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Opinion

The challenge of antimicrobial prescribing for hospital-acquired pneumonia

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The influential UK National Institute for Health and Care Excellence (NICE) has recently published prescribing guidelines for hospital-acquired pneumonia (HAP) [1]. The recognition is welcome as HAP is responsible for more deaths and greater morbidity than other healthcare-associated infections, with an estimated in-hospital mortality rate between 18% and 29% [2–4].

NICE bemoans 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 nine trials met the 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 recognize 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 that antibiotics should be administered within 4 h 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 *Clostridium difficile*, death and antimicrobial resistance attributed to some antibiotic classes [9]. In this context, NICE focuses on antibiotic stewardship, and reinforces 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 risk of resistant pathogens. Oral co-amoxiclav is recommended for adults and children with low clinical severity and low risk of resistant bacteria. The assessment of severity is based on 'clinical judgement' as 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 as NICE recognizes 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

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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 that antibiotics for meticillin-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 with 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 that low-risk patients who develop HAP between the third and fifth days of their admission should be treated empirically as per guidance for community-acquired pneumonia (CAP). 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. Therefore, some CAP are treated as HAP and some HAP are 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, namely the inadequacy of empirical prescribing. Rapid diagnostic platforms are emerging that may enable personalized antibiotic treatment. However, the clinical impact of these new platforms is unproven and must be evaluated in randomized 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 hospitalization. NICE have previously suggested that a key outcome would be demonstrating that new diagnostics can reduce antibiotic use whilst maintaining effectiveness. If this could be demonstrated in such a way as to be locally applicable, this would represent a huge step forward.

Conflict of interest statement

Dr Timothy Felton is listed as a topic specialist on the NICE committee membership for the 2019 NICE prescribing guidelines for Hospital Acquired Pneumonia which we comment on in this article.

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