a level of macrolide resistance of less than 5% should be used, and although I cannot find the article(s) that suggested that right now, I will continue to look. • From my reading and interpretation of the literature of RCTs and systematic reviews and meta-analyses, I think the case for corticosteroid use in severe CAP should be made stronger. • I think the evidence for use of beta-lactam/macrolide as an option for all non-critically ill, hospitalized, patients with CAP is not based on as strong evidence as it is for critically ill cases/ICU cases. • I am concerned about the recommendation of the routine use of antibiotics (together with antiviral agents), in outpatients with CAP due to influenza virus. Evidence for antibiotic use in more severely ill cases with influenza infection is based on much stronger evidence.	• Doxycycline monotherapy for outpatients with CAP would not be suitable in South Africa, and probably sub-Saharan Africa, because of high levels of resistance to this agent among pneumococci. • CA-MRSA causing CAP is not a condition that has been seen in South Africa and does, therefore, not feature as a consideration in local CAP guidelines. • I think the recommendation for fluoroquinolone use as an alternative routine agent (alone or in combination, depending on the circumstances), would not be suitable for areas with high tuberculosis prevalence, such as sub-Saharan Africa, because their use in patients with suspected CAP who actually have TB may potentially mask the diagnosis and

• Mention on the possible use of corticosteroids for certain patients with severe CAP and unresponsive septic shock, whereas there was no mention of the use of corticosteroids in the previous guideline. [However see comments regarding CS under point 2 below]. • A movement away from macrolide monotherapy, because of concerns about the impact of macrolide resistance, which now has a qualified use rather than a strong recommendation [However also see comments in point 2 below]	• Concern with the use of fluoroquinolones (alone or in combination, depending on circumstances) as a routine alternative therapy because of recognition of side effects. • There is no mention in the new guideline about CAP prevention, such as use of pneumococcal vaccination, influenza vaccination, smoking cessation etc.	also be associated with development of fluoroquinolone resistance among the TB microorganisms. There is also a considerable concern regarding fluoroquinolone side effects
• Abandoning use of HCAP: Component factors of the HCAP definition are not essential for antibiotic resistance, except prior hospitalization. Re-defining "CAP" including HCAP would be useful for many physicians. • Emphasizing risk assessment for drug resistance in selecting empirical antibiotics: This is the essential step for physicians to select antibiotics at the time of pneumonia diagnosis. As described in the new guidelines, "one size fits all" schema for empirical therapy for CAP was not created. I think that showing candidate risk factors for MRSA and *P. aeruginosa* may be helpful for physicians and facilitate local studies to investigate the risk factors. I would suggest we mention this in this commentary. • Clear description regarding use of corticosteroids • Macrolide monotherapy: Conditional recommendation for outpatients based on resistant level would be acceptable. However, I personally feel that macrolide	• Obtaining sputum for Gram stain and culture (CQ1) ○ This may be answered in your 3rd question. Sputum sample for Gram stain and culture should be obtained in outpatients if possible. For inpatients with CAP, sputum should be obtained in all of them. If their initial treatment was failed, the information would be helpful in some cases • Initial treatment strategy for outpatients with CAP (CQ8) ○ In Table 3, they mentioned risk factors for MRSA and *P. aeruginosa*. To my knowledge, the risk factors in outpatients are unknown. I think that this should be described as an expert opinion. • Initial treatment strategy for inpatients with CAP (CQ9) ○ Descriptions in Table 4 is reasonable. However, the evidence of statement on the strategy in non-severe CAP at risk for MRSA or *P. aeruginosa* is unclear. • Follow-up chest imaging (CQ16) ○ I disagree with the recommendation. In our pneumonia database in Japan, about 1-2% of patients with pneumonia were diagnosed as having malignant diseases after treatment of pneumonia. They mentioned that the rate of abnormal findings may reach 5%. I feel that this number is high.	• Obtaining sputum for Gram stain and culture (CQ1) ○ See my earlier answer (2a). Most of Japanese physicians usually try to obtain sputum sample for culture and Gram stain when pneumonia was diagnosed. • Macrolide monotherapy (CQ8) ○ In Japan, pneumococcal resistant rate is more than 80% in most regions. Therefore, monotherapy with a macrolide cannot be recommended in Japan.

monotherapy would be dangerous even if local pneumococcal resistant rate was < 25%.		

• Use of Urinary antigens. They were not included in the 2007 and now they are. Very useful to Taylor empirical treatment
• Recognition of a major benefit of a Beta-lactam + macrolide vs Beta-lactam + quinolone for severe CAP. A body of literature, mostly observational, recognizes better outcomes when adding macrolides to beta-lactams
• Recognition and recommendations for non-core pathogens. This is a step forward for the recognition of NON-core pathogens and their variability comparing different countries. They recommended local algorithms
• Recommend sputum culture in only severe disease or non-core pathogens
  ○ I agree with this statement. Gram stain + cultures of sputum would be probably beneficial in the most severe CAP and in those cases with suspected NON-core pathogens
• At least to cover the issue of corticosteroids
  ○ They reviewed corticosteroid treatment in a very simplistic way. They forgot that the mortality of SCAP is still very high
	• Macrolides alone for outpatients
	  ○ This is really very dangerous. The threshold of 25% resistance is weakly supported. Some people Will die due to this recommendation
	• Not recommending corticosteroids in severe CAP
	  ○ The recommendation of not giving steroids is too categorical. We Will lose an opportunity to improve mortality in the most severe
		• Yes: Mainly the recommendations for outpatient's Antibiotic treatment
		• We cannot treat in Spain, and in many parts of the world, including USA patients with macrolides in monotherapy. Very dangerous recommendation

• Expanding the indication for sputum gram stain and culture as well as blood cultures to all inpatients empirically treated for MRSA or Pseudomonas aeruginosa • Abandoning use of the prior categorization of healthcare-associated pneumonia to guide selection of extended antibiotic coverage • Recommending against using corticosteroids in adults with CAP	• Expanding the indication for sputum gram stain and culture • All patients able to provide sputum should be assessed by sputum Gram stain and culture routinely, but in particular those requiring ED or hospital admission or those with comorbidities could benefit from a microbiological diagnosis (the strong recommendation stands in contrast to very low quality evidence for not obtaining sputum in adults with CAP) • Recommending against the use of procalcitonin for antibiotic stewardship • Ignored the whole literature and base recommendations on a single study which excluded	• In Switzerland, sputum and blood cultures will be collected from all admitted patients. In addition, Legionella and pneumococcal urine antigen will be determined in all hospitalized cases. Upon negativity of these assays, macrolide therapy will typical be de-escalated. • Fluoroquinolones are not considered the therapy of choice as empiric monotherapy for CAP patients in adults without risks

	patients with reasonable changes to have CAP (Huang et al, NEJM 2019) • Recommending against follow-up imaging	factors for MRSA and P. aeruginosa in Switzerland • Most clinicians will recommend follow-up imaging in patients at higher risk for malignancy i.e. smokers

• Downgraded macrolide monotherapy for outpatients but still recommends this. Macrolide monotherapy is not used for any patients with CAP in the UK (unless they have allergy to other antibiotics). I would not promote the widespread use of macrolide monotherapy in outpatients and I think it drives resistance and adverse effects
• Biggest change from previous is the dropping of the HCAP category, which is a positive development but significant harm has been caused by this and it has taken 14 years to remove this from guidelines when it was clear 10 years ago that this was a bad concept. Brandon Webbs paper in ERJ recently demonstrates clearly adverse effects related to over-treatment. The HCAP story should be cautionary tale about making guideline recommendations on poor evidence.
 	
• Recommendations I agree with
  ○ Removal of HCAP
  ○ Non-recommendation of steroids. The evidence for steroids is very limited and the best studies are too small to recommend routine use in clinical practice. More studies are needed but they should not be recommended in guidelines in my opinion.
  ○ Beta-lactam macrolide combination for severe CAP
	• Beta-lactam macrolide combination for all hospitalized patients regardless of severity. The evidence for combinations is really in severe CAP. In patients with mild CAP, the role of macrolides is not established. The Dutch study by Bonten and colleagues has limitations mostly because the population is mild, but still shows in mild patients there is little advantage to macrolides. Over-treatment is not without costs and harms
	• There is a lot in the guidelines on MRSA and Pseudomonas which are obviously important in some centers in the US but are rare causes of CAP in Northern Europe (and many other parts of the world). Important to emphasize the point that local epidemiology has to guide what we do (which to be fair, is what the guidelines ultimately say). For someone in the Netherlands, UK, Sweden etc., then very few patients will ever need coverage of these organisms.
		• The guidelines are mostly sensible and methodologically sound but its important to remember they are primarily focused at the US and not meant to be the “global” CAP guideline, which is how they are often interpreted.

• Recognition that seeking a microbiological diagnosis has benefits for de-escalation. This is important as resistant trends change over	• No formal mention of the role for antibiotic stewardship in the management of CAP. AS is an important initiative that is globally supported; CAP is one of the	• I disagree with the recommendation for Ceftaroline as a first line agent for CAP. While this

time and implicitly recognizes the need for antimicrobial stewardship in CAP, e.g. de-escalation. • Abandonment of flawed HCAP guidelines. Led to huge increases in unnecessary broad spectrum use over last 10 years because of poor specificity. • Recommendation for locally validated prediction of drug resistant pneumonia. This importantly recognizes geographic and demographic differences in patient-level risk factors while at the same time allowing clinicians to validate and use tools that do work well in their hospital. • Recommendation against using anaerobic coverage for suspected aspiration unless empyema or putrid abscess. This aligns with pathophysiology (all pneumonia is aspiration) and microbiology (most oral flora, including oral anaerobes are still susceptible to beta lactams alone) • Not using corticosteroids for CAP	largest contributors to antibiotic use and AS provides important management resources for de-escalation, appropriate recognition of local resistance patterns and selection of empiric antibiotics. • Withholding broad spectrum antibiotics in non-severe patients with risk factors for drug resistance. Although there is no question that broad spectrum abx are overused, this recommendation is not supported by any clinical research of which I am aware. The question remains unanswered: is inadequate initial spectrum only associated with poor outcomes in severe CAP? • Use of the MRSA nasal swab to guide *initiation* of anti-MRSA therapy. This has also not been studied. We know that in certain high-pre test probability populations, the PPV of the MRSA nasal PCR is 30%; in areas with very low incidence the PPV is much lower and will lead to inappropriate use of anti-MRSA therapy. • The reality of the procalcitonin debate is that it is *already* widely used to support the diagnosis of primary viral etiology. While using this tool to withhold antibiotics may not be well supported by evidence, using it 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	may be appropriate in areas of the world with high ceftriaxone resistant rates for S. pneumo (South Africa?), it is not appropriate in most areas in the US and northern Europe and may lead to overuse of an important anti-MRSA agent
• Esclusion of HCAP definition. This is particularly important in Europe where the HCAP definition has been clearly demonstrated as unuseful. • Recognition of a major benefit of a Beta-lactam + macrolide vs Beta-lactam + quinolone for severe CAP. Not sure that this can apply to all hospitalised CAP, this is based on mostly observational studies • Recognition of the role of microbiology testing to limit broad spectrum antibiotic approach • Steroid use. I agree with the non-recommendation statement. The evidence is	• Macrolides alone for outpatients ○ I would not support the use of macrolide single therapy in Italy and probably in all Southern European Countries where pneumococcal resistance rate is fairly high (>20%)	• The rate of CA-MDR pathogens is much much lower in Europe compared with US. This has been demonstrated in different papers including different European Countries.

still not adequate to recommend the use in CAP. • I support the beta-lactams use in outpatients. To underline the indication of high dose use (amoxicillin), this prevents failure even if "pen-resistant" pneumococci are involved.		
• Exclusion of HCAP • Downgrading of outpatient macrolide treatment • recommendation for beta-Lactam/Macrolide combination over beta-lactam/fluoroquinolone for severe CAP • Broadening the recommendation for blood culture and sputum sampling • Advising against follow-up chest imaging	• Limiting sputum and blood culture diagnostics in hospitalized patients to only those with severe CAP and those with risk factors • Not mentioning steroids as adjunctive treatment in severe CAP	• Empiric coverage of MRSA in those with risk factors – MRSA has become very rare in Germany • Use of nasal PCR to screen for MRSA – same reason as above
• HCAP is out • A specific focus on MRSA and P. aeruginosa across different SOPs • The suggestion of oseltamivir regardless the days from S/S onset • Recommendations against the routine use of steroids • Beta-lactam macrolide combination for severe CAP	• The threshold of 25% for macrolide resistance and macrolide alone for outpatients • Recommendation against radiological follow up	• MRSA diagnostic and empiric therapy. In Italy we have a low prevalence of MRSA-CAP • Doxycycline monotherapy for outpatients with CAP • Macrolide monotherapy for outpatients
• Steroids are used more restrictively • There is more on de-escalation in the guideline • HCAP was abolished • Macrolides were downgraded	• macrolides still used too often • every patient with influenza should receive Tamiflu and antibiotics Here is missing: severity (X-ray is not a severity level) • criteria for "MRSA and Pseudomonas" => too broadly defined, lead to overtherapy	• risk criteria for MRSA and Pseudomonas, does not play such a role in Germany.