**The challenge of antimicrobial prescribing for Hospital Acquired Pneumonia**

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**The challenge of antimicrobial prescribing for hospital-acquired pneumonia**

The influential UK National Institute for Health and Care Excellence (NICE) have recently published Hospital Acquired Pneumonia (HAP) prescribing guidelines.[1] The recognition is welcome since HAP is responsible for more deaths and greater morbidity than other Healthcare Associated Infections (HCAIs) with an estimated in-hospital mortality between 18 and 29%.[2-4]

NICE bemoan the lack of evidence to support their recommendations and these frustrations echo the sentiments of recent American and European HAP guidelines.[5,6] No systematic reviews of HAP management are available and only 9 trials met NICE criteria. The UK contributed a total of 10 patients to the evidence base.[7] Extrapolating evidence from multi-centre clinical trials which recruited from multiple countries with markedly varying HAP aetiological and antimicrobial resistance profiles, is fraught with difficulty. Reflecting this, the guidelines recognise the importance of local antibiograms, even to the level of individual wards and many of NICE’s suggestions represent an attempt to provide pragmatic advice. For example, although "no suitable studies examining the timing of antibiotic administration in HAP were available” NICE suggests antibiotics are administered within 4 hours of x-ray confirmation of HAP which would allow pre-antibiotic, diagnostic specimens to be obtained.

A central tenet of antibiotic prescribing is to understand local epidemiology and studies have demonstrated major differences in the rates of pneumonia pathogens and resistance at national and continental level.[8] Empirical antibiotic choices must therefore balance adequate pathogen coverage with the increased risk of *Clostridioides difficile*, death, and antimicrobial resistance attributed to some antibiotic classes.[9] In this context, NICE focus on antibiotic stewardship and reinforce the importance of diagnostic microbiological samples such as sputum, nasopharyngeal swabs or tracheal aspirates.

These guidelines triage patients into two groups based on clinical severity and the risk of resistant pathogens. Oral co-amoxiclav is recommended for adults and children with low clinical severity and low risk of resistant bacteria. Severity assessment is to be based on “clinical judgement” since there are “no validated severity assessment tools”. Resistance risk includes “…recent use of broad-spectrum antibiotics” and “recent contact with health and social care settings”. These descriptions are ambiguous and it is likely that local interpretation will result in the majority of patients being assigned to the higher risk algorithm where the suggested options are: piperacillin-tazobactam, ceftazidime, ceftriaxone, cefuroxime, meropenem, ceftazidime-avibactam or levofloxacin. This list is worthy of comment since NICE recognise that high risk HAP is associated with *Pseudomonas aeruginosa* and organisms carrying extended-spectrum beta-lactamases (ESBLs). However, the inclusion of agents such as ceftriaxone and cefuroxime, which lack activity against *P. aeruginosa* and organisms carrying ESBLs, is counterintuitive and does not adhere to the principle of “start smart, then focus”.[10] The widespread usage of these agents risks further propagating the spread of ESBL and AmpC producing organisms, as well as exposing patients to an elevated risk of *C. difficile* disease. NICE recommends antibiotics for Methicillin Resistant Staphylococcus Aureus (MRSA) should only be considered in the presence of specific risk factors or when MRSA is confirmed. This guidance reflects the comparatively low rates of MRSA pneumonia in the UK compared to other countries and is aimed at avoiding unnecessary exposure to drug toxicity associated with MRSA treatment.[5,11]

However, the lack of evidence for some recommendations in this guideline risks worsening the already confusing system of pneumonia classification. NICE recommends low-risk patients who develop HAP between day three and five of their admission should be empirically treated as per CAP guidelines. This ambiguous situation – HAP being treated as CAP – adds to the current confusion stemming from the 2009 British Thoracic Society CAP guidelines.[12] Those guidelines specifically excluded patients who had a hospital admission within 10 days of developing pneumonia - regarding those patients as having HAP. So we have some CAP being treated as HAP and some HAP treated as CAP.

In summary, HAP represents a huge challenge for antibiotic stewardship and the new NICE guidelines begin to address this unmet need. However, the paucity of quality research available fails to address the root problem in pneumonia management which is the inadequacy of empirical prescribing. Rapid diagnostic platforms are emerging that may enable personalised antibiotic treatment. However, the clinical impact of these new platforms is unproven and must be evaluated in randomised controlled trials. Those trials will require novel designs and outcome measures to tease out the morbidity, mortality and costs that are attributable to HAP as opposed to the condition precipitating hospitalisation. NICE have previously suggested a key outcome would be demonstrating that new diagnostics can reduce antibiotic use whist maintaining effectiveness. If this could be demonstrated in such a way as to be locally applicable this would represent a huge step forward.

References

1. National Institute of Health and Social Care Excellence (NICE). Pneumonia (hospital-acquired): antimicrobial prescribing. <https://www.nice.org.uk/guidance/ng139>. Date last updated: 19/9/2019 Date last accessed: 1/10 2019.

2. Sopena N, Sabria M, Neunos 2000 Study Group. Multicenter study of hospital-acquired pneumonia in non-ICU patients. *Chest* 2005; 127: 213-219.

3. Burton LA, Price R, Barr KE, McAuley SM, Allen JB, Clinton AM, Phillips G, Marwick CA, McMurdo ME, Witham MD. Hospital-acquired pneumonia incidence and diagnosis in older patients. *Age Ageing* 2016; 45: 171-174.

4. Cassini A, Plachouras D, Eckmanns T, Abu Sin M, Blank HP, Ducomble T, Haller S, Harder T, Klingeberg A, Sixtensson M, Velasco E, Weiss B, Kramarz P, Monnet DL, Kretzschmar ME, Suetens C. Burden of Six Healthcare-Associated Infections on European Population Health: Estimating Incidence-Based Disability-Adjusted Life Years through a Population Prevalence-Based Modelling Study. *PLoS Med* 2016; 13: e1002150.

5. Aston SJ, Wootton DG. Community-acquired pneumonia due to drug-resistant Enterobacteriaceae: A global perspective. *Respirology* 2019.

6. Webb BJ, Sorensen J, Jephson A, Mecham I, Dean NC. Broad-spectrum antibiotic use and poor outcomes in community-onset pneumonia: a cohort study. *Eur Respir J* 2019; 54: 10.1183/13993003.00057-2019. Print 2019 Jul.

7. Public Health England. Antimicrobial Stewardship:Start smart then focus. <https://www.gov.uk/government/publications/antimicrobial-stewardship-start-smart-then-focus>. Date last updated: 3/2015 2015. Date last accessed: 10/2015 .

8. Waterer GW. Potential antibiotic resistant pathogens in community-acquired pneumonia: playing it safe is anything but. *Eur Respir J* 2019; 54: 10.1183/13993003.00870-2019. Print 2019 Jul.

9. Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney DA, Palmer LB, Napolitano LM, O'Grady NP, Bartlett JG, Carratala J, El Solh AA, Ewig S, Fey PD, File TM,Jr, Restrepo MI, Roberts JA, Waterer GW, Cruse P, Knight SL, Brozek JL. Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis* 2016; 63: e61-e111.

10. Torres A, Niederman MS, Chastre J, Ewig S, Fernandez-Vandellos P, Hanberger H, Kollef M, Li Bassi G, Luna CM, Martin-Loeches I, Paiva JA, Read RC, Rigau D, Timsit JF, Welte T, Wunderink R. International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia: Guidelines for the management of hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP) of the European Respiratory Society (ERS), European Society of Intensive Care Medicine (ESICM), European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and Asociacion Latinoamericana del Torax (ALAT). *Eur Respir J* 2017; 50: 10.1183/13993003.00582-2017. Print 2017 Sep.

11. Torres A, Zhong N, Pachl J, Timsit JF, Kollef M, Chen Z, Song J, Taylor D, Laud PJ, Stone GG, Chow JW. Ceftazidime-avibactam versus meropenem in nosocomial pneumonia, including ventilator-associated pneumonia (REPROVE): a randomised, double-blind, phase 3 non-inferiority trial. *Lancet Infect Dis* 2018; 18: 285-295.

12. Lim WS, Baudouin SV, George RC, Hill AT, Jamieson C, Le Jeune I, Macfarlane JT, Read RC, Roberts HJ, Levy ML, Wani M, Woodhead MA. BTS guidelines for the management of community acquired pneumonia in adults: update 2009. *Thorax* 2009; 64 Suppl 3: iii1-iii55.