



## Considered judgement on quality of evidence

### Key question: Should Choice of Antibiotic be included in the care bundle?

#### 1. Volume of evidence

Comment here on any issues concerning the quantity of evidence available on this topic and its methodological quality.

#### **Up to end of 2006**

We identified 14 relevant articles that were not included in the BTS 2001 Guideline or 2004 Update: 8 cohort studies (Baddour, Battleman, Dean, Harbarth, Hauck, Menendez, Shorr, Waterer), 4 systematic reviews (Bjerre, Mills, Oosterheert, Shefet), 1 controlled before and after study (CBA, Capelastegui) and 1 cluster RCT (Yealy). We have not reviewed individual studies that were included in the three systematic reviews.

The systematic reviews included patients from several countries; the remaining studies were from Spain, the USA or elsewhere (all continents). The systematic reviews did not include the number of hospitals, the remaining studies enrolled patients from 217 hospitals. The 13 articles include data about 67,411, 592, 622, ?, 107, 199 = 68931 patients.

All of the articles were of good methodological quality.

Three systematic reviews were of RCTs (Bjerre, Mills, Shefet) and one was of cohort studies (Oosterheert).

#### **2007-10**

The revised BTS guidelines for pneumonia have provided new advice on choice of therapy for various grades (CURB65) of pneumonia. 9 additional studies have been identified.

1. Retrospective cohort (Chokshi, USA) of 108 patients with bacteremic *Streptococcus pneumoniae* CAP compared monotherapy and combination therapy. No significant difference in mortality between 2 treatments after adjusting for severity of illness but lack of controls meant the two groups were effectively heterogeneous.

2. Prospective observational study of effect of compliance with guidelines on outcome in 780 patients (Dambava, Spain). Confirmed clinical benefits of adhering to guidelines but not possible to attribute findings to mono versus combination therapy due to other factors.

3. A review of 8 studies from Europe and USA (Feldman) compared monotherapy and combination therapy for pneumococcal bacteraemia. In severe CAP, a betalactam plus macrolide superior to fluoroquinolone monotherapy. In non-severe CAP fluoroquinolone monotherapy effective and benefit of adding macrolide to a betalactam is inconclusive. No convincing studies showing benefit of combination therapy in pneumococcal bacteraemia.

4. An Open-label, Randomized Comparison of Levofloxacin and Amoxicillin/Clavulanate plus Clarithromycin in 50 patients (Lin, Taiwan) showed that the combination had higher success rate in moderate to severe cases and levofloxacin had higher success rate in mild cases.

5. Comparison of  $\beta$ -Lactam and Macrolide Combination Therapy versus Fluoroquinolone Monotherapy in 515 patients (Lodise, USA) showed mortality lower in combination therapy group for PSI class V - 14 day (8.2% vs. 26.8%) and 30 day (18.4% vs. 36.6%).

6. Retrospective cohort study of bacteraemic pneumonia in 2209 patients comparing macrolides and fluoroquinolones (Metersky, USA) showed patients treated with a macrolide had lower in-hospital mortality (OR 0.59, p=0.01), 30 day mortality (OR 0.61, p=0.007) and readmission rate (0.591, p=0.004).

7. Retrospective cohort study of impact of macrolide therapy on mortality for 237 patients with severe sepsis due to pneumonia (Restrepo, USA) showed use of macrolide associated with reduced mortality at 30 days (HR 0.3) and 90 days (HR 0.3) including those patients with macrolide-resistant pathogens (HR 0.1).

8. Secondary analysis prospective cohort of 529 ITU patients (Rodriguez, Spain) studied effects of combination antibiotic therapy on survival in patients with CAP and shock. Combination therapy with a betalactam plus a macrolide or fluoroquinolone improves survival in the subset of patients with severe CAP and shock (HR 1.69, p=0.01).

9. Secondary analysis of an observational study of 1854 patients (Tessler, Germany) looked at the impact of intravenous  $\beta$ -lactam/macrolide versus  $\beta$ -lactam monotherapy on mortality.

Combination therapy associated with lower adjusted 14 day mortality (OR 0.53) and adjusted 14 day mortality risk clearly reduced with combination in patients with CRB65 score of 2 or above.

Combination therapy also had lower risk of treatment failure at 14 days (OR 0.65) and 30 days (OR 0.69) in subgroup of patients with CRB65 of 2 or above.

## **2. Applicability**

*Comment here on the extent to which the evidence is directly applicable to the NHS in Scotland.*

This is large body of evidence that should be directly applicable to the NHS in Scotland.

## **3. Generalisability**

*Comment here on how reasonable it is to generalise from the results of the studies used as evidence to the target population for this guideline.*

One systematic review (Mills) included some trials of patients with CAP managed in ambulatory care and another one (Bjerre) focused on outpatients with CAP. The other two systematic reviews and one narrative review (Feldman) only included patients with CAP managed in hospitals. All of the studies only included adult patients with CAP.

The mean mortality in the trials in the systematic review of RCTs in hospitalised patients was 3.5%, which is much lower than in studies of unselected patients hospitalised in Scotland (e.g. 19% in Barlow 2006). 30-day mortality in the CBA (10%, Capelastegui) and Cluster RCT (9%, Yealy) was higher than in the RCTs but still lower than in patients hospitalised in Scotland.

## **4. Consistency**

*Comment here on the degree of consistency demonstrated by the available of evidence. Where there are conflicting results, indicate how the group formed a judgement as to the overall direction of the evidence*

Outpatient systematic review: no difference between molecules (macrolides, FQ).

Both systematic reviews of RCTs concluded that there was no improvement in clinical outcome (clinical cure or improvement for Mills and mortality for Shefet) associated with empirical antibiotic therapy with drugs that are effective against atypical pathogens.

The conclusion of the systematic review of cohort studies was that all were vulnerable to residual confounding and that a randomized trial is warranted (Oosterheert). The authors also concluded that addition of a macrolide to beta-lactam regimens may be harmful but we do not agree that this is supported by the studies that were reviewed. The majority of the cohort studies show that combination therapy is associated with better outcome in patients with severe pneumonia and no study supports the suggestion that addition of a macrolide to beta-lactam regimens may be harmful, at least in the short term.

In 2 retrospective cohorts (Dean, Shorr), compliance with antibiotic guidelines was associated with a better outcome (mortality for Dean, duration of mechanical ventilation for Shorr), but that could only be the result of confounding factors.

In the CBA (Capelastegui), early administration of appropriate antibiotics was one of four components of a care pathway. The intervention was associated with an increase in the proportion of patients that received appropriate antibiotics and coverage of atypical pathogens. The intervention was also associated with a significant reduction in mortality and length of stay.

In the Cluster RCT (Yealy), appropriate antibiotic treatment was one of four recommended processes of care for inpatients. More inpatients in the high intensity

intervention group received all four processes of care but there was no associated improvement in outcome.	
<b>5. Clinical impact</b> <i>Comment here on the potential clinical impact that the intervention in question might have – e.g. size of patient population; magnitude of effect; relative benefit over other management options; resource implications; balance of risk and benefit.</i>	
One third of patients presenting to hospitals in Scotland with CAP are likely to have severe pneumonia and this is associated with high mortality so more effective antibiotic treatment is likely to have clinical impact in these patients. Resource implications are probably neutral because increased antibiotic cost is likely to be balanced by reduction in length of stay and transfer to high dependency care. Balance of risk and benefit: the main risk is increased use of combination antibiotic therapy for patients who do not have CAP. There are concerns that some drugs that are active against atypical pathogens may differentially increase the risk of <i>C difficile</i> associated diarrhoea. However, these risks should be minimised by measurement of compliance with local antibiotic policies.	
<b>6. Other factors</b> <i>Indicate here any other factors that you took into account when assessing the evidence base.</i>	
The current BTS recommendations are to use a combination of beta-lactam plus macrolide for all patients hospitalised with CAP but they say that beta-lactam monotherapy should be considered in low risk patients who were previously untreated in the community or admitted to hospital for other reason, with pneumonia which could be treated in the community. Implementation of the BTS guidelines (or current guidelines from the USA) is likely to increase the use of antibiotics in low and moderate risk patients, increasing antibiotic costs with no benefit to patients. <sup>1:2</sup> Furthermore the BTS guidelines recommend quinolones for patients with CAP who are allergic to beta-lactams and there is increasing evidence that quinolones are an important risk factor for <i>Clostridium difficile</i> associated diarrhoea. <sup>3</sup>	
<b>7. Evidence statement</b> <i>Please summarise the development group's synthesis of the evidence relating to this key question, taking all the above factors into account, and indicate the evidence level which applies.</i>	<b>Evidence level</b>
The systematic reviews of RCTs provide additional evidence to support the recommendation to use beta-lactam monotherapy in low risk patients who are hospitalised. The results of the cohort, CBA and cluster RCT are inconsistent. The cluster RCT has the lowest risk of confounding and suggest no benefit from coverage of atypical pathogens but this evidence is only applicable to low risk patients. The more recent cohort studies consistently show that coverage of atypical pathogens is associated with better outcome for patients with severe pneumonia.	1 <sup>++</sup> low risk patients 2 <sup>++</sup> high risk patients
<b>8. Recommendation</b> <i>What recommendation(s) does the guideline development group draw from this evidence? Please indicate the grade of recommendation(s) and any dissenting opinion within the group.</i>	<b>Grade of recommendation</b>
2010 update: The Care Bundle should recommend that patients with severe CAP receive IV combination therapy with betalactam and macrolide antibiotics.	<b>B</b>