Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The study examined a hospital protocol for the appropriate use of antibiotics in lower respiratory tract infections. The protocol was based on the use of procalcitonin levels, to rapidly and accurately differentiate clinically relevant bacterial lower respiratory tract infections from viral causes, in order to combat the increase of antibiotic-resistant microorganisms. A serum procalcitonin concentration of:

- 0.1 microg/L or less indicated an absence of bacterial infection, and the use of antibiotics was strongly discouraged;
- 0.1 - 0.25 microg/L indicated that bacterial infection was unlikely, and the use of antibiotics was discouraged;
- 0.25 - 0.5 microg/L indicated a possible bacterial infection, and the treating doctor was advised to initiate antimicrobial treatment;
- 0.5 microg/L or greater was judged suggestive of the presence of bacterial infection, and antibiotic treatment was strongly recommended.

For patients on antimicrobial therapy at the time of hospital admission, discontinuation of antibiotics was recommended if the procalcitonin concentration was less than 0.25 microg/L.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients admitted to the hospital with cough and/or dyspnoea, and a suspected lower respiratory tract infection as the main diagnosis. Lower respiratory tract infection included pneumonia, chronic obstructive pulmonary disease (COPD), acute bronchitis and asthma. Definitions of pneumonia, COPD, acute bronchitis and asthma were reported in detail. Severely immunocompromised patients (i.e. those with human immunodeficiency virus infection and a CD4 count less than 200 cells/mL) were excluded, as were neutropenic patients and stem-cell transplant recipients. Also excluded were those with cystic fibrosis or active tuberculosis, and individuals with nosocomial pneumonia.

Setting
The setting was a hospital (academic tertiary care hospital). The economic study was carried out in Switzerland.

Dates to which data relate
The effectiveness and resource use data were gathered between 16 December 2002 and 13 April 2003. The price year
was not reported.

**Source of effectiveness data**
The effectiveness evidence was derived from a single study.

**Link between effectiveness and cost data**
The costing was carried out prospectively on the same sample of patients as that included in the effectiveness study.

**Study sample**
Power calculations were carried out in the planning phase of the study. These suggested that a sample of 105 patients with completed follow-up in each group would have given the study 95% power to detect a 30% reduction in antibiotic exposure. Of the 597 patients presenting with dyspnoea and/or cough, 243 (41%) were eligible and were included in the study. Reasons why patients were excluded from the study groups were reported in detail. There were 119 patients (51% men) in the standard group and 124 (54% men) in the intervention group. The patients in the standard group had a mean age of 65.3 (+/- 17.3) years and 18% had received antibiotic pre-treatment. The patients in the intervention group had a mean age of 62.8 (+/- 19.8) years and 23% had received antibiotic pre-treatment.

**Study design**
This was a prospective, cluster-randomised, controlled, single-blinded intervention trial that was carried out at the University Hospital in Basel, Switzerland. The patients were blinded to their study group, whereas the doctors were not (i.e. they were aware of the patient's treatment). Patients were allocated to the study groups on the basis of a computer-generated weekly randomisation scheme. The length of follow-up was 10 to 14 days, but the sub-group of 60 patients with acute exacerbations of COPD was followed for 4 to 6 months. Five patients in the control group and 8 patients in the intervention group were lost to the follow-up assessment.

**Analysis of effectiveness**
The analysis of the clinical study was conducted on an intention to treat basis. The primary outcome measure was antibiotic usage. The secondary outcome measures were:

- quality of life score,
- visual analogue scale,
- body temperature,
- white-blood-cell count,
- C-reactive protein,
- procalcitonin,
- the number of patients admitted,
- the number of days admitted,
- the number of patients requiring stay in an intensive care unit (ICU), and
- the number of patients who died during the follow-up.

The results were presented for the whole sample and for the sub-group of patients with COPD. The study groups were comparable at baseline in terms of their demographic and clinical characteristics.
Effectiveness results
The rate of antibiotic prescription foreseen was 83% in the control group and 80% in the intervention group, (p=0.50).

The rate of antibiotics prescribed was 83% in the control group and 44% in the intervention group, (p<0.0001).

The duration of antibiotic treatment was 12.8 (+/- 5.5) days in the control group and 10.9 (+/- 3.6) days in the intervention group, (p=0.03).

The mean antibiotic use per 1,000 days of follow-up was 661 (+/- 398) in the control group and 332 (+/- 433) in the intervention group, (p<0.0001).

The relative risk of antibiotic exposure in patients with lower respiratory tract infections in the procalcitonin group was 0.39 (95% confidence interval, CI: 0.36 - 0.42; p<0.0001). The absolute risk reduction was 50% (95% CI: 47 - 53; p<0.0001).

After adjusting for potential confounding factors and possible cluster-effects, the relative risk of antibiotic exposure in the procalcitonin group was 0.49 (95% CI: 0.44 - 0.55; p<0.0001).

The analysis showed that most infections were of viral nature.

In the standard group, the odds of being treated with antibiotics increased by 6.5% with every additional year of age (95% CI: 3.4 - 9.8; p<0.0001). Conversely, in the procalcitonin group, no such age relation could be found (95% CI: -1.2 - 2.4; p=0.53).

The other clinical outcomes were comparable between groups since none of the differences reached statistical significance.

A sub-group analysis showed that antibiotic use was significantly reduced in all diagnostic sub-groups. In particular, in the sub-group of patients with COPD, the rate of antibiotics prescribed was 87% in the control group and 38% in the intervention group, (p<0.0001). The mean antibiotic use per 1,000 days of follow-up was 689 (+/- 369) in the control group and 269 (+/- 414) in the intervention group, (p<0.0001). Again, the other clinical outcomes were similar between the two groups.

Clinical conclusions
The effectiveness analysis showed that the guidelines significantly reduced antibiotic use without affecting other aspects of health and health care.

Measure of benefits used in the economic analysis
The health outcomes were left disaggregated and no summary benefit measure was used in the economic evaluation. In effect, a cost-consequences analysis was carried out.

Direct costs
The perspective adopted in the study was not stated. Only the costs of antimicrobial agents used during hospital stay were taken into consideration. The unit costs were not presented separately from the quantities of resources used. Resource use was based on data derived from the sample of patients included in the clinical trial. The costs came from average wholesale prices of antimicrobial agents in Switzerland. Discounting was not relevant since the costs per patient were incurred during a short timeframe. The price year was not reported.

Statistical analysis of costs
A standard statistical test was used to test the statistical significance of cost-differences.
**Indirect Costs**
The indirect costs were not considered.

**Currency**
US dollars ($). The exchange rate from US dollars to Swiss francs (CHF) was $1 = CHF 1.34.

**Sensitivity analysis**
Sensitivity analyses were not carried out.

**Estimated benefits used in the economic analysis**
See the 'Effectiveness Results' section.

**Cost results**
In the whole sample, the average antibiotic costs per patient were $202.5 (+/- 250.6) in the control group and $96.3 (+/- 172.8) in the intervention group, (p<0.0001).

In the sub-group of patients with COPD, the average antibiotic costs per patient were $101.4 (+/- 75.9) in the control group and $64.7 (+/- 105.4) in the intervention group, (p<0.01).

**Synthesis of costs and benefits**
A synthesis of the costs and benefits was not relevant as a cost-consequences analysis was carried out.

**Authors' conclusions**
The implementation of guidelines for the appropriate use of antibiotics in patients admitted with a suspected lower respiratory tract infection led to a reduced use of antibiotics and cost-savings, without affecting the patients' health.

**CRD COMMENTARY - Selection of comparators**
The selection of the comparator was appropriate as it reflected the standard approach for the treatment of patients suspected of having lower respiratory tract infections. You should decide whether this represents a valid comparator in your own setting.

**Validity of estimate of measure of effectiveness**
The effectiveness evidence came from a well-conducted clinical trial. The method of randomisation was reported and the sample selection was extensively described. Details of the inclusion criteria and loss to follow-up were also reported. The use of random allocation and blinding should limit the impact of confounding factors and selection or assessment bias. The authors noted that the treating physicians were aware of the patient's treatment group, which might have affected the conclusions of the analysis. Power calculations were carried out to ensure the appropriate size of the sample. However, sample size calculations referred to the main outcome measure, whereas the statistical significance of differences in other clinical outcomes was not assessed on the basis of power calculations. Statistical analyses were carried out to adjust some clinical estimates, and sub-group analyses were also carried out. Few patients were lost to follow-up, and the analysis was conducted on an intention to treat basis. These issues tend to enhance the robustness of the analysis. The evidence came from a single study, thus caution is required since the study sample might not be completely representative of the patient population.

**Validity of estimate of measure of benefit**
No summary benefit measure was used in the analysis because a cost-consequences analysis was conducted. Please refer
to the comments in the 'Validity of estimate of measure of effectiveness' field (above).

Validity of estimate of costs
The analysis of the costs was very limited since only the costs of antimicrobial therapy were considered. The cost analysis did not take other important categories of costs, such as those associated with hospital stay, into account. The source of the costs was reported, whereas information on the unit costs and quantities of resources used was not. This limits the possibility of replicating the results of the analysis in other settings. The cost estimates were specific to the study setting and statistical analyses were carried out only to test the significance of cost-differences. The price year was not reported, which makes reflation exercises in other time periods difficult.

Other issues
The authors did not make extensive comparisons of their findings with those from other studies. They also did not extensively address the issue of the generalisability of the study results to other settings. In effect, sensitivity analyses were not carried out and this reduces the external validity of the study. However, the authors stated that there are large differences in antibiotic prescribing patterns among countries, and that the prescription rate might be lower in Switzerland than in other countries such as France or the USA. The study referred to patients with suspected lower respiratory tract infections and this was reflected in the authors’ conclusions.

Implications of the study
The study results suggested that procalcitonin levels might safely and efficiently be used to guide decisions about antibiotic usage in patients with suspected lower respiratory tract infections.

Source of funding
Supported by Freiwillige Akademische Gesellschaft Basel, and the Department of Internal Medicine and the Divisions of Endocrinology and Pneumology.

Bibliographic details

PubMedID
14987884

DOI
10.1016/S0140-6736(04)15591-8

Other publications of related interest


Indexing Status
Subject indexing assigned by NLM
MeSH
Acute Disease; Aged; Anti-Bacterial Agents /therapeutic use; Bacterial Infections /blood /drug therapy; Bronchitis /blood /drug therapy; Calcitonin /blood; Drug Utilization Review; Female; Humans; Male; Middle Aged; Pneumonia /blood /drug therapy; Protein Precursors /blood; Pulmonary Disease, Chronic Obstructive /blood /drug therapy; Respiratory Tract Infections /blood /drug therapy /microbiology; Single-Blind Method; Treatment Outcome

AccessionNumber
22004008091

Date bibliographic record published
31/05/2006

Date abstract record published
31/05/2006