Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America

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By definition, community-acquired pneumonia (CAP) is an acute infection of the lung parenchyma. Pneumonia is associated with considerable morbidity and mortality, which increase with a patient's age and comorbidities; the management of CAP is based on epidemiologic and microbiologic considerations.[1–4]

The latest Clinical Practice Guideline of the American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA) on CAP was published in 2019[5] and used a slightly different approach to more clearly deliver recommendations. The format was to answer all clinically relevant questions to unify current practice. These experts used the Patient or Population, Intervention, Comparison, Outcome (PICO) framework instead of the prior narrative style of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) format.[3] We have reviewed the latest ATS and IDSA recommendations to evaluate the quality and potential performance of the recommendations and summarize them here.

Q1: In adults with CAP, should a Gram stain of the lower respiratory secretions be obtained at the time of diagnosis?

The panel **strongly recommends not** to obtain respiratory samples in outpatients, based on very low quality of evidence. Since these patients should be in relatively stable conditions to be considered for outpatient treatment and respiratory samples have a relatively low yield, these recommendations seem appropriate.

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Regarding inpatient management of CAP, the recommendation is more **complex**. Their approach requires evaluation of patients with IDSA/ATS criteria for severity of pneumonia. In case of severe pneumonia or if coverage for methicillin-resistant *Staphylococcus aureus* (MRSA) or *Pseudomonas aeruginosa* is being considered, the recommendation is to obtain a sputum culture and Gram stain (very low-quality evidence). These recommendations follow the rationale of antimicrobial stewardship and possible data gathering for future recommendations. A shortcoming can occur in cases with no coverage for MRSA or *Pseudomonas aeruginosa* in less sick patients and potential under treatment.

Q2: In adults with CAP, should blood cultures be obtained at the time of diagnosis?

The recommendation for outpatients with CAP is **not** to obtain blood cultures based on very low quality of evidence. Again, considering the relatively stable clinical status of the patients, this recommendation seems safe and efficient.

For the inpatient management of CAP, the recommendation is **not** to routinely obtain blood cultures based on very low quality of evidence. But in this case, and even as mentioned in the references evaluated by the panel, one large observational study showed lower mortality associated with blood cultures at the time of admission.[6]

The ATS and IDSA panel makes an argument based on reduced length of stay (LOS) in a large retrospective study.[7] This study shows that LOS was longer in patients who had blood cultures done, underwent mechanical ventilation, and were admitted to ICU. This indicates that patient who had blood cultures done were likely sicker. The ATS/IDSA panel does recommend obtaining blood cultures in patients

with more severe CAP, but it should be clear that the increase LOS is not a consequence of getting blood culture. Also considering very low quality of evidence, we believe that there is potential benefit of getting blood cultures for all patients admitted to the hospital, since patients with the same type of infection can exhibit different severity of symptoms and knowing a positive blood culture result can potentially and appropriately increase the duration of treatment, as, for example, in cases of hard to eradicate pathogens like *Staphylococcus aureus*.

Q3. In adults with CAP, should legionella and pneumococcal urine antigen testing be performed at the time of diagnosis?

This recommendation is based on low quality of evidence and is **not** to routinely test for these antigens. This recommendation is conditional and recommends testing for these antigens in severe CAP and in patients with recent travel or near a recent outbreak of legionella in the community.

This recommendation is based on large observational studies showing mortality reductions but without the establishment of a direct effect.

Q4. In patients with CAP, should a respiratory sample be tested for influenza virus at the time of diagnosis?

For influenza testing, the panel recommended **strongly in favor** of testing based on moderate quality of evidence. The rationale is the established benefit of antiviral therapy in addition to infection control implications.

Q5. In adults with CAP, should serum procalcitonin plus clinical judgment or clinical judgment alone be used to withhold the initiation of antibiotic treatment?

The Panel **strongly recommended starting antibiotics** regardless of the procalcitonin level based on moderate quality evidence. It should be noted that higher levels of procalcitonin are strongly correlated with an increased probability of a bacterial infection. But it is also important to note that even in patients with elevated procalcitonin levels greater than 0.5, only 21% of the patients had positive microbiological evidence of infection with typical bacteria, and 55% did not have any microbiological evidence of an infection.[10]

Q6. Should a clinical prediction rule for prognosis plus clinical judgment or clinical judgment alone be used to determine in-patient vs outpatient treatment locations for adults with CAP?

A **strong recommendation** was given based on moderate quality of evidence to use the pneumonia severity index (PSI) over the CURB-65. Based on current data, PSI identifies a bigger proportion of patients as low risk and has higher discriminative power in predicting mortality.

When using PSI, we should remember possible shortcomings of PSI use, including social and psychological aspects of the patients, possible underestimation of the PSI in younger individuals, and the clinically insignificant baseline low blood pressure in some patients.

Q7. Should a clinical prediction rule for prognosis plus clinical judgment or clinical judgment alone be used to determine inpatient general medical vs higher levels of inpatient treatment (ICU, step-down, or telemetry unit) for adults with CAP?

A **strong recommendation** based on low quality evidence was given. This recommendation was conditional on the severity of the disease using multiple scoring systems. In addition to the need for vasopressors and mechanical ventilation, these scoring systems evaluate multiple parameters of the patient's clinical status and have common criteria. Also, the recommendation adds the clinical judgment of the providers that makes it more conservative and potentially safer for the patients.

Q8. In the outpatient setting, which antibiotics are recommended for empiric treatment of CAP in adults?

The recommendation is based on all available information, including inpatient data, with moderate quality of evidence for single agent regimens. In

patients without comorbidity, the panel recommended ampicillin 1-gram q 8 hours. In patients with higher risk and more comorbidities, the coverage becomes broader as one would expect. Providers should know the percentage of resistant pneumococci in their community if they want to use macrolide as a single agent.

Q9. In the inpatient setting, which antibiotic regimens are recommended for empiric treatment of CAP in adults without risk factors for MRSA and Pseudomonas aeruginosa?

9-1: A **strong recommendation** based on high quality of evidence was given for regimens with beta-lactams and macrolides combination or fluoroquinolones alone for non-severe CAP. In case of contraindications for both macrolides and fluoroquinolones, the recommendation is based on low quality evidence for combination therapy with beta lactams and doxycycline as coverage for atypical infections. It should be noted that high quality data currently exist for fluoroquinolone and macrolide, and doxycycline is an alternative regimen. Also there are promising data for omadacycline which has fewer side effects and lower rates of *Clostridium difficile* infection as a potential alternative for fluoroquinolones.[11,12]

9-2: In severe CAP, a **strong recommendation** based on moderate quality of evidence was given for beta-lactam and macrolide and low quality of evidence for beta-lactam and fluoroquinolone combination. It should be noted that meta-analysis of large observational studies showed 18% mortality reduction in beta-lactam and macrolide combination vs beta-lactam only treatment. Also, in a systemic review of 17 observational studies, Vardakas et al found higher mortality in patients treated with a fluoroquinolone and beta-lactam combination vs a macrolide and beta-lactam. Due to the overall low quality of evidence, no recommendation for a preferred regimen was made.

Q10. In the inpatient setting, should patients with suspected aspiration pneumonia receive additional anaerobic coverage beyond standard empiric treatment for CAP?

A recommendation was made in form of a suggestion and was based on very low quality of evidence **not** to routinely cover anaerobic microorganisms. It should be noted that one of the references used for this recommendation had only one positive anaerobic culture in 185 episodes of VAP and 25 episodes of aspiration pneumonia. Also, the recommendation is based on possible harm due to *Clostridium difficile* infection using clindamycin.

The recommendation does not comment about metronidazole use in aspiration pneumonia, which is less likely to be associated with *Clostridium difficile*. Metronidazole is part of the recommended regimens for treatment of the lung abscess to cover for anaerobic microorganisms.[13]

Q11. In the inpatient setting, should adults with CAP and risk factors for MRSA and *Pseudomonas aeruginosa* be treated with extended-spectrum antibiotic therapy instead of standard CAP regimen?

Strong recommendation based on moderate quality evidence was given **not** to cover any recently hospitalized patient for MRSA and *Pseudomonas aeruginosa* unless epidemiology of the region shows risk for these pathogens. The authors eliminated the use of health care associated pneumonia (HCAP) term for choosing antibiotic regimens. Recommendations are based on de-escalation after 48 hours and a MRSA nasal swab. It is important to note that even in case of a positive nasal swab for MRSA, physicians can still consider de-escalation based on sputum and blood culture results and the overall patient's clinical course.

Q12. In the inpatient setting, should adults with CAP be treated with corticosteroids?

Strong recommendation was given **not** to routinely use corticosteroids in adults with severe CAP, based on high quality of evidence. The authors suggested **not** to routinely use corticosteroids in adults with severe CAP, conditional to an absence of refractory septic shock and based on moderate quality of evidence. Also, in adults with severe influenza pneumonia, the panel suggested **not** to routinely use corticosteroids, conditional again on the absence of refractory septic shock. This recommendation was based on low quality of evidence.

The panel endorsed the use of corticosteroids in refractory septic shock patients. It should be noted that a large RCT has already been done (clinicaltrials.gov NCT01283009), and the results are going to be released soon. We recommend following the results of that study for more reliable evidence-based practice.

Q13. In adults with CAP who test positive for influenza, should the treatment regimen include antiviral treatment?

A **strong recommendation** was given to treat all patients independent of the duration of illness. It was based of moderate quality of evidence for in-patients and low quality of evidence for outpatients. It should be noted that no study had been done to evaluate the effect of antiviral medication in an outpatient setting for patients with pneumonia.

Q14. In adults with CAP who test positive for influenza, should the treatment regimen include antibacterial therapy?

A **strong recommendation** was given based on low quality of evidence to start antibiotics in both inpatient and outpatient settings. The suggested approach for treatment of such patients is to get respiratory cultures and procalcitonin and adjust treatment in 48 to 72 hours accordingly.

Q15. In outpatient and inpatient adults with CAP who are improving, what is the appropriate duration of antibiotic treatment?

A **strong recommendation** was given based on moderate quality of evidence to treat **no fewer than 5 days** and monitor the patient's symptoms.

Note that studies had been done to monitor procalcitonin level in order to avoid excess treatment, but the data showed that this approach potentially could increase duration of treatment. Also, failure to achieve clinical stability within 5 days is associated with higher mortality and worse clinical outcomes. Reevaluation for possible resistant pathogen or complications should be performed.

Q16. In adults with CAP who are improving, should follow-up chest imaging be ordered?

Recommendation is based on low quality of evidence **not** to routinely check follow-up chest imaging. This recommendation is conditional, and the main concern is in patients with pneumonia due to underlying mass. It was noted that a large number of high-risk patients for lung cancer are already eligible to be screened for lung cancer.

Summary

After reviewing the 2019 ATS/IDSA recommendations for the management of CAP, we believe the latest recommendations are more helpful and answer more questions with a more specific approach.

Our recommendation is to treat CAP in the outpatient setting as recommended.[5] Remember in case of monotherapy with macrolides, the rate of resistant pneumococci should be less than 25% in the epidemiologic reports of the region of practice.

We recommend obtaining blood cultures for all patients who are being admitted to the hospital. Our recommendation is for all patients and differs from the ATS/IDSA recommendation, which is not to routinely obtain blood cultures. We believe the ATS/IDSA panel did provide convincing rationale not to obtain blood cultures in all patients, but positive culture results can provide crucial information in some patients. In an outpatient setting we agree with not obtaining blood cultures.

We recommend not to routinely test for legionella and pneumococcal urine antigen except in patients with severe CAP or who are at high risk for legionella or if the clinical suspicion is high (altered mental status, gastrointestinal symptoms, hyponatremia, etc.); consider sending respiratory samples for legionella PCR or culture as the urine antigen tests only for serogroup one legionella.

We recommend testing all patients who are being admitted to the hospital for influenza and treat with antiviral and antibiotics in both inpatient and outpatient

settings. The treatment can be adjusted based on respiratory cultures and procalcitonin results in the in-patient setting.

We recommend using clinical judgment rather than the procalcitonin level for initiation of antibiotics and perhaps using procalcitonin as a monitoring tool for the duration or need for antibiotic treatment.

We recommend using the PSI over the CURB-65 for deciding inpatient vs outpatient management of patients.

We recommend direct admission to the critical care unit for patients with hypotension requiring vasopressors or respiratory failure requiring mechanical ventilation. For other cases of severe pneumonia, we recommend using the ATS/IDSA 2007 minor severity criteria[3] in addition to clinical judgment for the determination of the appropriate level of care.

We recommend treatment of non-severe CAP in patients with no risk factors for MRSA or *Pseudomonas aeruginosa* in the inpatient setting with a combination of beta-lactam and macrolide, fluoroquinolone alone, or beta-lactam and doxycycline combination as an alternative in case of contraindication for both macrolide and fluoroquinolone. For severe CAP we recommend combination treatment with beta-lactam either with macrolide or with fluoroquinolone. Remember current data show possible benefits of using macrolide vs fluoroquinolone in patients with severe CAP.[14]

We recommend not using empirical coverage for MRSA and *Pseudomonas aeruginosa* in all patients with recent health care encounters unless the local epidemiology is high risk for these infections. Patients should be evaluated individually if they have history of such infections or if they have risk factors for acquiring these infections. In the case of starting extended spectrum antibiotics, de-escalation should be considered based on a MRSA nasal swab and respiratory and blood cultures in 48 hours.

We recommend not using corticosteroids routinely in patients with CAP. We endorse corticosteroids use in refractory septic shock.

We recommend a minimum treatment of five days with antibiotics in the outpatient setting and daily clinical evaluation of the patients in the inpatient setting for resolution of the pneumonia or for further need of antibiotics. Follow up chest X-ray should not be obtained for monitoring the resolution of pneumonia unless the patients have risk factors for underlying malignancy.

Keywords: guidelines, community acquired pneumonia, diagnosis, treatment

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