

## 2019 CAP Treatment Guidelines – The Need for a Change Towards a More Parsimonious Antibiotic Use?

*Benedikt Huttner<sup>1,2</sup>, Bernadette Cappello<sup>1</sup>, Graham Cooke<sup>3</sup>, Sumanth Gandra<sup>4</sup>, Stephan Harbarth<sup>2</sup>, Monica Imi<sup>5</sup>, Marc Mendelson<sup>6</sup>, Lorenzo Moja<sup>1</sup>, Céline Pulcini<sup>7</sup>, Mike Sharland<sup>8</sup>, Mei Zeng<sup>9</sup>, Nicola Magrini<sup>1</sup>* on behalf of the WHO EML Antibiotic Working Group

### Affiliations:

<sup>1</sup>Department of Essential Medicines and Health Products, World Health Organization, Geneva 1211, Switzerland

<sup>2</sup>Division of Infectious Diseases, Geneva University Hospital and Faculty of Medicine, University of Geneva, Geneva, Switzerland

<sup>3</sup>Department of Infectious Disease, Imperial College London, London, UK

<sup>4</sup>Division of Infectious Diseases, Washington University School of Medicine, St Louis, MO, USA

<sup>5</sup>Medical Internist, Practicing Clinician and Technical Adviser to the Ministry of Health, Kampala, Uganda

<sup>6</sup>Division of Infectious Diseases and HIV Medicine, Department of Medicine, University of Cape Town, Cape Town, South Africa

<sup>7</sup>Department of Infectious Diseases and APEMAC, Université de Lorraine, Université de Lorraine, Nancy, France

<sup>8</sup>Paediatric Infectious Diseases Research Group, Institute for Infection and Immunity, St George's University of London, London, UK

<sup>9</sup>Department of Infectious Diseases, Children's Hospital of Fudan University, Shanghai, China

**Funding:** no specific funding

Correspondence: [benedikt.huttner@hcuge.ch](mailto:benedikt.huttner@hcuge.ch)

To the Editor:

The American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) recently published updated guidelines on the diagnosis and treatment of adults with community-acquired pneumonia (CAP).(1) In the 12 years since the previous edition of the guidelines, the importance of incorporating antimicrobial stewardship principles into treatment guidelines has been increasingly recognized.(2) In 2017, the United States (US) Healthcare Infection Control Practices Advisory Committee (HICPAC) provided guidance regarding this issue for US treatment guidelines. One of the recommendation states that *“when multiple therapeutic options are available, a hierarchy of antibiotic treatment recommendations should be provided with ‘first choice’ options being those with adequate therapeutic efficacy, the lowest risk of facilitating antimicrobial resistance, and the lowest risk of promoting C. difficile and other adverse events, with consideration of healthcare value.”*(3) The World Health Organization has recently developed the AWaRe (Access, Watch and Reserve) framework for classifying antibiotics based on antibiotic stewardship principles and recommends its use in treatment guidelines.(4, 5)

We are therefore concerned that the 2019 version of the ATS/IDSA CAP guidelines seems to give disappointingly little weight to such antibiotic stewardship principles when continuing to recommend WHO Watch and Reserve antibiotics as first line options for CAP for most of the target populations. We suggest that Access antibiotics would be sufficient for many patients and preferable from an antibiotic stewardship perspective. Amoxicillin, the first-choice treatment for CAP based on the 2019 WHO Model List of Essential Medicines and listed also as first-choice option in many guidelines outside the USA, is recommended in the ATS/IDSA guidelines, together with doxycycline and macrolides as equivalent options, only

recommended for patients without comorbidities (very broadly stated as “chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancy; or asplenia”).(6, 7)

Since in the United States, 6 in 10 adults have one chronic disease and 4 in 10 adults have two or more chronic diseases, the recommendation for amoxicillin will be applicable to a minority of adults with CAP.(<https://www.cdc.gov/chronicdisease/pdf/infographics/chronic-disease-H.pdf>) US physicians will therefore most likely continue to treat many patients with the Watch group respiratory fluororoquinolones - a class of antibiotic with well documented propensity to favour the emergence and spread of AMR and *Clostridoides difficile* infections, as well as an increased risk of adverse events (FDA alert).(8, 9)

This will hamper CDC efforts to reduce overall antibiotic consumption and reduction of fluoroquinolone use in the United States.(10) The HICPAC antibiotic stewardship principles also suggest including recommendations for patient education on antibiotic therapy when appropriate. Accordingly, the CAP guidelines could have considered providing guidance to physicians on selection of Access group antibiotics such as amoxicillin or doxycycline for selected patients with stable comorbid conditions with close monitoring and adequate patient education.

Even more surprising is the listing of the Reserve group fifth-generation cephalosporin ceftaroline as a first-choice empiric treatment option of CAP (in combination with a macrolide) in hospitalized adults without risk factors for MRSA and *P. aeruginosa*. Ceftaroline efficacy data from phase III trials suggesting superiority compared to ceftriaxone with regard to clinical cure require further scrutiny and its current listing as first-choice option violates basic antibiotic stewardship considerations.(11, 12)

Given that respiratory tract infections are one of the most frequent reasons for antibiotic prescriptions worldwide and that in many countries the United States treatment recommendations are still considered an important reference, it seems to us – as the WHO EML antibiotic working group - that this presents a lost opportunity for antibiotic stewardship. We believe there is a clear need for better alignment of all treatment guidelines to the same guiding principles and to reach a global set of evidence-based recommendations with a focus on enhancing the use of Access group antibiotics.

**REFERENCES:**

1. Metlay JP, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K, Cooley LA, Dean NC, Fine MJ, Flanders SA, Griffin MR, Metersky ML, Musher DM, Restrepo MI, Whitney CG. 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. [statement] *Am J Respir Crit Care Med* 2019; 200: e45-e67.
2. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, Dowell SF, File TM, Jr., Musher DM, Niederman MS, Torres A, Whitney CG, Infectious Diseases Society of A, American Thoracic S. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis* 2007; 44 Suppl 2: S27-72.
3. Committee HICPA. Antibiotic Stewardship Statement for Antibiotic Guidelines – Recommendations of the Healthcare Infection Control Practices Advisory Committee 2017.
4. Sharland M, Pulcini C, Harbarth S, Zeng M, Gandra S, Mathur S, Magrini N, et al. WHOECoS, Use of Essential M. Classifying antibiotics in the WHO Essential Medicines List for optimal use-be AWaRe. *Lancet Infect Dis* 2018; 18: 18-20.
5. Sharland M, Gandra S, Huttner B, Moja L, Pulcini C, Zeng M, Mendelson M, Cappello B, Cooke G, Magrini N, Group obotEECaAW. Encouraging AWaRe-ness and discouraging inappropriate antibiotic use—the new 2019 Essential Medicines List becomes a global antibiotic stewardship tool. *Lancet Infect Dis* 2019 (accepted for publication).

6. Wiersinga WJ, Bonten MJ, Boersma WG, Jonkers RE, Aleva RM, Kullberg BJ, Schouten JA, Degener JE, van de Garde EMW, Verheij TJ, Sachs APE, Prins JM. Management of community-acquired pneumonia in adults: 2016 guideline update from the Dutch Working Party on Antibiotic Policy (SWAB) and Dutch Association of Chest Physicians (NVALT). *Neth J Med* 2018; 76: 4-13.
7. The National Institute for Health and Care Excellence. Pneumonia (community-acquired): antimicrobial prescribing. 2019.
8. de Lastours V, Fantin B. Impact of fluoroquinolones on human microbiota. Focus on the emergence of antibiotic resistance. *Future Microbiol* 2015; 10: 1241-1255.
9. FDA. FDA warns about increased risk of ruptures or tears in the aorta blood vessel with fluoroquinolone antibiotics in certain patients. 2018.
10. US Department of Health and Human Services C. Antibiotic Use in the United States, 2018 Update: Progress and Opportunities. . 2019.
11. Lan SH, Chang SP, Lai CC, Lu LC, Chao CM. Efficacy and Safety of Ceftaroline for the Treatment of Community-Acquired Pneumonia: A Systemic Review and Meta-Analysis of Randomized Controlled Trials. *J Clin Med* 2019; 8.
12. Taboada M, Melnick D, Iaconis JP, Sun F, Zhong NS, File TM, Llorens L, Friedland HD, Wilson D. Ceftaroline fosamil versus ceftriaxone for the treatment of community-acquired pneumonia: individual patient data meta-analysis of randomized controlled trials. *J Antimicrob Chemother* 2016; 71: 862-870.