Economic report

Procalcitonin to differentiate bacterial lower respiratory tract infections from non-bacterial causes

CEP10036

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Procalcitonin is a laboratory blood test that can be used in secondary care to determine whether a lower respiratory tract infection (LRTI) has a bacterial cause [1].

The potential value of the procalcitonin test is that it helps to guide hospital doctors to prescribe antibiotics for patients with a high likelihood of a bacterial LRTI, and to withhold antibiotics for patients whose LRTI is likely to be due to a non bacterial cause (eg a virus) [2]. Antibiotics are unhelpful for viral infections, sometimes cause unpleasant side effects and their unwarranted use has been linked to the emergence of antibiotic-resistant strains of bacteria [3,4]. Evidence from randomised trials indicates that use of a procalcitonin test reduces the rate of prescribing of antibiotics for patients with LRTI without compromising recovery rates or causing longer hospital stays [5-9].

A cost effectiveness analysis was conducted to examine procalcitonin testing when added to the standard diagnostic pathway in secondary care. The cost effectiveness analysis considered the cost of introducing the procalcitonin test and the cost of antibiotics. The benefit was measured as the number of additional patients that are correctly treated (given or not given antibiotics) as a result of the test. The analysis made the following assumptions:

- that a procalcitonin test costs £30 to perform per patient based on two measurements and that a course of antibiotics costs between £5.00 and £16.63
- that procalcitonin test sensitivity is within the range 66%-86% and specificity 68%-82%
- that 86% patients receive antibiotics for LRTI under standard care
- that the true prevalence of bacterial LRTI is between 20% and 37%.

The analysis calculated the incremental cost effectiveness ratio (ICER). The ICER is the ratio of the difference in costs to the difference in benefits [10], between procalcitonin testing and standard care. It represents the additional expenditure required per additional patient who is correctly treated (given or not given antibiotics) as a result of the procalcitonin test.

The ICER was estimated at between £45 and £120 per additional correctly treated case. The costs used in the analysis are small relative to the total cost of care of patients with LRTI [11]. The ICER values should be considered against the two most important benefits of using the procalcitonin test that were not quantified in the analysis:

- reduction in patient exposure to the side effects of antibiotics
- reduced likelihood of emergence of further antibiotic resistant strains of bacteria.
Lower respiratory tract infections (LRTI) are a very common cause of illness, representing a high proportion of consultations with GPs and also hospital admissions [12].

The following illnesses are different types of LRTI:

- bronchitis
- exacerbation of chronic obstructive pulmonary disease (ECOPD)
- pneumonia, including community acquired pneumonia (CAP).

Both in primary care and in hospitals doctors frequently use antibiotics to treat LRTI. Antibiotics are the appropriate therapy when the cause of LRTI is a pathogenic bacteria but are unhelpful when the LRTI has a viral or fungal origin [3,4]. It is estimated that most LRTIs do not have a bacterial origin and that antibiotics are over used [4]. Antibiotics frequently cause side effects including nausea, vomiting, diarrhoea and skin rashes. Also, the over use of antibiotics has been linked to the emergence of bacterial strains that are resistant to standard antibiotic therapy, and which can cause infections that are difficult to treat [3,4].

For these reasons development of a reliable clinical test that could guide doctors in deciding when to safely reduce the use of antibiotics would be useful in reducing the side effects of antibiotics and as an effort against the emergence of resistant bacterial strains.

**Standard treatment of lower respiratory tract infection**

Patients admitted to hospital with suspected LRTI undergo clinical examination and a series of investigations which may include:

- Sputum culture – to detect bacteria
- Blood culture – to detect bacteria
- Chest X Ray
- Standard blood tests, including arterial blood gases
- Blood tests for biomarkers of inflammation or infection eg C-reactive protein
- Urine test for Legionella antigen
- Nose/throat swabs to detect viral infection.

The aims of the medical investigations are to differentiate LRTI from other chest illnesses (eg pulmonary embolism), identify the LRTI subtype (bronchitis, ECOPD or pneumonia) and to guide the correct therapy.

The decision on whether LRTI has a bacterial cause is reached by clinical judgement and considering the whole clinical picture including the patient’s history, prior treatment and current condition, and also the results of numerous diagnostic investigations. No single diagnostic investigation is totally infallible in distinguishing a
bacterial cause of LRTI from other causes of LRTI. Bacterial cultures grown from samples of sputum or blood contribute to the overall clinical picture but are not totally reliable [13].

Antibiotics are reportedly over used in LRTI [14] and strategies for optimal use of antibiotics include [12,13,15,16]:

- avoiding antibiotic use in cases where it is safe to do so and where antibiotics are unlikely to be of benefit to the patient
- using targeted antibiotics against specific bacterial pathogens.

Patients who are treated without antibiotics receive supportive care which may include physiotherapy, oxygen and drugs to relieve airway constriction and reduce inflammation.

Figure 1 shows a simplified treatment pathway for hospitalised patients with LRTI, based on Cardiff and Vale University Health Board, a large, tertiary care provider [17].
Figure 1. Treatment of patients admitted to hospital with LRTI [17]

Note: the standard care pathway is shown. Procalcitonin is not in routine use for patients with LRTI but the point in the care pathway at which procalcitonin is introduced is illustrated.

Patient with LRTI

Sputum culture (if purulent)
Blood culture (if fever present)
Chest X Ray
Arterial blood gas
Standard blood tests
Urine test for Legionella antigen
Nose/throat swabs for virology

COPD/bronchitis:
Antibiotics given if there is increased sputum purulence or increased sputum volume

Pneumonia:
Treatment depends on the severity of the patient's illness

Severity low
Oral Amoxycillin or Oral Doxycycline / oral Levofloxacin

Severity moderate or high
Oral Amoxycillin or Oral clarithromycin or Oral Levofloxacin

IV co-amoxiclav plus oral clarithromycin or Oral Levofloxacin
Introduction

Procalcitonin test

Procalcitonin is a laboratory blood test that is used to determine whether an infection has a bacterial cause. In a normal, healthy state, blood levels of procalcitonin are negligible but become elevated in response to bacterial infection [1]. Procalcitonin testing has been used to detect sepsis, a severe whole body inflammatory response to infection [18]. Procalcitonin testing has been further developed to enable detection of LRTI of bacterial cause. This requires a procalcitonin assay capable of detecting lower blood levels of procalcitonin than assays used to detect sepsis [19].

Use and interpretation of the procalcitonin test

Use of the procalcitonin test requires prompt access to a hospital laboratory to process the blood sample. The test result needs to be made available to the clinical staff within a few hours so that it may inform prompt treatment of the patient.

Blood levels of procalcitonin are interpreted as shown in table 1 [19].

<table>
<thead>
<tr>
<th>Blood PCT level</th>
<th>Advised action</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCT&lt; 0.1 ng/ml</td>
<td>Indicates absence of bacterial infection. Use of antibiotics strongly discouraged, also in the presence of impaired pulmonary reserve.</td>
</tr>
<tr>
<td>0.1&gt;PCT&lt;0.25 ng/ml</td>
<td>Bacterial infection unlikely. The usage of antibiotics is discouraged.</td>
</tr>
<tr>
<td>0.25&gt;PCT&lt;0.5 ng/ml</td>
<td>Bacterial infection is possible. Advice to initiate antibiotic therapy.</td>
</tr>
<tr>
<td>PCT&gt;0.5 ng/ml</td>
<td>Suggestive of the presence of bacterial infection. Antibiotic treatment strongly recommended.</td>
</tr>
</tbody>
</table>

The blood procalcitonin level is interpreted in four categories of likelihood of bacterial cause of LRTI, corresponding with recommendations for and against the use of antibiotics.

The procalcitonin test is often repeated between 6 – 24 hours of the initial measurement and possibly on subsequent days, in order to monitor the course of illness and response to therapy. For patients with LRTI two measurements of procalcitonin level are likely to be sufficient [20].

Doctors do not decide whether to prescribe or withhold antibiotics on the basis of the procalcitonin test result alone, but by considering also the patient’s medical history, previous treatment, current symptoms and signs, and the results of the battery of investigations employed routinely as part of standard care [19]. The procalcitonin test is intended as an additional test to the standard diagnostic pathway, to provide a further piece of information to the overall clinical picture. Doctors consider this overall clinical picture when making a clinical judgement to prescribe or withhold antibiotics.
and doctors sometimes overrule the procalcitonin level when under 0.25 ng/ml and prescribe antibiotics, to avert the risk of under-treating a patient.

It may be unlikely for example, that antibiotics would be stopped in a patient admitted to an emergency unit with LRTI who started antibiotic therapy in primary care, on the strength of a low procalcitonin value. It is also possible that a patient admitted to hospital with a viral LRTI may develop a secondary bacterial infection.

Limitations

It is important to consider the following limitations of the procalcitonin assay [21]:

- Low PCT levels may occur in the presence of a bacterial infection if the sample is taken for PCT measurement early in the course of an infection whilst it is still very localised. However, follow-up analysis would register an increase in PCT concentration. Low PCT levels may also occur if the patient is taking steroids as they can inhibit the pathway for PCT production [2]. This is important in patients with chronic lung conditions such as COPD, asthma or pulmonary fibrosis.

- Increased PCT levels may not always be related to systemic infection and moderately elevated values may occur in major trauma, surgery, severe cardiogenic shock, burns and in some cancer patients [19,22]. However, PCT values would show a rapid decline in any follow-up measurements.

Aim

The aim of this report is to analyse the cost-effectiveness of procalcitonin as a test to identify bacterial infections in LRTI. More detailed information on the clinical effectiveness of the procalcitonin test in LRTI is available in the CEP evidence review [21].

An interactive model complements this economic report [23]. The model is a Microsoft Excel spreadsheet containing the formulae behind the cost-effectiveness analysis used in this report. NHS organisations can use the interactive model to calculate cost-effectiveness based on their local data.

Scope

This economic report will cover procalcitonin as a test to identify a bacterial origin of LRTI in secondary care and to guide decisions on antibiotic prescribing in secondary care. It does not cover procalcitonin testing in children with febrile illness, patients with suspected sepsis or patients with non lung infections.

Patients with LRTI are treated in primary care and secondary care depending on the severity of their illness. The procalcitonin test requires rapid access to a medical laboratory bench top analyzer; these are routinely available in secondary care.

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Although a Swiss study [5] has evaluated procalcitonin testing in primary care using a bench top analyser, this equipment is not generally available in primary care in the UK. For this reason, and in the absence of a smaller, point of care procalcitonin platform, the procalcitonin test is not currently feasible in primary care and the focus of this economic report is mostly on secondary care.

**National and international guidance**

The threat of the emergence of bacterial strains that are resistant to antibiotic treatment is widely recognised [3,4,12-14,24] and in the UK national guidelines and strategies aim to use antibiotic prescriptions for cases where they are most appropriate, and to minimise the emergence of bacterial resistance by reduced prescribing where it can be achieved safely [3,4,12,13,15,24].

A recent NICE guideline on respiratory tract infections in primary care reported that these infections account for up to 75% of antibiotic prescriptions in primary care despite the fact that many have a viral cause [12]. With the aim of reducing unnecessary use of antibiotics in primary care, NICE recommended three antibiotic prescribing strategies for General Practitioners [12]:

- no prescribing – for generally healthy patients
- delayed prescribing – issue of a prescription which the patient can choose to use if symptoms do not improve
- immediate prescribing – for patients in poorer health or in high risk groups.

Another NICE guideline for patients with COPD recommends that antibiotics should be used to treat ECOPD where there is purulent sputum [15]. Patients with EOCPD without purulent sputum do not need antibiotic therapy unless there is consolidation on a chest radiograph or clinical signs of pneumonia [15].

The Task Force of the European Respiratory Society and the European Society for Clinical Microbiology and Infectious Diseases produced a guideline for the management of adult LRTI [16]. The guideline recommends consideration of antibiotic treatment in the following cases [16]:

- patients with suspected or definite pneumonia
- patients with ECOPD and with increased dyspnoea; increased sputum volume; and increased sputum purulence
- patients aged 75 years or more with fever
- patients with cardiac failure, insulin dependent diabetes mellitus, and serious neurological disorder (eg stroke).

Tetracyclines and amoxicillin are the recommended first choice of antibiotics, but considering also the national and local resistance rates [16]. When there are clinically relevant bacterial resistance rates against all first-choice agents, treatment with levofloxacin or moxifloxacin may be considered [16].
The guidelines aim to promptly treat patients with antibiotics where the LRTI is more severe or where the patient is at increased risk of complications or deterioration, and the guidelines identify groups in whom antibiotics may be withheld [12,13,15,16]. However the guidelines do not define a discrete group of patients who have bacterial LRTI, and there appears to be no better reference standard for bacterial LRTI than the final diagnosis reached as a clinical judgement, reached by considering the patient’s history, condition and the results of numerous medical investigations. The British Thoracic Society’s guidelines for patients with CAP [13] report that microbial cultures grown from samples of sputum and blood have low sensitivity and often do not change initial antibiotic management.

The rate of increase in resistance among respiratory pathogens has tended to level off in recent years [13]. This implies that efforts to reduce overall antibiotic prescribing have had a positive impact. The putative value of the procalcitonin test is as an additional piece of information to the standard diagnostic pathway to help doctors decide for an individual patient, whether antibiotics are the appropriate therapy, and the test may have potential to reduce overall antibiotic use in patients with LRTI.
Methods

Table 2 shows the research question used to direct the literature search.

Table 2. Research question

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with LRTI</td>
<td>PCT test to guide AB prescribing</td>
<td>Standard diagnostic work up without PCT test</td>
<td><strong>Diagnostic test outcomes</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>The aim is to correctly identify LRTI of bacterial origin using definitive diagnosis as reference standard:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>▪ Sensitivity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>▪ Specificity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Standard decision making to guide antibiotic prescribing.</td>
<td><strong>Cost outcomes</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cost of procalcitonin test</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rate of antibiotic use</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Duration of antibiotic use</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cost of antibiotic use</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rate of antibiotic adverse effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Clinical outcomes</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Treatment success rate (and occurrence of adverse events eg mortality)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Length of hospital stay</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Recurrence of LRTI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Readmission to hospital</td>
</tr>
</tbody>
</table>

A series of searches to identify research evidence on procalcitonin in LRTI was performed. These are described below.

Search for economic evaluations

Searches were performed on the databases detailed in table 3 to identify economic evaluations on the use of procalcitonin to differentiate between bacterial and viral infections in LRTI. The search strategies used are detailed in appendix 2.
Table 3. Electronic databases searched for economic evaluations

<table>
<thead>
<tr>
<th>Resource</th>
<th>Interface/URL</th>
<th>Issues searched</th>
<th>Search date</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEDLINE</td>
<td>OvidSP</td>
<td>Ovid MEDLINE(R) 1950 to present</td>
<td>26/01/10</td>
</tr>
<tr>
<td>MEDLINE IN-PROCESS</td>
<td>OvidSP</td>
<td>Ovid MEDLINE(R) In-Process &amp; Other Non-Indexed Citations</td>
<td>26/01/10</td>
</tr>
<tr>
<td>EMBASE</td>
<td>OvidSP</td>
<td>Ovid EMBASE 1980 to present</td>
<td>28/01/10</td>
</tr>
<tr>
<td>HMIC</td>
<td>OvidSP</td>
<td>January 2010</td>
<td>28/01/10</td>
</tr>
<tr>
<td>HTA</td>
<td><a href="http://www.crd.york.ac.uk/crdweb">www.crd.york.ac.uk/crdweb</a></td>
<td>20/01/10</td>
<td>20/01/10</td>
</tr>
<tr>
<td>NHS EED</td>
<td><a href="http://www.crd.york.ac.uk/crdweb">www.crd.york.ac.uk/crdweb</a></td>
<td>20/01/10</td>
<td>20/01/10</td>
</tr>
<tr>
<td>DARE</td>
<td><a href="http://www.crd.york.ac.uk/crdweb">www.crd.york.ac.uk/crdweb</a></td>
<td>20/01/10</td>
<td>20/01/10</td>
</tr>
</tbody>
</table>

Search for clinical studies of procalcitonin

Additional searches were performed on the databases detailed in table 4 to find the diagnostic performance of the procalcitonin test. The search strategies used are detailed in appendix 2.

Table 4. Resources searched for clinical studies of diagnostic test performance

<table>
<thead>
<tr>
<th>Resource</th>
<th>Interface/URL</th>
<th>Issues searched</th>
<th>Search date</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEDLINE</td>
<td>OvidSP</td>
<td>Ovid MEDLINE(R) &lt;1950 to present</td>
<td>26/01/10</td>
</tr>
<tr>
<td>EMBASE</td>
<td>OvidSP</td>
<td>Ovid EMBASE &lt;1980 to present</td>
<td>28/01/10</td>
</tr>
</tbody>
</table>

Exclusion criteria

We excluded studies of procalcitonin testing for patients treated in hospital (particularly critical care departments) for sepsis. In these studies there is a high degree of heterogeneity in the patient groups, with infections of sources other than LRTI. In addition the procalcitonin test for sepsis uses a higher threshold than for LRTI and in a sense, is a different test [19]. Studies were restricted to English language papers and studies of human subjects.
Results

The search revealed a lack of economic studies of procalcitonin testing in LRTI. We included clinical studies as follows.

Volume and quality of studies

We included 5 randomised controlled trials comparing use of a procalcitonin test for patients with LRTI to guide antibiotic prescribing versus standard antibiotic prescribing [5-9]. The five randomised trials are of reasonable size and quality. We also included one UK-based case series study [25] and one planned, retrospective analysis [26] of data from two of the randomised controlled trials [6,7].

External validity of studies

The randomised controlled trials [5-9] were all conducted in Switzerland, which has a different healthcare system to that of the UK. The trials were conducted by the same team of researchers. Prospective randomised trials also have stringent patient eligibility criteria and careful monitoring of patients. For these reasons the results should be extrapolated to scenario of routine care in the UK with caution.

Four of the trials study patients in hospital [6-9] and one studies patients treated in primary care, including patients with upper respiratory tract infections [5], which include minor illnesses such as coughs and colds.

Antibiotic use

Five randomised trials provide evidence that use of a procalcitonin guided algorithm reduces the rate of prescribing of antibiotics for patients with LRTI [5-9]. In the control arms of the studies (ie reflecting standard care), 88% of patients on average, received antibiotics whereas in the procalcitonin test arms 54% of patients on average, received antibiotics. The greatest reduction of antibiotics use was in a study based in primary care [5], which included a proportion of patients with upper respiratory tract infections and in which, patients may have tended to have had less severe LRTI than the hospital based studies.

Considering only the hospital based studies [6-9] the average rate of antibiotic use is 86% under standard care and 61% with procalcitonin testing with a relative reduction (expressed as a ratio: procalcitonin:control) of 71% ie a reduction by 29%. Table 5 shows the rates of antibiotic use in each trial.
Table 5. Rates of antibiotic use in randomised controlled trials of procalcitonin test versus standard care

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>AB prescribing rate (%)</th>
<th>Relative reduction, PCT:control (%)</th>
<th>Absolute reduction, control minus PCT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>PCT</td>
<td>Control</td>
<td></td>
</tr>
<tr>
<td>Stolz 2007 [9]</td>
<td>ECOPD</td>
<td>40</td>
<td>72</td>
<td>56</td>
</tr>
<tr>
<td>Shuetz 2009 [8]</td>
<td>LRTI</td>
<td>75</td>
<td>88</td>
<td>85</td>
</tr>
<tr>
<td>Mean (all studies)</td>
<td></td>
<td>54</td>
<td>88</td>
<td>61</td>
</tr>
<tr>
<td>Mean (excluding Briel et al. 2008) [5]</td>
<td></td>
<td>61</td>
<td>86</td>
<td>71</td>
</tr>
</tbody>
</table>

A UK based, non randomised study introduced procalcitonin to routine care (ie outside the context of a randomised trial) and reported on a series of patients with LRTI [25]. Antibiotic therapy was continued in 35% of patients for whom the procalcitonin test result indicated stopping antibiotic therapy. This was a higher rate than the 10% reported in a Swiss randomised trial [6]. The UK study calculated that running the procalcitonin test in 219 patients cost £6750 and saved £1306 in the antibiotic budget [25].

Clinical outcome

The four hospital based randomised trials indicate that the procalcitonin guided algorithm for antibiotics prescribing does not result in inferior clinical outcomes for patients treated for LRTI when compared to standard prescribing [6-9]. The clinical outcomes studied varied, but included rate of mortality, complications of LRTI, improvement or worsening of LRTI, need for care in an intensive care unit, length of hospital stay and re-admission to hospital.

In the study of patients in primary care [5] there was no difference between groups for disruption of patients' normal activities, days missed at work or persistent/recurrent infection at one month, but patients in the procalcitonin arm reported greater discomfort at 14 days than those in the standard treatment group (although discomfort was much reduced in both groups from baseline levels).
Procalcitonin as a diagnostic test

All five randomised trials [5-9] used procalcitonin to determine the likelihood of bacterial LRTI as described by Brahms [19] and as shown in table 1. In a UK based case series study [25] the procalcitonin algorithm advised the use of antibiotics for patients with a blood level of procalcitonin greater than 0.25 ng/ml.

One paper by Muller et al. 2007 presents results of a planned, retrospective analysis [26] of the diagnostic performance of procalcitonin in detecting bacteraemia in the subgroup of patients with CAP recruited into two of the randomised trials [6,7]. The paper presents results as receiver operator characteristics curves (ROC). The area under the curve represents the overall accuracy of the procalcitonin test in detecting bacteraemia in patients with CAP, at 85% (95%CI 80% to 91%). Accuracy represents the proportion of patients given the correct result by the test. Accuracy is closely related to two other measures which describe the performance of a diagnostic test, namely sensitivity and specificity:

- Sensitivity measures the test’s ability to identify the proportion of patients who have the condition [27], in this case, bacterial CAP as opposed to CAP of other causes
- Specificity measures the test’s ability to identify the proportion of patients who do not have the condition [27].

Sensitivity and specificity of the procalcitonin diagnostic test are considered in relation to a reference standard, which is the best available information on the true state of the LRTI (of either bacterial or non bacterial cause). The reference standard is the definitive diagnosis reached as a result of considering the whole clinical picture, and including numerous medical investigations.

On the ROC curve the Q* point summarises the overall performance of the procalcitonin test and represents optimal sensitivity and specificity [18]. In the study by Muller et al. 2007 [26] the Q* point provides a value of approximately 76% for both sensitivity and specificity; this is shown in figure 2 by the intersect of the straight diagonal line with the procalcitonin ROC curve [26]. This single value overcomes the problem of summarising procalcitonin as a diagnostic test with four categories of likelihood of bacterial cause of LRTI, as opposed to a simpler, dichotomous result seen in many other diagnostic tests. Figure 2 also shows ROC curves for three other potential diagnostic indicators outside of the scope of this report, namely, C-reactive protein level, leukocyte (white blood cell) count and body temperature.

In the study by Muller et al. 2007 [26] sensitivity and specificity do not refer to the procalcitonin assay’s ability to measure the blood level of procalcitonin. Sensitivity and specificity refer to the ability of the information provided by the procalcitonin test to agree with the definitive diagnosis of bacterial CAP [26].
Figure 2. ROC curve of procalcitonin and other parameters in predicting bacteraemia in CAP (reproduced with permission from Muller et al. 2007 [26]); straight diagonal line and Q* point added to original illustration.
Objectives

A cost effectiveness analysis for procalcitonin testing of patients with LRTI is described. A cost effectiveness analysis considers the cost of an intervention and benefits of using the intervention that are disease-specific [28].

Procalcitonin testing incurs a new cost over standard care, including purchase of test consumables, use and maintenance of a hospital laboratory bench top analyzer (usually already present in hospitals and used for routine hospital blood tests) and laboratory staff time to conduct the procalcitonin test.

The principle benefit of procalcitonin testing is to increase the number of patients with LRTI that are correctly treated in terms of antibiotic use. In effect this means a reduction in overall antibiotic use through identification of patients in whom the LRTI is of non bacterial cause, and for whom antibiotics are not the correct therapy. This patient group is spared the risk of adverse effects of antibiotics and the overall reduction is antibiotic use represents a measure against the emergence of antibiotic resistant strains of bacteria.

The cost effectiveness analysis compares use of procalcitonin test with standard care and quantifies the following costs:

- the cost of using the procalcitonin test
- the cost of antibiotics.

The cost effectiveness analysis therefore considers the reduction in cost of antibiotics as a result of procalcitonin testing but the two most important benefits arising from procalcitonin testing are not quantified in monetary terms:

- reduction in patient exposure to the side effects of antibiotics
- reduced likelihood of emergence of further antibiotic resistant strains of bacteria.

Use of sensitivity and specificity of the procalcitonin test

The study by Muller et al. 2007 [26] provides a summary value for both sensitivity and specificity of 76%. Sensitivity and specificity originate from a comparison of a diagnostic test against a reference standard, usually using a 2 x 2 contingency table as shown in table 6 [27].
Table 6. 2 x 2 contingency table

<table>
<thead>
<tr>
<th>PCT test</th>
<th>Reference standard</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bacterial cause</td>
<td>Non bacterial cause</td>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacterial cause likely</td>
<td>a</td>
<td>b</td>
<td>a+b</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacterial cause unlikely</td>
<td>c</td>
<td>d</td>
<td>c+d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>a+c</td>
<td>b+d</td>
<td>a+b+c+d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sensitivity = \( \frac{a}{a+c} \)

Specificity = \( \frac{d}{b+d} \)

The cost effectiveness analysis uses values of sensitivity and specificity based on the study by Muller et al. 2007 of patients with CAP [26] and extrapolates them to patients with LRTI. The reference standard is the final diagnosis determined by numerous medical investigations.

The cost effectiveness analysis considers 1000 theoretical patients with LRTI who undergo procalcitonin testing with sensitivity and specificity of 76% [26]. The analysis also requires a value for prevalence i.e the proportion of patients with bacterial LRTI as attributed by reference standard; values from the literature are used [9,14].

The parameters sensitivity, specificity and prevalence give rise to four theoretical patient groups for the analysis, represented by cells a, b, c and d in table 6:

1. True positive results (cell a): these patients are correctly identified by procalcitonin as having LRTI of bacterial cause, and antibiotic therapy is the optimal therapy
2. True negative results (cell d): these patients are correctly identified by procalcitonin as having LRTI of non bacterial cause, and antibiotic therapy is withheld
3. False positive results (cell b): these patients are falsely identified by procalcitonin as having LRTI of bacterial cause, and antibiotic therapy is given, but is not the optimal therapy. This can occur when high blood levels of procalcitonin occur due to trauma, surgery, cardiogenic shock, burns, cancer [19,22]. However, procalcitonin values would show a rapid decline in follow-up measurements
4. False negative results (cell c): these patients are falsely identified by procalcitonin as having LRTI of non bacterial cause, and antibiotic therapy is withheld although it is the optimal therapy. This situation may arise when patients have been prior treated with steroids [2] or antibiotics. In many such instances doctors would override a low procalcitonin level and prescribe antibiotics where they suspected bacterial LRTI based on other diagnostic information.
This approach is shown in figure 3.

**Figure 3. diagnostic test outcomes for procalcitonin testing in LRTI and subsequent treatment**

<table>
<thead>
<tr>
<th>Reference standard</th>
<th>Test result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial infection present</td>
<td></td>
</tr>
<tr>
<td>a: True positive</td>
<td>Antibiotics correctly prescribed</td>
</tr>
<tr>
<td>c: False negative</td>
<td>Antibiotics incorrectly withheld</td>
</tr>
<tr>
<td>d: True negative</td>
<td>Antibiotics correctly withheld</td>
</tr>
<tr>
<td>b: False positive</td>
<td>Antibiotics incorrectly prescribed</td>
</tr>
</tbody>
</table>

**Assumptions and limitations**

Using the single value for sensitivity and specificity of 76% assumes that the two parameters are equal, when in reality one may be higher than the other. For any test there is a trade off between sensitivity and specificity and 76% is the optimised, summary value based on an analysis by Muller et al. 2007 [26].

A second limitation is that the value of 76% for sensitivity and specificity [26] is for the procalcitonin test in detecting bacterial cause of CAP, rather than LRTI. CAP represents the most serious condition in the spectrum of diseases that come under the definition of LRTI. It is an assumption that the procalcitonin test has the same performance in detecting bacterial cause in bronchitis or ECOPD.

A third limitation of this approach is that in reality, doctors do not prescribe or withhold antibiotics on the strength of the procalcitonin test alone, but by considering the patient’s history, condition, risk factors and the results of other investigations. This is illustrated by table 1, which shows that the procalcitonin level guides doctors based on the likelihood of bacterial LRTI, but considering also the overall clinical picture [29].

CEP10036: March 2010
Finally there is some uncertainty around the reference standard to identify bacterial LRTI. Some studies use the final diagnosis to attribute the status of LRTI (bacterial versus non bacterial) whereas others use positive culture from blood, sputum or bronchoalveolar lavage fluid. Some authors argue that when a bacterium is grown from a sputum culture, this may represent colonisation rather than infection [6].

**Estimation of quantifiable costs**

**Procalcitonin test**

Brahms holds the patent for the procalcitonin assay and there are three suppliers of procalcitonin test to the UK market. Each supplies a procalcitonin assay in a test kit that is compatible with their own laboratory bench top analyzer machine. For an NHS organisation considering introducing procalcitonin testing, the choice of procalcitonin supplier is likely to depend upon which bench top analyzer is already used in hospital. Details are shown in table 7.

**Table 7. Suppliers and prices for consumable procalcitonin test kits**

<table>
<thead>
<tr>
<th>PCT test kit supplier</th>
<th>Bench top analyzer</th>
<th>Cost per kit</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAHMS UK Ltd.</td>
<td>BRAHMS Kryptor</td>
<td>£15</td>
</tr>
<tr>
<td>Siemens Centaur</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roche Diagnostics Ltd.</td>
<td>Roche Elecyss</td>
<td>£11.04</td>
</tr>
<tr>
<td>BioMerieux UK</td>
<td>Biomerieux Vidas</td>
<td>£10.92</td>
</tr>
</tbody>
</table>

Estimates in the literature of the total cost of running a procalcitonin measurement, to include assay material, reagents, technician time and purchase and maintenance of a bench top analyzer are approximately US$30 to £30 [7,25]. However discussions with Brahms UK and Poole Hospital NHS Foundation Trust [30] inform a realistic estimate of the cost per procalcitonin measurement (including all overheads) of £15.

In addition use of procalcitonin testing usually involves repeated testing within 6-24 hours and often on subsequent days, with an average of three procalcitonin tests performed in clinical trials [5-9,25]. Outside of clinical trials Brahms UK report that two procalcitonin measurements are likely to be sufficient as part of the diagnostic pathway for patients with LRTI. Therefore it is useful to estimate the cost per patient episode of procalcitonin testing as follows:

£15 x 2 = £30
Antibiotics

The antibiotics considered in the analysis are those used for LRTI in the treatment pathway provided by Cardiff and Vale UHB [17], a large secondary care health provider. Prices are cited from the British National Formulary [31] and wherever possible, prices for non proprietary drugs are used.

Table 8 shows the cost of each antibiotic regimen [17] and also a mean cost based on all regimens, estimated at £16.63. This estimate makes the assumption that 18% of patients with LRTI have CAP [32] and are treated with antibiotics at a cost of £31.93 (table 8) and that therefore 82% of patients have either bronchitis or ECOPD and are treated with antibiotics at a cost of £12.90.

There is likely to be wide variation in the combinations of antibiotics used to treat patients with LRTI in secondary care across the UK. An analysis published in 1997 [32] estimated that the total antibiotic cost to the NHS for patients with CAP that year was £12,859,900 for a total of 83,153 hospital admissions for CAP. This suggests that the average antibiotic cost for a patient admitted to hospital with CAP was £154.65 in 1997. Patients with CAP are likely to receive more antibiotics and more expensive antibiotics than all patients with LRTI, but the 1997 value of £154.65 per admission shows that antibiotic costs are potentially high.

NHS organisations are urged to use the interactive model which accompanies this report to input their own local antibiotic cost information [23].
Table 8. Cost of antibiotics

<table>
<thead>
<tr>
<th>LRTI subtype</th>
<th>Typical antibiotic therapy</th>
<th>Cost per treatment course</th>
<th>Mean cost for each LRTI subtype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchitis / ECOPD (7 day regimen)</td>
<td>Amoxicillin (Non-proprietary) 500mg TDS PO, or</td>
<td>£1.53</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Doxycycline (Non-proprietary) 100mg OD, or</td>
<td>£1.00</td>
<td>£12.90</td>
</tr>
<tr>
<td></td>
<td>Levofloxacin (Sanofi-Aventis) 500mg OD PO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia, low severity (7 day regimen)</td>
<td>Amoxicillin (Non-proprietary) 500mg TDS PO, or</td>
<td>£1.53</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clarithromycin (Non-proprietary) 500mg BD, or</td>
<td>£6.60</td>
<td>£14.77</td>
</tr>
<tr>
<td></td>
<td>Levofloxacin (Sanofi-Aventis) 500mg BD PO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia, moderate or high severity (10 day regimen)</td>
<td>Co-amoxiclav (Non-proprietary) 500/125 TDS PO and Clarithromycin (Non-proprietary) 500mg BD, or</td>
<td>£18.51 + £9.43 = £27.94</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Co-amoxiclav (Non-proprietary) 500/125 TDS PO AND Levofloxacin (Sanofi-Aventis) 500mg BD PO</td>
<td>£18.51 + £51.70 = £70.21</td>
<td></td>
</tr>
<tr>
<td>Mean AB cost: pneumonia (low, moderate and severe)</td>
<td></td>
<td></td>
<td>£31.93</td>
</tr>
<tr>
<td>Estimated standard AB cost: LRTI, assuming 18% pneumonia, 82% bronchitis or COPD</td>
<td></td>
<td></td>
<td>£16.63</td>
</tr>
</tbody>
</table>

Base case analysis

The cost-effectiveness analysis considers 1000 patients who receive procalcitonin testing using multiple procalcitonin cut-off values [19] as shown in table 1 and assumes a procalcitonin test sensitivity of 76% [26], specificity of 76% [26], and a prevalence of bacterial LRTI of 20%, as estimated by the World Health Organisation [14]. Using these values a 2 x 2 contingency table is shown as table 9.
Economic analysis

Table 9. 2 x 2 contingency table for procalcitonin test used in 1000 patients with LRTI (sensitivity 76%, specificity 76%, prevalence 20%)

<table>
<thead>
<tr>
<th>Reference standard</th>
<th>Bacterial cause</th>
<th>Non bacterial cause</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCT test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacterial cause likely</td>
<td>152</td>
<td>192</td>
<td>344</td>
</tr>
<tr>
<td>Bacterial cause unlikely</td>
<td>48</td>
<td>608</td>
<td>656</td>
</tr>
<tr>
<td>Total</td>
<td>200</td>
<td>800</td>
<td>1000</td>
</tr>
</tbody>
</table>

The costs are estimated at £16.63 per course of antibiotic treatment and £30 per patient episode of procalcitonin testing that involves two measurements [20].

The analysis requires an estimate of the proportion of patients who receive antibiotics under standard care ie with no procalcitonin test. In the control arms of the randomised trials conducted in secondary care an average of 86% of patients received antibiotics [6-9]. The analysis assumes that the 14% of patients who do not receive antibiotics are patients without bacterial disease and therefore correctly treated. At a prevalence of 20%, 200 patients correctly receive antibiotics whereas 660 patients receive antibiotics yet do not benefit from them, under standard care.

The cost-effectiveness analysis calculates the incremental cost effectiveness ratio (ICER) of using the procalcitonin test compared to standard care. The ICER is the ratio of the difference in costs to the difference in benefits [10], between procalcitonin testing and standard care. It represents the additional expenditure required per additional patient who is correctly treated as a result of the procalcitonin test. The ICER is calculated as follows:

\[
\text{ICER} = \frac{\text{total cost of procalcitonin test} - \text{total cost of standard care}}{\text{no. patients treated correctly using procalcitonin test} - \text{no. patients treated correctly using standard care}}
\]

The values used in the ICER calculation are shown in table 10.

Table 10. Correctly treated patients and costs: procalcitonin versus standard care

<table>
<thead>
<tr>
<th>Correctly treated cases</th>
<th>Costs AB</th>
<th>Costs PCT testing</th>
<th>Costs Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>AB given</td>
<td>200</td>
<td>£14,301.80</td>
<td>£14,301.80</td>
</tr>
<tr>
<td>AB withheld</td>
<td>140</td>
<td>£0</td>
<td>£0</td>
</tr>
<tr>
<td>Total</td>
<td>340</td>
<td>£14,301.80</td>
<td>£14,301.80</td>
</tr>
<tr>
<td>PCT test</td>
<td>152</td>
<td>£5,720.72</td>
<td>£30,000</td>
</tr>
<tr>
<td>608</td>
<td></td>
<td></td>
<td>£35,720.72</td>
</tr>
<tr>
<td>760</td>
<td></td>
<td></td>
<td>£35,720.72</td>
</tr>
<tr>
<td>Difference</td>
<td>420</td>
<td>£21,418.92</td>
<td>£21,418.92</td>
</tr>
<tr>
<td>ICER</td>
<td></td>
<td></td>
<td>£51</td>
</tr>
</tbody>
</table>
Table 10 shows that an additional 420 patients are treated correctly when the procalcitonin test is used, but at an additional total cost of £21,418.92. The ICER is therefore:

\[
\frac{£21,418.92}{420} = £51 \text{ per correctly treated patient (nearest whole £)}.
\]

Therefore the ICER suggests that it costs an additional £51 to correctly treat (give or withhold antibiotics) an additional patient using the procalcitonin test, compared to standard care.

**Interpretation of the incremental cost effectiveness ratio**

The use of an ICER is coupled with a value judgement of the benefits achieved [10,28]. The ICER can be considered in the context of the cost effectiveness plane, as shown in figure 4 and reproduced from Phillips (2005) [10].

The cost effectiveness analysis suggests that the procalcitonin test, when added to standard care, is more effective than standard care alone in correctly treating patients with LRTI with regard to prescribing or withholding antibiotics. Use of the procalcitonin test incurs an additional cost of £51 per additional correctly treated case, and belongs in the top right hand box in figure 4. An NHS organisation is required to make a value judgement of whether it is worth £51 to successfully treat (give or withhold antibiotics) each additional patient, given that use of the procalcitonin test is likely to bring about an overall reduction in antibiotic use. The value judgement should consider the two most important benefits that arise from reduced use of antibiotics but that are not included in the model:

- reduction in patient exposure to the side effects of antibiotics
- reduced likelihood of emergence of further antibiotic resistant strains of bacteria.
**Sensitivity analysis**

**Adjustment of estimated values of sensitivity and specificity of the procalcitonin test**

The analysis above uses a fixed and equal optimised sensitivity and specificity of 76% based on a retrospective analysis (figure 2) [26] from two randomised trials [6,7]. This summarises the test performance but there is a possibility that sensitivity and specificity may not be equal; in any diagnostic test there is a trade-off between sensitivity and specificity. For this reason it is useful to repeat the analysis using a sensitivity value either side of 76%, at 86% and at 66%, to explore the effect on the ICER. Using figure 2, a sensitivity value of 86% is associated with a specificity value of 68% and a sensitivity value of 66% is associated with a specificity value of 82%.

The results of these further analyses are shown below in tables 11 to 14.
Table 11. 2 x 2 contingency table for procalcitonin test used in 1000 patients with LRTI (sensitivity 86%, specificity 68%, prevalence 20%)

<table>
<thead>
<tr>
<th>Reference standard</th>
<th>Bacterial cause</th>
<th>Non bacterial cause</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCT test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacterial cause likely</td>
<td>172</td>
<td>256</td>
<td>428</td>
</tr>
<tr>
<td>Bacterial cause unlikely</td>
<td>28</td>
<td>544</td>
<td>572</td>
</tr>
<tr>
<td>Total</td>
<td>200</td>
<td>800</td>
<td>1000</td>
</tr>
</tbody>
</table>

Table 12. Correctly treated patients and costs: procalcitonin (sensitivity 86%, specificity 68%) versus standard care, prevalence 20%

<table>
<thead>
<tr>
<th>Correctly treated cases</th>
<th>Correctly treated cases</th>
<th>Correctly treated cases</th>
<th>Costs</th>
<th>Costs</th>
<th>Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>AB given</td>
<td>AB withheld</td>
<td>Total</td>
<td>AB</td>
<td>PCT testing</td>
<td>Total</td>
</tr>
<tr>
<td>Standard care</td>
<td>200</td>
<td>140</td>
<td>340</td>
<td>£14,301.80</td>
<td>£0.00</td>
</tr>
<tr>
<td>PCT test</td>
<td>172</td>
<td>544</td>
<td>716</td>
<td>£7,117.64</td>
<td>£30,000.00</td>
</tr>
<tr>
<td>Difference</td>
<td>376</td>
<td></td>
<td></td>
<td>£37,116.64</td>
<td></td>
</tr>
<tr>
<td>ICER</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>£61.00</td>
</tr>
</tbody>
</table>

Table 13. 2 x 2 contingency table for procalcitonin test used in 1000 patients with LRTI (sensitivity 66%, specificity 82%, prevalence 20%)

<table>
<thead>
<tr>
<th>Reference standard</th>
<th>Bacterial cause</th>
<th>Non bacterial cause</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCT test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacterial cause likely</td>
<td>132</td>
<td>144</td>
<td>276</td>
</tr>
<tr>
<td>Bacterial cause unlikely</td>
<td>68</td>
<td>656</td>
<td>724</td>
</tr>
<tr>
<td>Total</td>
<td>200</td>
<td>800</td>
<td>1000</td>
</tr>
</tbody>
</table>

Table 14. Correctly treated patients and costs: procalcitonin (sensitivity 66%, specificity 82%) versus standard care, prevalence 20%

<table>
<thead>
<tr>
<th>Correctly treated cases</th>
<th>Correctly treated cases</th>
<th>Correctly treated cases</th>
<th>Costs</th>
<th>Costs</th>
<th>Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>AB given</td>
<td>AB withheld</td>
<td>Total</td>
<td>AB</td>
<td>PCT testing</td>
<td>Total</td>
</tr>
<tr>
<td>Standard care</td>
<td>200</td>
<td>140</td>
<td>340</td>
<td>£14,301.80</td>
<td>£0.00</td>
</tr>
<tr>
<td>PCT test</td>
<td>132</td>
<td>656</td>
<td>788</td>
<td>£4,589.88</td>
<td>£30,000.00</td>
</tr>
<tr>
<td>Difference</td>
<td>448</td>
<td></td>
<td></td>
<td>£20,288.08</td>
<td></td>
</tr>
<tr>
<td>ICER</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>£44.00</td>
</tr>
</tbody>
</table>
Adjustment of the estimated prevalence of bacterial LRTI

Due to the uncertainty surrounding final diagnosis as the reference standard it is useful to perform a sensitivity analysis by varying the prevalence of true bacterial LRTI. The effect of raising the prevalence from 20% as estimated by the World Health Organisation [14] to 37% is shown in tables 15 to 20 below. The figure of 37% is based on the proportion of patients for whom sputum cultures yield bacterial growth as reference standard, reported in a randomised trial of procalcitonin testing [9].

This calculation keeps the proportion of patients receiving antibiotics under standard care at 86% [6-9] and makes the same assumption as in the calculations above: that under standard care the 14% of patients who do not receive antibiotics are patients without bacterial disease and therefore correctly treated. In tables 15 to 20 the calculations are performed for the test sensitivity 76%, 86% and 66%, with respective specificity values 76%, 68% and 82%.

Table 15. 2 x 2 contingency table for procalcitonin test used in 1000 patients with LRTI (sensitivity 76%, specificity 76%, prevalence 37%)

<table>
<thead>
<tr>
<th>Reference standard</th>
<th>Bacterial cause</th>
<th>Non bacterial cause</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial cause likely</td>
<td>281</td>
<td>151</td>
<td>432</td>
</tr>
<tr>
<td>Bacterial cause unlikely</td>
<td>89</td>
<td>479</td>
<td>568</td>
</tr>
<tr>
<td>Total</td>
<td>370</td>
<td>630</td>
<td>1000</td>
</tr>
</tbody>
</table>

Table 16. Correctly treated patients and costs: procalcitonin (sensitivity 76%, specificity 76%) versus standard care, prevalence 37%

<table>
<thead>
<tr>
<th></th>
<th>Correctly treated cases AB given</th>
<th>Correctly treated cases AB withheld</th>
<th>Correctly treated cases Total</th>
<th>Costs AB</th>
<th>Costs PCT testing</th>
<th>Costs Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard care</td>
<td>370</td>
<td>140</td>
<td>510</td>
<td>£14,301.80</td>
<td>£0.00</td>
<td>£14,301.80</td>
</tr>
<tr>
<td>PCT test</td>
<td>281</td>
<td>479</td>
<td>760</td>
<td>£7,190.81</td>
<td>£30,000.00</td>
<td>£37,190.81</td>
</tr>
<tr>
<td>Difference</td>
<td>250</td>
<td></td>
<td></td>
<td>£7,190.81</td>
<td>£30,000.00</td>
<td>£37,190.81</td>
</tr>
<tr>
<td>ICER</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>£92</td>
</tr>
</tbody>
</table>
### Economic analysis

Table 17. 2 x 2 contingency table for procalcitonin test used in 1000 patients with LRTI (sensitivity 86%, specificity 68%, prevalence 37%)

<table>
<thead>
<tr>
<th>PCT test</th>
<th>Reference standard</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bacterial cause</td>
</tr>
<tr>
<td>Bacterial cause likely</td>
<td>318</td>
</tr>
<tr>
<td>Bacterial cause unlikely</td>
<td>52</td>
</tr>
<tr>
<td>Total</td>
<td>370</td>
</tr>
</tbody>
</table>

Table 18. Correctly treated patients and costs: procalcitonin (sensitivity 86%, specificity 68%) versus standard care, prevalence 37%

<table>
<thead>
<tr>
<th></th>
<th>Correctly treated cases</th>
<th>Correctly treated cases</th>
<th>Correctly treated cases</th>
<th>Costs</th>
<th>Costs</th>
<th>Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AB given</td>
<td>AB withheld</td>
<td>Total</td>
<td>AB</td>
<td>PCT testing</td>
<td>Total</td>
</tr>
<tr>
<td>Standard care</td>
<td>370</td>
<td>140</td>
<td>510</td>
<td>£14,301.80</td>
<td>£0.00</td>
<td>£14,301.80</td>
</tr>
<tr>
<td>PCT test</td>
<td>318</td>
<td>428</td>
<td>747</td>
<td>£8,644.27</td>
<td>£30,000.00</td>
<td>£38,644.27</td>
</tr>
<tr>
<td>Difference</td>
<td>237</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>£24,342.47</td>
</tr>
<tr>
<td>ICER</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>£103</td>
</tr>
</tbody>
</table>

Table 19. 2 x 2 contingency table for procalcitonin test used in 1000 patients with LRTI (sensitivity 66%, specificity 82%, prevalence 37%)

<table>
<thead>
<tr>
<th>PCT test</th>
<th>Reference standard</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bacterial cause</td>
</tr>
<tr>
<td>Bacterial cause likely</td>
<td>244</td>
</tr>
<tr>
<td>Bacterial cause unlikely</td>
<td>126</td>
</tr>
<tr>
<td>Total</td>
<td>370</td>
</tr>
</tbody>
</table>

Table 20. Correctly treated patients and costs: procalcitonin (sensitivity 66%, specificity 82%) versus standard care, prevalence 37%

<table>
<thead>
<tr>
<th></th>
<th>Correctly treated cases</th>
<th>Correctly treated cases</th>
<th>Correctly treated cases</th>
<th>Costs</th>
<th>Costs</th>
<th>Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AB given</td>
<td>AB withheld</td>
<td>Total</td>
<td>AB</td>
<td>PCT testing</td>
<td>Total</td>
</tr>
<tr>
<td>Standard care</td>
<td>370</td>
<td>140</td>
<td>510</td>
<td>£14,301.80</td>
<td>£0.00</td>
<td>£14,301.80</td>
</tr>
<tr>
<td>PCT test</td>
<td>244</td>
<td>517</td>
<td>761</td>
<td>£5,946.89</td>
<td>£30,000.00</td>
<td>£35,946.89</td>
</tr>
<tr>
<td>Difference</td>
<td>251</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>£21,645.09</td>
</tr>
<tr>
<td>ICER</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>£86</td>
</tr>
</tbody>
</table>
Adjustment of the price of antibiotics

The base case analysis uses a cost of £16.63 per course of antibiotics, assuming that 18% of patients with LRTI have CAP [32] and are treated with antibiotics at a cost of £31.93 and that 82% of patients have either bronchitis or ECOPD and are treated with antibiotics at a cost of £12.90 (table 8).

Patients with pneumonia have more severe illness that patients with other types of LRTI and doctors are likely to be more reluctant to withhold antibiotics in patients with pneumonia, irrespective of the procalcitonin test result. It is patients with pneumonia that tend to be treated with more expensive regimens of antibiotics (table 8). It is therefore plausible that most of the antibiotic use avoided on the strength of the procalcitonin test result represents cheaper regimens that would have been indicated for patients with less severe LRTI.

The effect of increasing the proportion of expensive antibiotics avoided through use of procalcitonin testing is to lower the ICER, making procalcitonin testing more cost effective than in the base case analysis. However this is not likely to be the case in clinical practice for the reasons discussed above.

It is more useful to examine the effect on the ICER of lowering the cost of antibiotics, to reflect the possible bias towards cheaper antibiotics that are avoided through use of procalcitonin testing. The likely effect of assuming that cheaper antibiotics are used is to raise the ICER, representing reduced cost-effectiveness of the test. If an arbitrary value of £5 per course of antibiotics is used, the effect is to raise the ICER by only a relatively small increment (from £45 to £60 in the lowest ICER scenario and from £103 to £120 in the highest ICER scenario). This is summarised in table 21.
Table 21 summarises the ICER for procalcitonin test under the twelve scenarios considered. The ICER represents the additional cost per additional patient that is treated correctly due to the introduction of the procalcitonin test to the care pathway compared with standard care.

Table 21. ICER for procalcitonin test to guide antibiotic therapy in LRTI versus standard care

<table>
<thead>
<tr>
<th>Prevalence of bacterial LRTI</th>
<th>PCT sensitivity</th>
<th>PCT specificity</th>
<th>% of patients treated with antibiotics under standard care (total: correctly plus incorrectly)</th>
<th>% of patients treated with antibiotics under PCT (total: correctly plus incorrectly)</th>
<th>ICER (antibiotic cost £16.63)</th>
<th>ICER (antibiotic cost £5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20%</td>
<td>76%</td>
<td>76%</td>
<td>86%</td>
<td>34%</td>
<td>£51</td>
<td>£65</td>
</tr>
<tr>
<td>20%</td>
<td>86%</td>
<td>68%</td>
<td>86%</td>
<td>43%</td>
<td>£61</td>
<td>£74</td>
</tr>
<tr>
<td>20%</td>
<td>66%</td>
<td>82%</td>
<td>86%</td>
<td>28%</td>
<td>£45</td>
<td>£60</td>
</tr>
<tr>
<td>37%</td>
<td>76%</td>
<td>76%</td>
<td>86%</td>
<td>43%</td>
<td>£92</td>
<td>£111</td>
</tr>
<tr>
<td>37%</td>
<td>86%</td>
<td>68%</td>
<td>86%</td>
<td>52%</td>
<td>£103</td>
<td>£120</td>
</tr>
<tr>
<td>37%</td>
<td>66%</td>
<td>82%</td>
<td>86%</td>
<td>36%</td>
<td>£86</td>
<td>£110</td>
</tr>
</tbody>
</table>

The ICER varies from £45 to £120 in the twelve scenarios. The ICER uses the cost of the procalcitonin test at £30 per patient for two procalcitonin measurements and also two different antibiotics costs, £16.63 and £5.00 per treatment course. Both the cost of the procalcitonin test and the costs of antibiotics are small relative to the total cost of hospital admissions for LRTI. A published study estimated the total cost per hospital admission for ECOPD to be £2500 in the year 1996/7 [11]. In situations where the cost of antibiotics is higher, the ICER per correctly treated case is likely to be lower, representing greater cost effectiveness of procalcitonin. One published study estimated that the average antibiotic cost for a patient admitted to hospital with CAP was £154.65 in 1997 [32].

The analysis estimated that between 28% and 52% of patients receive antibiotics when procalcitonin testing is used. This proportion is lower than in the procalcitonin arms of four randomised trials conducted in secondary care [6-9], where a mean of 61% of patients received antibiotics. This may arise from assumptions made in the analysis concerning:

- sensitivity and specificity of the procalcitonin test
- prevalence of bacterial LRTI.
The effect may be to overestimate the cost effectiveness of the procalcitonin test. NHS organisations are encouraged to use the interactive model to input their local information and further data as further studies of procalcitonin are published.

The cost-effectiveness analysis examined the effect of adjusting the values for procalcitonin sensitivity from 76% to 86% and 66%. Respective values for specificity were 76%, 68% and 82%. These values are derived from a ROC curve in a retrospective analysis [26] from two randomised trials [6,7] (figure 2). The ICER values tend to be lower at low sensitivity and high specificity (i.e., showing the test to be more cost effective) than at high sensitivity and low specificity.

The cost-effectiveness analysis shows that the effect of increasing prevalence of bacterial LRTI from 20% to 37% is to increase the ICER from within the range £45-£74 to within the range £86-£120. It is difficult to determine the true prevalence of bacterial LRTI in the absence of a well-defined reference standard, but if prevalence is higher than 37% the ICER per correctly treated case may be higher than the values shown i.e., representing lower cost effectiveness of the procalcitonin test. This is because at higher prevalence in the analysis, more patients are correctly treated with antibiotics under standard care.

Using the value of 86% for the proportion of patients with LRTI who are treated with antibiotics under standard care is reasonable since it is based on the control arms of randomised trials in secondary care [6-9]. However, this estimate may not reflect the setting outside of a randomised trial. The Swiss randomised trials [6-9] have limited applicability to the routine care situation in the UK. The ICER for procalcitonin is likely to be lower in settings where the proportion of patients with LRTI who are treated with antibiotics under standard care is greater (i.e., showing the test to be more cost effective).

The sensitivity analysis reduced the cost of antibiotics from £16.63 per regimen to £5.00 per regimen, to investigate the effect on the ICER of a potential bias whereby clinicians are more likely to withhold cheaper antibiotics on the strength of the procalcitonin test i.e., in patients with less severe LRTI. The effect is to raise the ICER (lowering cost effectiveness), but by only a relatively small increment (table 21).

The cost-effectiveness analysis considers only the costs of procalcitonin testing and antibiotic use and the benefit of correctly treating (giving or withholding antibiotics) patients with LRTI. The two most important benefits arise from reduced use of antibiotics but are unfeasible to quantify in monetary terms. Firstly, antibiotics side effects are reduced, which include rashes, nausea, diarrhoea and vomiting. Secondly, reduction in unwarranted use of antibiotics is an effort to reduce the emergence of new strains of bacteria that are resistant to antibiotics. These benefits should be considered when an NHS organisation considers the ICER values for procalcitonin testing in patients with LRTI.
The threat of the emergence of bacterial strains that are resistant to antibiotic treatment is widely recognised [3,4,12-14,24]. UK national guidelines and strategies for patients with LRTI recommend the use antibiotic prescriptions for cases where they are most appropriate, and to minimise the emergence of bacterial resistance by reduced prescribing where it can be achieved safely [3,4,12,13,15,24].

Evidence from randomised trials conducted in secondary care suggests that use of a procalcitonin test reduces the rate of prescribing of antibiotics for patients with LRTI [5-9] when added to the standard diagnostic pathway. When used for hospitalised patients [6-9] the average rate of antibiotic use is 86% under standard care and 61% with procalcitonin testing with a relative reduction (expressed as a ratio: procalcitonin:control) by 29%. The trials found that use of the procalcitonin test did not result in a longer hospital stay, worsening of LRTI or delayed recovery from LRTI [6-9].

Many patients with LRTI are managed in primary care. In a randomised trial in primary care the reduction in antibiotic use was greater: 97% under standard care and 25% with procalcitonin testing with a relative reduction by 74% [5]. However procalcitonin testing requires use of a hospital bench top analyser and a rapid turn around time (within hours) for the test result to be available to treating staff, and so is unlikely to be feasible widely in primary care, unless a point of care assay becomes available.

Doctors do not decide whether to prescribe or withhold antibiotics on the basis of the procalcitonin test result alone, but by considering also the patient’s medical history, previous treatment, current symptoms and signs, and the results of numerous investigations employed routinely as part of standard care [19]. The procalcitonin test is intended as an additional test to the standard diagnostic pathway, to provide a further piece of information to the overall clinical picture. In some instances where the procalcitonin test result points to a non bacterial cause of LRTI, doctors may overrule the result and prescribe antibiotics to avert the risk of under-treating the patient.

The cost effectiveness analysis of procalcitonin testing considered the cost of introducing the procalcitonin test and the cost of antibiotics. The benefit was measured as the number of additional patients that are correctly treated (given or not given antibiotics) as a result of the test. The analysis made the following assumptions:

- that a procalcitonin test costs £30 to perform per patient based on two measurements and that a typically used course of antibiotics costs between £5.00 and £16.63
- that procalcitonin test sensitivity is within the range 66%-86% and specificity 68%-82%
- that 86% patients receive antibiotics for LRTI under standard care
that the true prevalence of bacterial LRTI is between 20% and 37%.

The analysis estimated the ICER at between £45 and £120 per additional correctly treated case. The costs used in the analysis are small relative to the total cost of care of patients with LRTI. The ICER values should be considered against the two most important benefits that were not quantified in the analysis:

- reduction in patient exposure to the side effects of antibiotics
- reduced likelihood of emergence of further antibiotic resistant strains of bacteria.
We should like to thank the following for their contribution to this report.

Martin Stephens, National Clinical Director for Hospital Pharmacy, Department of Health

Monica Spiteri, Professor in Respiratory Medicine & Director of Lung Research, University Hospital of North Staffordshire

Ben Hope-Gill, Consultant Respiratory Physician & Lead Clinician Respiratory Medicine, Cardiff and Vale University Health Board

Armaiti Batki, Clinical Evaluator, Wolfson Applied Technology Laboratory, University of Birmingham

Pamela Nayyar, Clinical Evaluator, Wolfson Applied Technology Laboratory, University of Birmingham

Biomerieux UK

BRAHMS UK Limited

Roche Diagnostics Limited

(2) Al-Nakeeb S, Claremont G. Procalcitonin testing has the potential to reduce unnecessary antibiotic use in patients with suspected lower respiratory tract infections. (2005).


Last accessed: 12/02/2010


Last accessed: 12/02/2010

Last accessed: 12/02/2010


Last accessed: 12/02/2010
(20) BRAHMS UK Ltd. Correspondence between BRAHMS UK Ltd and Cedar, Cardiff and Vale University Health Board to discuss measurement and interpretation of blood procalcitonin levels in patients with lower respiratory tract infections. (2010).

Last accessed: 12/02/2010


Last accessed: 12/02/2010

Last accessed: 12/02/2010


e_values
Last accessed: 12/02/2010

(30) Poole Hospital NHS Foundation Trust. Correspondence between CEDAR, Cardiff and Vale University Health Board with Brahms UK and Medical Laboratory Services at Poole Hospital NHS Foundation Trust re: cost of performing procalcitonin testing. (2010).

Last accessed: 12/02/2010


Last accessed: 12/02/2010
## Appendix 1: Supplier contact details

<table>
<thead>
<tr>
<th>Supplier</th>
<th>Biomerieux UK Ltd</th>
<th>Brahms UK Ltd</th>
<th>Roche Diagnostics Ltd</th>
<th>Siemens</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Address</strong></td>
<td>Grafton Way Basingstoke Hampshire RG22 6HY</td>
<td>6 Tunbridge Court Tunbridge Lane Bottisham CB25 9TU</td>
<td>Charles Avenue Burgess Hill West Sussex RH15 9RY</td>
<td>Brahms UK Ltd are the supplier for the Siemens Centaur machine and assay.</td>
</tr>
<tr>
<td><strong>Telephone</strong></td>
<td>01256 461881</td>
<td>01223 811083</td>
<td>01444 256000</td>
<td></td>
</tr>
<tr>
<td><strong>Fax</strong></td>
<td>01256 816863</td>
<td>01223 812257</td>
<td>01444 256206</td>
<td></td>
</tr>
<tr>
<td><strong>Website</strong></td>
<td><a href="http://www.biomerieux.co.uk">www.biomerieux.co.uk</a></td>
<td><a href="http://www.brahms-uk.com">www.brahms-uk.com</a></td>
<td><a href="http://www.roche-diagnostics.co.uk">www.roche-diagnostics.co.uk</a></td>
<td></td>
</tr>
</tbody>
</table>
This section details the literature search strategies used for this project.

**Search for economic evaluations of procalcitonin**

Ovid **MEDLINE(R)** <1950 to present> Searched 26/01/10

1. exp Respiratory Tract Infections/ (240983)
2. procalcitonin.mp. (1334)
3. 1 and 2 (164)
4. Animals/ (4467813)
5. Humans/ (10952773)
6. 4 not (4 and 5) (3333690)
7. 3 not 6 (164)
8. Economics/ (25679)
9. exp "costs and cost analysis"/ (145993)
10. "quality of life"/ or "value of life"/ (82778)
11. exp economics, hospital/ (16216)
12. economics, medical/ (8213)
13. (econom$ or costs or cost or costly or costing or price or prices or pricing).ti,ab. (308194)
14. (expenditure$ not energy).ti,ab. (12848)
15. (value adj2 money).ti,ab. (583)
16. exp models, economic/ or monte carlo method/ (19882)
17. Markov Chains/ (5973)
18. decision model$.ti,ab. (898)
19. or/8-18 (491846)
20. 7 and 19 (7)

Seven records were identified.

Ovid **EMBASE** <1980 to present> Searched 26/01/10

1. exp Respiratory Tract Infections/ (119484)
2. procalcitonin.mp. (1654)
3. 1 and 2 (256)
4. Animals/ (23983)
5. Humans/ (6788099)
6. 4 not (4 and 5) (18181)
7. 3 not 6 (256)
8. Economics/ (6897)
9. exp "costs and cost analysis"/ (134789)
10. "quality of life"/ or "value of life"/ (138186)
11. exp economics, hospital/ (248994)
12. economics, medical/ (11101)

CEP10036: March 2010
Appendix 2: Literature search strategies

13 (econom$ or costs or cost or costly or costing or price or prices or pricing).ti,ab. (247177)
14 (expenditure$ not energy).ti,ab. (10448)
15 (value adj2 money).ti,ab. (517)
16 exp models, economic/ or monte carlo method/ (30390)
17 Markov Chains/ (27641)
18 decision model$.ti,ab. (824)
19 or/8-18 (561493)
20 7 and 19 (26)
21 from 20 keep 4-10,12-13,15-17,20-24 (17)

Seventeen records were identified.

HMIC Health Management Information Consortium Searched 28/01/10

1 exp Respiratory Tract Infections/ (294)
2 procalcitonin.mp. (1)
3 1 and 2 (1)
4 Animals/ (508)
5 Humans/ (8489)
6 4 not (4 and 5) (215)
7 3 not 6 (1)
8 Economics/ (502)
9 exp "costs and cost analysis"/ (0)
10 "quality of life"/ or "value of life"/ (1815)
11 exp economics, hospital/ (0)
12 economics, medical/ (0)
13 (econom$ or costs or cost or costly or costing or price or prices or pricing).ti,ab. (24713)
14 (expenditure$ not energy).ti,ab. (2729)
15 (value adj2 money).ti,ab. (794)
16 exp models, economic/ or monte carlo method/ (3)
17 Markov Chains/ (0)
18 decision model$.ti,ab. (32)
19 or/8-18 (28548)
20 7 and 19 (0)

No records were identified.

HTA (CRD website www.crd.york.ac.uk/crdweb ) Searched 20/01/10

1 Procalcitonin (4)
2 PCT (6)
3 "respiratory tract infections" AND procalcitonin (1)
Appendix 2: Literature search strategies

NHS EED (CRD website www.crd.york.ac.uk/crdweb) Searched 20/01/10

1. Procalcitonin (1)
2. PCT (8)
3. “respiratory tract infections” AND procalcitonin (1)

DARE (CRD website www.crd.york.ac.uk/crdweb) Searched 20/01/10

1. Procalcitonin (11)
2. PCT (10)
3. “respiratory tract infections” AND procalcitonin (1)

Nine records were identified.

In addition, searches were run on the Medline In-Process database.

Search for clinical studies of PCT

Ovid MEDLINE(R) <1950 to present> Searched 26/01/10

1. exp Respiratory Tract Infections/ (240983)
2. procalcitonin.mp. (1334)
3. 1 and 2 (164)
4. Animals/ (4467813)
5. Humans/ (10952773)
6. 4 not (4 and 5) (3333690)
7. 3 not 6 (164)
8. exp "sensitivity and specificity"/ (299057)
9. accuracy.mp. (138253)
10. or/8-9 (402152)
11. 7 and 10 (67)
12. from 11 keep 2,7,9-11,13-14,20-22,24,29-31,34-35,41-42,47-48,51,60(22)

22 records were identified.

Ovid EMBASE <1980 to present> Searched 26/01/10

1. exp Respiratory Tract Infections/ (119484)
2. procalcitonin.mp. (1654)

CEP10036: March 2010
Sixteen records were identified.
The table below shows the key data and methodological quality of each study included in the systematic literature review. The format of the table is based on that recommended in the NICE Guidelines Manual [33]

**Abbreviations**

LRTI: lower respiratory tract infection  
COPD: chronic obstructive pulmonary disease  
ECOPD: exacerbations of chronic obstructive pulmonary disease  
AB: Antibiotic  
PCT: procalcitonin  
RR: relative risk  
ARR: absolute risk reduction  
NNT: number needed to treat  
ARDS: acute respiratory distress syndrome  
ARTI: acute respiratory tract infection  
OR: odds ratio  
CAP: community acquired pneumonia  
SIRS: systemic inflammatory response syndrome

<table>
<thead>
<tr>
<th>Bibliographic reference</th>
<th>Study type, size &amp; quality</th>
<th>Patient Characteristics</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Length of follow up</th>
<th>Outcome measures and effect size</th>
<th>Additional comments</th>
</tr>
</thead>
</table>
| Stolz et al. 2007 [9]   | RCT  
Quality score: ++  
n=226  
Switzerland | Patients age ≥40 years admitted to hospital with ECOPD  
| AB therapy decision made on the basis of PCT test (Kryptor, Brahms), PCT level (ng/ml):  
<0.1: AB discouraged  
0.1-0.25: AB use depending on patient stability  
>0.25 AB encouraged.  
Result available | AB therapy decision made on the basis of current guidelines | 6 months (most outcomes reported during acute phase) | Cultures from sputum yielded pathogenic bacteria as follows: PCT group: 37 (36%)  
Control group: 40 (38%), p=0.886  
Rate of AB use at index exacerbation: PCT group: 40%  
Control group: 72%, p<0.0001  
RR for AB use PCT:Control 0.56 [95%CI 0.43-0.73], p<0.0001  
ARR for AB use: 31.5% [95%CI 18.7-44.3%]; NNT 3.2 [95%CI 2.3-5.3]  
Time to next exacerbation treated with AB (relapse): PCT: 76.7 days  
Control: 76.1 days, p=0.819  
Dichotomous outcome: clinical success | Patients comparable at baseline except that PCT group had statistically significantly lower forced expiratory volume.  
Statistical power calculation performed.  
Investigators blinded to allocation.  
Analysis by intention to treat.  
Source of funding: Clinic of Pulmonary Medicine; the Clinic of Endocrinology, Diabetes and Clinical Nutrition; and the Emergency Department of the University Hospital Basel.  
BRAHMS provided PCT assays for this investigator |
<table>
<thead>
<tr>
<th>Bibliographic reference</th>
<th>Study type, size &amp; quality</th>
<th>Patient Characteristics</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Length of follow up</th>
<th>Outcome measures and effect size</th>
<th>Additional comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bignardi et al. 2006 [25]</td>
<td>Case series (reported as a letter)</td>
<td>Patients with LRTI; 188 ‘care of the elderly’ ward patients and 31 chest medicine patients. UK</td>
<td>within 1 hour. PCT repeated 6-24 hours later in cases where AB withheld</td>
<td>(improvement in symptoms) versus clinical failure (no change or worsening of symptoms): Success rate: PCT: 82.4% Control: 83.9%, p=0.853</td>
<td>driven study.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>n=219</td>
<td>No comparison group</td>
<td>PCT result was &lt;0.25ng/ml in 131 of 219 patients (60%). Of these 121 patients: 42 (35%) continued on AB, 45 (37%) remained off AB, 34 (28%) stopped AB after PCT result</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Authors report:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• other savings (eg through prevention of c difficile and MRSA infections) cannot be easily estimated.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• A cheaper PCT test made available on the same platform for routine laboratory tests would be useful.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• There was a significant amount of inappropriate requesting for PCT</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• The 35% figure for continuation of AB despite low PCT result (in routine care) is higher than 10% reported in a previously published RCT:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schuetz et al. 2009 [8]</td>
<td>RCT, multicentre</td>
<td>n=1381 Age &gt;18 with</td>
<td>PCT test (Brahms Kryptor): AB use in accordance with</td>
<td>Primary outcome: noninferiority of PCT-based AB use, defined as a maximum difference in the rate of adverse</td>
<td>Concealment of computer-based random allocation. Physicians not blinded when</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Outcomes assessed within a</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CEP10036: March 2010
## Appendix 3: Evidence table

<table>
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<tr>
<th>Bibliographic reference</th>
<th>Study type, size &amp; quality</th>
<th>Patient Characteristics</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Length of follow up</th>
<th>Outcome measures and effect size</th>
<th>Additional comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>physicians trained to apply study algorithm using web-based system. PCT level (ng/ml):</td>
<td>published guidelines</td>
<td>30 day period</td>
<td>outcome between groups of 7.5%. Adverse outcome defined as death, pneumonia, lung abscess, empyema, ARDS, LRTI recurrence in need of AB. Secondary outcomes: AB use, adverse events due to AB (nausea, diarrhoea, rash), length of hospital stay.</td>
<td>assessing outcome. Groups were similar at baseline for demographic and LRTI-related variables. 22 patients withdrew consent and left the trial. Analysis by intention to treat. Source of funding: Swiss National Science Foundation, Sante' Suisse, Gottfried and Julia Bangerter-Rhyner-Foundation, University Hospital Basel, Medical University Clinic Liestal, Medical Clinic Buergerspital Solothurn, Cantonal Hospitals Muensterlingen, Aarau and Lucerne, Swiss Society for Internal Medicine, Department of Endocrinology, Diabetology and Clinical Nutrition, University Hospital Basel. BRAHMS Inc, provided all assay-related material, Kryptor machines if not already available onsite, and kits and maintenance required for 10 000 measurements related to the study.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;0.1: AB strongly discouraged</td>
<td></td>
<td></td>
<td>PCT: 103 (15.4%) Control: 130 (18.9%) Risk difference: -3.5% [95% CI -7.6% to 0.4%]</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;0.25: AB discouraged</td>
<td></td>
<td></td>
<td>Mean AB exposure (days): PCT: 5.7 Control: 8.7 Relative risk reduction: -34.8% [95% CI - 40.3% to -28.7%]</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt;0.25: AB encouraged</td>
<td></td>
<td></td>
<td>AB prescription rate: PCT: 506 (75.4%) Control: 603 (87.7%) Relative risk reduction: -12.2 [95% CI - 16.3 to -8.1]</td>
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<td>&gt;5: AB strongly encouraged</td>
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<td></td>
<td>AB adverse event rate: PCT: 133 (19.8%) Control: 193 (28.1%) Relative risk reduction: -8.2 [95% CI -12.7 to -3.7]</td>
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<td>For patients with initial PCT &gt;10, the algorithm recommended stopping AB when PCT decreased by 80% and strongly recommended stopping AB when PCT decreased by 90%</td>
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<td></td>
<td>Mean length of hospital stay (days): PCT: 9.4 Control: 9.2 Relative risk reduction 1.8 [95% CI -6.9 to 11.0]</td>
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<td>PCT test repeated at 6-24 hours and at 3, 5 and 7</td>
<td></td>
<td></td>
<td>30 day period</td>
<td>PCT and Control groups were similar at baseline for demographic and LRTI-related variables. 22 patients withdrew consent and left the trial. Analysis by intention to treat. Source of funding: Swiss National Science Foundation, Sante' Suisse, Gottfried and Julia Bangerter-Rhyner-Foundation, University Hospital Basel, Medical University Clinic Liestal, Medical Clinic Buergerspital Solothurn, Cantonal Hospitals Muensterlingen, Aarau and Lucerne, Swiss Society for Internal Medicine, Department of Endocrinology, Diabetology and Clinical Nutrition, University Hospital Basel. BRAHMS Inc, provided all assay-related material, Kryptor machines if not already available onsite, and kits and maintenance required for 10 000 measurements related to the study.</td>
</tr>
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</table>
## Appendix 3: Evidence table

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0.1-0.25: AB not recommended  
>0.25: AB recommended  
PCT test was repeated at 6-24 hours (when AB withheld) and at 3 days (when AB given). | Standard prescribing based on evidence-based guidelines | 28 days | In the PCT group, adherence by physicians to the algorithm was 85%  
No. of days during which normal activities (work or recreation) were disrupted due to ARTI:  
PCT: 8.7 days  
Control: 8.6 days  
Adjusted difference: 0.1 days [95%CI -0.6 to 0.8 days]; ITT analysis  
AB prescription rate: no. patients (%)  
PCT: 58 (25%)  
Control: 219 (97%)  
OR 0.01 [95%CI 0.002 to 0.02]  
Duration of AB treatment (days)  
PCT: 6.2  
Control: 7.1  
Adjusted difference -1.0 [95%CI -2.1 to -0.1]  
AB adverse effect rate  
PCT: 2.3  
Control: 3.6  
Adjusted difference -1.1 [95%CI -2.1 to -0.1]  
Degree of discomfort from ARTI marked on scale of 0-10 (10 being a great deal of discomfort)  
PCT: 1.9  
Control: 1.1  
Adjusted difference 0.8 [95%CI 0.4 to 1.2]  
Days with adverse effects of AB  
PCT: 2.3  
Control: 3.6  
Adjusted difference -1.1 [95%CI -2.1 to -0.1]  
Study population includes patients with upper respiratory tract infections (eg common colds, tonsillitis).  
Random allocation by central, computerised process.  
Groups were similar at baseline.  
Data collection performed by blinded medical students (physicians unblinded).  
Analyses are a mixture of intention to treat and per protocol analyses  
Source of funding: Swiss National Science Foundation, Association for the Promotion of Science and Postgraduate Training of the University Hospital Basel, Sante'Suisse, Solothurn, Switzerland, Gottfried and Julia Bangerter-Rhyner-Foundation, Berne, Switzerland. Freiwillige Akademische Gesellschaft, Department of Endocrinology, Diabetology, and Clinical Nutrition and the Department of Clinical Chemistry, University Hospital Basel. Brahms AG. |
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<td>Christ-Crain et al. 2004 [6]</td>
<td>RCT</td>
<td>Patients with LRTI, excluding those with hospital acquired pneumonia, Switzerland.</td>
<td>n=243</td>
<td>PCT test using Brahms Kryptor assay: Physicians had to state whether they intended to prescribe AB before using the PCT algorithm. PCT level (ng/ml): &lt;0.1: AB strongly discouraged 0.1-0.25: AB discouraged 0.25-0.5: AB advised &gt;0.5 AB strongly advised PCT test was repeated at 6-24 hours</td>
<td>Standard prescribing based on evidence-based guidelines</td>
<td>Use of AB was the intended action at outset in 83% of the control group and 80% of the PCT group; p=0.5.</td>
<td>Single blinded study. Cluster random allocation by computer program Analysis is by intention to treat Quality of life score not fully described Losses to follow up: PCT: 5 Control: 8</td>
</tr>
</tbody>
</table>

Days of work missed PCT: 4.9 Control: 4.8 Adjusted difference 0.3 [95%CI -0.6 to 1.2]
No. patients reporting persistent or recurrent ARTI within 28 days PCT: 69 Control: 67 Adjusted OR 1.0 [95%CI 0.7 to 1.5]

Length of hospital stay (days): Control: 10.8 PCT: 13.7; p=0.25 There were no statistically significant differences between groups for quality of

Cost of AB treatment per patient (US$): Control: 202.5 PCT: 96.3; p<0.0001

Commonest ABs used were: Amoxicillin-clavulanate (n=108) Clarithromycin (n=53) Ceftriaxone (n=33) Others (n=64)

Duration of AB treatment (days): Control: 12.8 PCT: 10.9; p=0.03

AB prescription rate: Control: 90 (83%) PCT: 55 (44%); p<0.0001
RR of AB treatment PCT:Control, adjusted for confounding factors and cluster effects: 0.49 [95%CI 0.44-0.55]; p<0.0001

Outcomes assessed at 10-14 days after inclusion. Patients followed up for further events for 6 months.
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<td>Christ-Crain et al. 2006 [7]</td>
<td>RCT</td>
<td>Patients with CAP Switzerland.</td>
<td>n=302</td>
<td>PCT test using Brahms Kryptor assay: PCT level (ng/ml): &lt;0.1: AB strongly discouraged 0.1-0.25: AB discouraged 0.25-0.5: AB advised &gt;0.5 AB strongly advised</td>
<td>PCT test was repeated at 6-24 hours (when AB withheld) and at 4, 6 and 8 days. ABs were discontinued using the same threshold PCT values. For patients with initial PCT &gt;10, the algorithm</td>
<td>Outcomes assessed at days 4, 6 and 8 and at 6 weeks.</td>
<td>AB pre-treatment: PCT: 27 Control: 34 A causative bacterial microorganism was identified in 80 patients overall (28%). AB prescription rate: PCT: 128 (85%) Control: 149 (99%); p&lt;0.001 AB therapy duration (days): PCT: 5.8 Control: 12.9; p&lt;0.001 AB cost per patient (US$) PCT: 100 Control: 190; p&lt;0.001 Treatment success rate: PCT: 84% Control: 82%; p&lt;0.65</td>
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<td>Muller et al. 2007 [26]</td>
<td>Retrospective diagnostic study (pre-planned analysis of patients recruited into two different RCTs listed above [6,7]. Quality score: retrospective analysis)</td>
<td>n=373 Patients with final diagnosis of CAP. Switzerland</td>
<td>PCT test as defined above in two RCTs [6,7]</td>
<td>Other diagnostic parameters.</td>
<td>Based on follow up in two RCTs [6,7]</td>
<td>To predict bacteremia in patients with CAP, PCT had an area under the ROC curve (accuracy) of 0.85 [95%CI 0.80 to 0.91]. Q point inferred from ROC curve as 0.75 (ie optimal sensitivity/specificity).</td>
<td>Patients are derived from two trials. The reference standard used in this study is final diagnosis at follow-up, based on a battery of investigations, including growing cultures from respiratory specimens, blood, and urine samples, and by ruling out bacterial CAP in cases of negative culture or in cases where the patient recovers without antibiotic therapy. Of 373 patients with CAP as final diagnosis, 42 (11.3%) had blood culture confirmed bacteremia. It is not reported whether all 373 patients underwent blood culture; methods may assume that they did. Source of funding: as per two studies above [6,7].</td>
</tr>
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</table>

Recommended stopping AB when PCT decreased by 90%.

Stiftung Forschung Infektionskrankheiten (SFI), and, mainly, from the Departments of Endocrinology and Pulmonary Medicine, University Hospital Basel, Switzerland.
Economic report: Procalcitonin to differentiate bacterial lower respiratory tract infections from non-bacterial causes

Andrew Cleves, Joelle Williams, Grace Carolan-Rees

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For more information on CEDAR and our earlier reports visit
www.cedar.wales.nhs.uk

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