Antibiotics for community-acquired pneumonia

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Antibiotic guidelines for community-acquired pneumonia (CAP) often recommend broad-spectrum agents for severe pneumonia. While these may be entirely appropriate in terms of their spectrum of activity and efficacy, there is a risk that such recommendations could result in over-prescribing of broad-spectrum agents with consequent ‘collateral damage’, meaning superinfection by resistant pathogens, or selection of antibiotic resistance. Narrow-spectrum agents are often as effective and result in less collateral damage. National and local antibiotic guidance should promote choices of agents for narrow-spectrum prescribing even for severe CAP where appropriate.

Keywords: CAP, guidelines, prescribing, antibiotic policy, antibiotic stewardship, collateral damage

The British Thoracic Society (BTS) has recently published updated guidelines for the treatment of community-acquired pneumonia (CAP).1 This comprehensive document was produced following widespread consultation among professional societies with an interest in infection and antibiotics, including the BSAC. The Pneumonia Guidelines sub-committee of the BTS Standards of Care Committee reviewed the most recent data on epidemiology, aetiology, diagnosis and treatment of CAP and issued recommendations for diagnosis and management of CAP that are likely to have considerable impact on hospital antibiotic policy choices. The BSAC was invited to nominate a representative for the Guideline Committee and was offered the opportunity to participate in the consultation process. The BSAC endorses the BTS guidelines as a thorough review of the available evidence with clearly reasoned recommendations linked to evidence. However, the BSAC was unable to reach agreement with the Guideline Committee on their recommendations for antibiotic treatment of severe pneumonia, which was one of their recommendations based on expert opinion. In the absence of publication of an alternative expert opinion, hospitals and doctors opting for antibiotic regimens for CAP that are not endorsed by the BTS guidelines may be vulnerable to medicolegal negligence claims. The purpose of this article is to provide an alternative expert opinion that gives greater weight to collateral damage from antibiotics in risk assessment of antibiotic policies.2 We have performed an informal survey with responses from 77 hospitals across the UK, with 19 (25%) who currently recommend narrower spectrum therapy for severe CAP than is recommended in the BTS guidelines.

While the antibiotic choices in the BTS guidelines are entirely appropriate in terms of their spectrum of activity and there is good evidence that they are effective in the treatment of CAP, there is also a risk that the guidelines could result in over-prescribing of broad-spectrum agents with consequent ‘collateral damage’, meaning superinfection by resistant bacteria, Clostridium difficile and fungi because of the effect of antibiotics on normal bacterial flora and the pressure on susceptible bacteria to develop or acquire mechanisms for antibiotic resistance.2 Since these guidelines are likely to influence the choice of antibiotic therapy for this common infection, and therefore the selection pressure for antibiotic resistance in the UK over the next 5–10 years, this is an extremely important public health issue.

The impact of the BTS guidelines as a quality standard cannot be overstated. It is therefore important that they do not undermine recent work in antibiotic stewardship that has promoted appropriate narrow-spectrum and low-risk prescribing.3 Some of the classes of antibiotics recommended in the guidelines such as cephalosporins or quinolones have been strongly associated with C. difficile-associated diarrhoea (CDAD) and methicillin-resistant Staphylococcus aureus (MRSA),4,5 and have therefore been decreasingly used in UK hospitals in recent years, in adherence with the UK Department of Health (DoH) guideline ‘Clostridium difficile infection: How to deal with the problem’.6 It would be counter-intuitive to recommend these agents, even as second-line therapy, when many hospitals in the UK have removed these classes from their local guidelines. Emerging evidence suggests that co-amoxiclav may also

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predispose patients to CDAD\(^7\) and a number of UK hospitals have moved away from co-amoxiclav as well as cephalosporins for the treatment of CAP in an attempt to reduce the risk of CDAD infection. Some are recommending benzylpenicillin with macrolides or tetracyclines, even for severe pneumonia. This suggests that the BTS guidelines, as they stand, will not be consistent with current clinical practice.

Cephalosporins and quinolones are useful agents in the therapeutic armamentarium, but while CDAD and MRSA remain a challenge, it is prudent not to encourage their use. There is no high-quality evidence that cephalosporins or respiratory fluoroquinolones are more clinically or cost-effective in respiratory infections compared with other agents. Indeed there is emerging evidence that narrow-spectrum prescribing is as effective as broad-spectrum prescribing, even for severe pneumonia.\(^8\) In a prospective study of the aetiology and treatment of CAP in Australia,\(^9\) the authors call for a treatment regimen of benzylpenicillin plus (a macrolide or doxycycline) to be the first-line treatment for severe CAP. In that study the microbial aetiology was identified for 46% of 885 episodes of CAP. In only 48 (5.4%) of these 885 episodes of CAP was a pathogen found that would not be adequately treated with benzylpenicillin plus either doxycycline or a macrolide. In most of these 48 patients there were significant risk factors to alert clinicians to the unusual pathogen [including chronic obstructive pulmonary disease (COPD), extensive co-morbidities or residence in long-term care facilities]. The risk of requiring ventilatory or inotropic support was significant for pneumococcal and legionella pneumonia (and these were covered by the penicillin/macrolide-based regimen) and for picornavirus and influenza, which would not be covered by any antibiotics. In 94 patients who required mechanical ventilation, non-invasive ventilation or inotropes, only 7 (7.4%) had infection caused by resistant organisms (including some with \textit{Pseudomonas} species that would not be susceptible to co-amoxiclav, cefuroxime or levofloxacin).

Next there is the issue of over-diagnosis. It is not uncommon on medical emergency wards for there to be elderly confused patients who are slightly dehydrated with a raised serum urea and who also have some physical respiratory signs that may be inflammatory or cardiogenic. These patients can easily be misdiagnosed as having CAP and would fit the BTS CURB65 category for severe pneumonia, with resulting treatment with the broad-spectrum agents described in the guidelines. If the BTS guidelines are followed for these patients, there will be inevitable over-prescribing of broad-spectrum agents and further ecological selection pressure for resistant organisms including \textit{Escherichia coli} expressing extended-spectrum \textit{β}-lactamases (ESBLs).\(^9\) There needs to be more support for clinical diagnostic decision making in terms of point of care or rapid testing—for example urinary pneumococcal and legionella antigens and respiratory PCR panels. Non-specific markers of bacterial infection such as serum procalcitonin have been shown to reduce inappropriate antibiotic prescribing.\(^10\)

Those with bacterial infection but who do not require critical care are likely to be the largest cohort of inpatients. For those able to take oral therapy, doxycycline covers a broad range of respiratory pathogens, is taken once or twice daily and is generally considered to be less likely to cause CDAD than co-amoxiclav or combination regimens.\(^11,12\) For non-critical care patients requiring intravenous therapy, a macrolide alone or in combination with benzylpenicillin is less likely to cause CDAD than broader-spectrum regimens, although co-amoxiclav or other agents may be required for patients with major co-morbidities at risk of severe \textit{Haemophilus influenzae} infection. Other agents, such as trimethoprim, co-trimoxazole, chloramphenicol, linezolid, piperacillin/tazobactam and tigecycline, may have a useful role in specific circumstances.

For severe pneumonia the BTS guidelines\(^1\) recommend intravenous co-amoxiclav plus clarithromycin. Alternative regimens recommended are benzylpenicillin plus levofloxacin or a cephalosporin plus clarithromycin. The BSAC endorses benzylpenicillin plus a macrolide or doxycycline as the first-line therapy for moderately severe and severe CAP. Such a regimen is likely to apply the least bacterial ecological pressure while still being clinically effective. Alternatives in patients who are genuinely allergic to penicillin are co-trimoxazole, chloramphenicol, linezolid and tigecycline. \textit{S. aureus} should be considered in pneumonia associated with influenza, although this organism is still not as common a cause as \textit{Streptococcus pneumoniae}, or in the recent outbreak, \textit{Streptococcus pyogenes}. Linezolid may be the most effective treatment for pneumonia caused by \textit{S. aureus}, particularly those strains producing Pantone–Valentine leucocidin.\(^13\) Doctors should be encouraged to be vigilant for patients with risk factors such as COPD, extensive co-morbidities or residence in a long-term care facility and to use appropriate broad-spectrum regimens first line in these patients, such as the agents described for penicillin-allergic patients.

What solutions can be found for these dilemmas? The first might be for hospital antibiotic management teams to use the BTS CAP guidelines to inform their own local guidelines on the basis of local epidemiology. Where there is no problem with antibiotic resistance, MRSA, ESBL-producing Gram-negative bacteria and CDAD, the recommendations for broader-spectrum prescribing in the BTS guidelines for severe CAP can be followed in patients with critical illness and co-morbidities. Narrow-spectrum prescribing is appropriate for most patients with CAP. In centres where there are problems with resistance, it would be prudent to follow a narrow-spectrum approach, and where co-morbidities warrant broader-spectrum agents, avoid cephalosporins and quinolones.

Secondly, it would be worth improving the sensitivity of CAP severity diagnosis by incorporating more features than in the existing CURB65 score, for example, inclusion of the systemic inflammatory response syndrome (‘SIRS’) criteria and the use of rapid diagnostic tests, of which serum procalcitonin seems most effective at distinguishing bacterial infection from other causes.\(^10\) Doctors should have access to regular education in antibiotic stewardship and the public health consequences of prescribing broad-spectrum agents. They should also have protection against the tendency for defensive prescribing with support from robust local antibiotic prescribing policies, combined with regular prescribing and outcome audits.

The BSAC has an important role in supporting physician colleagues in managing pneumonia effectively but also in minimizing selection pressure for CDAD and resistant bacteria. We support antimicrobial management teams to make a careful risk assessment based on their local data, which may result in restriction of co-amoxiclav, cephalosporins or levofloxacin treatment regimens even for patients with severe CAP. We believe that in some hospitals these drugs should be reserved for the small percentage of patients who are critically ill with pneumonia and require high-dependency care. The winning of an immediate
battle using broad-spectrum agents may ultimately contribute to losing the war against pathogens, emerging resistance and antibiotic-associated complications.

Transparency declarations

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References