Swine flu and antibiotics

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Health services worldwide are likely to be hard-pressed by swine flu-related illness in the months ahead. Secondary infections with *Streptococcus pneumoniae*, other streptococci (e.g. *Streptococcus pyogenes*), *Haemophilus influenzae* and *Staphylococcus aureus* are likely to be important causes of morbidity and mortality. The UK Department of Health recently published clinical pathways for the management of swine flu. Suggested severity criteria have not been validated in respiratory infection and are different from those previously published. Antibiotics are recommended for all patients assessed at hospital, regardless of severity of illness; cephalosporins or quinolones are suggested for inpatients with pneumonia. These recommendations will jeopardize recent decreases in *Clostridium difficile*-associated diarrhoea (CDAD) and methicillin-resistant *S. aureus* (MRSA) in UK hospitals. This article, written on behalf of the BSAC Council, considers these recommendations and provides alternative antibiotic regimens for a range of clinical scenarios.

Keywords: influenza, pneumonia, lower respiratory tract infections

Introduction

Since the WHO declared a global influenza pandemic on 11 June 2009, it has become clear that health services in the UK and worldwide are likely to be hit by a tidal wave of flu-related illness in the months ahead, as has already occurred in Mexico. Secondary bacterial infections, particularly with *Streptococcus pneumoniae*, other streptococci (e.g. *Streptococcus pyogenes*), *Haemophilus influenzae* and *Staphylococcus aureus* are likely to be important causes of morbidity and mortality. The UK Department of Health (DoH) recently published pathways for the clinical management of swine flu that include advice on antibiotic prescribing. The adult hospital pathway starts by recommending seven criteria (Table 1) upon which the site-of-care decision (i.e. inpatient versus outpatient) should be based. Although accurate assessment of severity of illness is undoubtedly the key critical process when making decisions about antibiotic therapy and other aspects of care for infections, the DoH pathway recommends an antibiotic for all patients, regardless of severity assessment or whether secondary bacterial infection is likely. This article, written on behalf of the BSAC Council, considers these recommendations and suggests alternative antibiotic strategies and regimens that hospitals and healthcare staff could employ during the pandemic.

Severity assessment

The DoH severity criteria (Table 1) have not been validated in respiratory infection and are different from those (the CURB-65 criteria) recommended in existing guidelines for the management of influenza-associated pneumonia, the development of which were supported by the DoH. CURB-65 (Table 1), which has been validated in multiple studies internationally as having moderate performance in the prediction of mortality in community-acquired pneumonia (CAP), is simple and widely recognized and used in the UK, and in other countries. This is important, as familiarity with pneumonia severity criteria has previously been shown to be poor in the UK. CURB-65 also appears to be useful in predicting mortality in non-respiratory infections. The pathway’s criteria for admission to hospital and subsequent management strategies are set at a high threshold, presumably aimed at peaks of activity when admission to hospital may have to be ‘rationed’. However, either side of such peaks or if the pandemic places a lower burden on hospitals than expected, these criteria could lead to unnecessary mortality by denying access to hospital care. That physiological signs can deteriorate late (i.e. close to death) in young patients with serious illness, including pneumonia, is a common concern expressed by experienced clinicians. The DoH criteria do not consider co-morbidity or pre-morbid functional status, which are important considerations in the site-of-care decision. Application of the DoH criteria in determining the need for inpatient care could be considered as being below the standard of acceptable clinical practice.

Severity assessment should be based on existing familiar criteria, although these should be prospectively validated, and if necessary modified, during the pandemic. Early evidence from the UK and elsewhere suggests that asthma requiring...
Severe respiratory distress. Severe breathlessness, e.g. unable to complete sentences in one breath. Use of accessory muscles, supra-clavicular recession, tracheal tug or feeling of suffocation.

Increased respiratory rate measured over at least 30 s. Over 30 breaths per min.

Oxygen saturation ≤92% on pulse oximetry, breathing air or on oxygen. Absence of cyanosis is a poor discriminator for severe illness.

Respiratory exhaustion. New abnormal breathing pattern, e.g. alternating fast and slow rate or long pauses between breaths.

Evidence of severe clinical dehydration or clinical shock. Systolic blood pressure < 90 mmHg and/or diastolic blood pressure < 60 mmHg. Sternal capillary refill time > 2 s, reduced skin turgor.

Altered conscious level. New confusion, striking agitation or seizures.

Causing other clinical concern to the clinical team or specialist doctor e.g. a rapidly progressive or an unusually prolonged illness.

CURB-65 criteria

Based on the presence or absence of the following criteria (1 point for each): new confusion; urea > 7 mmol/L; respiratory rate ≥ 30/min; systolic blood pressure < 90 mmHg or diastolic blood pressure ≤ 60 mmHg; and age ≥ 65 years.

Severe (admit to hospital) 3 or more

Non-severe, moderate risk (admit to hospital) 2

Non-severe, low risk (treat at home or as outpatient) 0 or 1

Antibiotics

The advocated ‘broad-brush’ approach to antibiotic prescribing during a pandemic is in sharp contrast to usual clinical practice for seasonal influenza and will undermine the considerable antibiotic stewardship achievements that have contributed to decreases in Clostridium difficile-associated diarrhoea (CDAD) and methicillin-resistant S. aureus (MRSA) in many UK hospitals. An increase in such problems during a pandemic is likely to place an additional burden on health services at a time of extreme strain. The antibiotic guidance also contradicts the existing guidelines (to which the DoH contributed), which advocate a more selective approach (Table 2).\(^2\) Hospitalization and mortality rates due to swine flu in the UK do not currently warrant widespread antibiotic prescribing, although the threshold for prescribing may have to change if the swine flu virus evolves to become more virulent. The lack of consistency between existing DoH guidelines will cause confusion in healthcare professionals and unnecessary variation in clinical practice. The widespread use of antibiotics during a pandemic for patients who do not need them could also jeopardize the availability of a vital resource for patients who do.

Later in the pathway, a ‘broad-spectrum cephalosporin or quinolone (clarithromycin may be added)’ is recommended for all hospitalized patients with pneumonia. Specific agents, doses and the intended route of administration are not provided. Cephalosporin and quinolone antibiotics have been strongly associated with CDAD and MRSA,\(^14,15\) and have therefore been decreasingly used in UK hospitals in recent years, in adherence with the DoH guideline ‘Clostridium difficile infection: how to deal with the problem’.\(^16\) There is no high quality evidence that cephalosporins or respiratory fluoroquinolones are more clinically effective or cost-effective in respiratory infections compared with other agents. This recommendation also assumes that all hospitalized patients will be severely ill, which may not be the case. If clinicians follow this recommendation, a considerable number of patients will receive unnecessarily broad-spectrum therapy.

The term ‘quinolone’ is confusing because the most commonly used quinolone antibiotic in the UK is ciprofloxacin. This is not a respiratory quinolone and has suboptimal activity against S. pneumoniae. Although existing guidelines recommend ‘a fluoroquinolone with enhanced activity against pneumococci’ (in the UK, levofloxacin or moxifloxacin),\(^2\) the DoH and hospitals should be cautious in advocating these agents as they have also been associated with CDAD,\(^17\) and an increasing proportion of methicillin-susceptible S. aureus (MSSA) (e.g. 30% in Hull and East Yorkshire) and almost all MRSA are now resistant to fluoroquinolones.

So what antibiotics should be prescribed and when during a pandemic? The answer to this depends on several factors, including whether the patient has symptoms, signs or
For influenza not complicated by pneumonia

a. Previously well adults with acute bronchitis complicating influenza, in the absence of pneumonia, do not routinely require antibiotics.

b. Antibiotics should be considered in those previously well adults who develop worsening symptoms (recrudescence fever or increasing dyspnoea).

c. Patients at high risk of complications or secondary infection should be considered for antibiotics in the presence of lower respiratory features.

d. Most patients can be adequately treated with oral antibiotics.

e. The preferred choice includes co-amoxiclav or a tetracycline.

f. A macrolide such as clarithromycin (or erythromycin) or a fluoroquinolone active against Streptococcus pneumoniae and Staphylococcus aureus is an alternative choice in certain circumstances.

Non-severe influenza-related pneumonia

a. Most patients can be adequately treated with oral antibiotics.

b. Oral therapy with co-amoxiclav or a tetracycline is preferred.

c. When oral therapy is contraindicated, recommended parenteral choices include iv co-amoxiclav, or a second- or third-generation cephalosporin (cefuroxime or cefotaxime). A macrolide (erythromycin or clarithromycin) or a fluoroquinolone active against S. pneumoniae and S. aureus is an alternative regimen where required, e.g. for those intolerant of penicillins. Currently, levofloxacin and moxifloxacin are the only recommended fluoroquinolones licensed in the UK.

For severe influenza-related pneumonia

a. Patients with severe pneumonia should be treated immediately after diagnosis with parenteral antibiotics.

b. An iv combination of a broad-spectrum β-lactamase stable antibiotic such as co-amoxiclav or a second-generation (e.g. cefuroxime) or third-generation (e.g. cefotaxime) cephalosporin together with a macrolide (e.g. clarithromycin or erythromycin) is preferred.

c. An alternative regimen includes a fluoroquinolone with enhanced activity against pneumococci together with a broad-spectrum β-lactamase stable antibiotic or a macrolide. Currently, levofloxacin is the only fluoroquinolone with an iv formulation licensed in the UK.

Leading article

Table 2. Antibiotic recommendations from the 2006 guidelines for pandemic flu from the British Infection Society, British Thoracic Society and Health Protection Agency in collaboration with the Department of Health

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Table 3. Potentially useful antibiotic regimens for bacterial infections in swine flu

<table>
<thead>
<tr>
<th>Antibiotic regimen (doses provided are for adults)</th>
<th>Antibacterial activity</th>
<th>Ecological risk&lt;sup&gt;a,b,14,17,24&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outpatients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxycycline&lt;sup&gt;c&lt;/sup&gt; 200 mg once and then 100 mg every 24 h</td>
<td>SP, strep&lt;sup&gt;d&lt;/sup&gt;, H, MC, MSSA, MRSA, atypicals</td>
<td>low</td>
</tr>
<tr>
<td>Co-amoxiclav 625 mg every 8 h</td>
<td>SP, strep, H, MC, MSSA, GNEB</td>
<td>moderate</td>
</tr>
<tr>
<td>Erythromycin&lt;sup&gt;f&lt;/sup&gt; 500 mg every 6 h or clarithromycin 500 mg every 12 h</td>
<td>SP, strep&lt;sup&gt;d&lt;/sup&gt;, MC, MSSA, atypicals</td>
<td>moderate</td>
</tr>
<tr>
<td>Levofloxacin&lt;sup&gt;f&lt;/sup&gt; 500 mg every 24 h or moxifloxacin&lt;sup&gt;f&lt;/sup&gt; 400 mg every 24 h</td>
<td>SP, strep, H, MC, MSSA, GNEB, atypicals</td>
<td>high</td>
</tr>
<tr>
<td><strong>Non-severe inpatients, oral</strong> [as for outpatients (see above)]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzylpenicillin 1.2 g every 6 h</td>
<td>SP, strep, H</td>
<td>moderate</td>
</tr>
<tr>
<td>Amoxicillin 500 mg to 1 g every 8 h</td>
<td>SP, strep, H, MC, MSSA, atypicals</td>
<td>moderate</td>
</tr>
<tr>
<td>Clarithromycin 500 mg every 12 h</td>
<td>SP, strep, MC, MSSA, atypicals</td>
<td>moderate</td>
</tr>
<tr>
<td>Flucloxacillin 1 g every 6 h plus clarithromycin 500 mg every 12 h</td>
<td>SP, strep, H, MC, MSSA, GNEB</td>
<td>moderate to high</td>
</tr>
<tr>
<td>Co-amoxiclav 1.2 g every 8 h plus clarithromycin 500 mg every 12 h</td>
<td>SP, strep, H, MC, MSSA, atypicals</td>
<td>moderate to high</td>
</tr>
<tr>
<td>Levofloxacin&lt;sup&gt;f&lt;/sup&gt; 500 mg every 24 h or cefotaxime 1 g every 8 h</td>
<td>SP, strep, H, MC, MSSA, GNEB, atypicals</td>
<td>high</td>
</tr>
<tr>
<td>Cefuroxime 750 mg every 8 h or cefotaxime 1 g every 8 h</td>
<td>SP, strep, H, MC, MSSA, GNEB, atypicals</td>
<td>high</td>
</tr>
<tr>
<td>Levofloxacin&lt;sup&gt;f&lt;/sup&gt; 500 mg every 24 h</td>
<td>SP, strep, H, MC, MSSA, GNEB, atypicals</td>
<td>high</td>
</tr>
<tr>
<td><strong>Severe inpatients</strong> (patients who require critical care, whether a bed is available or not; all regimens to be given iv initially)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Co-amoxiclav 1.2 g every 8 h plus clarithromycin 500 mg every 12 h</td>
<td>SP, strep, H, MC, MSSA, GNEB, atypicals</td>
<td>moderate to high</td>
</tr>
<tr>
<td>Cefuroxime 750 mg every 8 h or cefotaxime 1 g every 8 h plus clarithromycin 500 mg every 12 h</td>
<td>SP, strep, H, MC, MSSA, GNEB, atypicals</td>
<td>high</td>
</tr>
<tr>
<td>Levofloxacin&lt;sup&gt;f&lt;/sup&gt; 500 mg every 24 h</td>
<td>SP, strep, H, MC, MSSA, GNEB, atypicals</td>
<td>high</td>
</tr>
<tr>
<td>Benzylpenicillin 1.8–2.4 g every 4 h plus clindamycin 600 mg every 6 h</td>
<td>for proven life-threatening Lancefield group A, C or G streptococcal infection</td>
<td>high (clindamycin)</td>
</tr>
<tr>
<td><strong>MRSA</strong> (in the UK, only for patients with proven MRSA)</td>
<td>SP, strep, MSSA, MRSA</td>
<td>low</td>
</tr>
<tr>
<td>Linezolid&lt;sup&gt;g&lt;/sup&gt; 600 mg iv/oral every 12 h</td>
<td>SP, strep, MSSA, MRSA</td>
<td>low</td>
</tr>
<tr>
<td><strong>Other agents that may be useful in specific circumstances</strong> (e.g. if microbiological results are available)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trimethoprim 200 mg oral every 12 h</td>
<td>H&lt;sup&gt;h&lt;/sup&gt;, some MSSA/MRSA, some GNEB</td>
<td>low</td>
</tr>
<tr>
<td>Co-trimoxazole 960 mg oral every 12 h (iv: 960 mg to 1.44 g every 12 h)</td>
<td>SP, strep, H, MC, MSSA, some MRSA, GNEB</td>
<td>low to moderate</td>
</tr>
<tr>
<td>Piperacillin/tazobactam 4.5 g iv every 8 h</td>
<td>SP, strep, H, MC, MSSA, GNEB (±Ps)</td>
<td>moderate</td>
</tr>
<tr>
<td>Tigecycline&lt;sup&gt;i&lt;/sup&gt; 100 mg iv once then 50 mg iv every 12 h</td>
<td>SP, strep&lt;sup&gt;j&lt;/sup&gt;, H, MC, MSSA, MRSA, GNEB, atypicals</td>
<td>unclear, probably low to moderate</td>
</tr>
</tbody>
</table>

**NOTE:** The antibiotic recommendations must be considered in light of local antibiotic resistance patterns. When the prescriber is not familiar with the drug or is in doubt, the British National Formulary (BNF) should be consulted regarding cautions and contraindications, interactions with other drugs, renal and liver impairment, and pregnancy and breastfeeding.


<sup>a</sup> Ecological risk means the risk of *C. difficile*-associated diarrhoea and the emergence of antibiotic-resistant pathogens such as MRSA.

<sup>b</sup> Based on references and experience of BSAC Council members.

<sup>c</sup>Doxycycline should not be used in pregnancy, breastfeeding and children under 12 years old.

<sup>d</sup>45% resistance to tetracycline in group G streptococci in the UK<sup>31</sup>.

<sup>e</sup>23% resistance to erythromycin in group G streptococci in the UK.<sup>31</sup>

<sup>f</sup>Quinolones should not be used in pregnancy and breastfeeding, and are best avoided in children and adolescents if alternative agents are available.

<sup>g</sup>Linezolid should only be used in pregnancy when the benefit outweighs the risk; avoid in breastfeeding.

<sup>h</sup>21% resistance in the UK.<sup>31</sup>

<sup>i</sup>Tigecycline should only be used in adults, but not in pregnancy or breastfeeding.

<sup>1</sup>21% resistance in the UK.<sup>31</sup>

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narrowest spectrum possible (e.g. from co-amoxiclav/macrolide dual therapy to benzylpenicillin monotherapy in patients with *S. pneumoniae* infection).23

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.24 For non-critical care patients requiring intravenous (iv) therapy, a macrolide alone or in combination with flucloxacinil is less likely to cause CDAD than broader spectrum regimens, although co-amoxiclav or other agents may need to be considered for patients at risk of *H. influenzae* infection. Other agents, such as trimethoprim, co-trimoxazole and tigecycline, may have useful roles in specific circumstances. Length of therapy is also an important predictor of CDAD and the emergence of antibiotic resistance.10,25 In uncomplicated, non-critical care patients, 5–7 days of oral therapy will suffice in most patients.26 In severe pneumonia initially treated with iv antibiotics, patients should be switched to oral therapy as soon as clinical stability has occurred, in keeping with published evidence.27,28

Local epidemiological factors, such as the pattern of antibacterial resistance in MSSA and other respiratory bacteria, and the incidence of community-associated MRSA also need to be considered and reviewed as the pandemic evolves. It is well recognized that older patients are more likely to get CDAD, so alternative prescribing strategies, using effective but lower risk regimens, may be warranted in this and other CDAD high risk groups.10 Particularly for sicker patients, clinicians may also wish to consider the theoretical non-antibacterial effects of some antibiotics; for example, doxycycline has been shown to have potentially useful immune modulation properties and macrolide-containing regimens have been shown to improve outcomes in some studies of severe bacteraemic pneumococcal pneumonia.29,30

To be used widely and provide a consistent standard of healthcare during a pandemic, national recommendations must be simple and easy to implement, adaptable to local circumstances, trusted by clinicians, be based on existing practice, evidence and guidelines (whenever possible), and have the necessary flexibility to account for emerging research evidence and evolution, in whatever direction, of the pandemic. This is not the case for the current DoH adult hospital pathway for swine flu. Until revised, clinicians and hospitals will be better served using existing guidance and adapting their clinical practice, if needed, from a starting point of what they consider to be the current minimum standards of care.

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**References**


17. Muto CA, Pokrywka M, Shutt K et al. A large outbreak of *Clostridium difficile*-associated disease with an unexpected proportion of deaths and colectomies in a teaching hospital following increased


