Inpatient care of community-acquired pneumonia: the effect of antimicrobial guidelines on clinical outcomes and drug costs in Canadian teaching hospitals

Marras T K, Jamieson L, Chan C K

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 use of antimicrobial guidelines for the treatment of community-acquired pneumonia (CAP) was investigated before and after their revision (1993 Canadian Thoracic and Infectious Diseases Societies' empirical antibiotic guidelines and 1998 Infectious Diseases Society of America guidelines, respectively). The revised guidelines included the use of respiratory quinolones (e.g. levofloxacin).

The study also investigated the use of different types of antimicrobials, in particular, quinolone monotherapy, cephalosporin monotherapy, cephalosporin plus macrolide, macrolide monotherapy, and an anaerobic regimen.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with pneumonia and potentially overlapping diagnostic codes, including chronic bronchitis, emphysema and asthma. Eligible cases required at least one symptom (dyspnoea, cough, or fever), a consistent radiograph and antibiotic treatment for CAP.

Setting
The study setting was tertiary care. The economic study was carried out at the University of Toronto, Canada.

Dates to which data relate
The effectiveness and resource use were gathered between November 1997 and June 2000. The early cohort period was from November 1997 to October 1998, while the recent cohort period was from November 1998 to June 2000. The price year was 2000.

Source of effectiveness data
The effectiveness data were derived from a single study.

Link between effectiveness and cost data
The costing was undertaken retrospectively on the same patient sample as that used in the effectiveness study.

Study sample
Owing to resource limitations, the authors could only review 70% of cases admitted during each time period. The authors explicitly reported that no power calculations were performed. Hence, 1,682 (72%) of the 2,324 potentially eligible cases were reviewed, and 984 found to be ineligible. Reasons for ineligibility were recent hospital discharge (416 cases; 42%), co-existing infection (342 cases; 35%), symptomatic or radiographic criteria for CAP were not met (108 cases; 11%) and immune suppressed (118 cases; 12%). Of the 698 eligible cases identified and reviewed in full, 280 were cases treated before the guidelines were revised. The remaining 418 cases were treated after the guidelines were revised. The median age for guideline adherent cases was 78 years in the early and recent cohort groups. The proportion of females in each of these two groups was 42% (early cohort) and 37% (recent), respectively.

Of the 636 guideline-adherent cases, 254 (100 females) were treated with quinolone monotherapy, 229 (77 females) with cephalosporin monotherapy, 96 (38 females) with cephalosporin plus macrolide, 26 (11 females) with macrolide monotherapy, and 58 (28 females) with an anaerobic regimen. The median ages in these groups were, respectively, 77, 78, 80, 64 and 82 years.

Study design
This was a retrospective cohort study that was undertaken in two tertiary care sites affiliated to the University of Toronto, Canada. The length of follow-up was 42 days, as the authors assumed that events after 42 days were unlikely to be directly related to the CAP episode, an assumption supported by published literature. As this was a retrospective cohort study there was no loss to follow-up.

Analysis of effectiveness
All of the patients included in the study were accounted for in the analysis. The primary outcomes used were the proportion of guideline adherent cases in each cohort group, and the mortality rate for each guideline group (i.e. early or recent) and for each antibiotic therapy group. No significant differences in baseline characteristics were found between the two guideline groups. However, between the various antibiotic therapy groups, significant differences were found in age, proportion in long-term care, pneumonia severity and time to first antibiotic dose. Consequently, multivariable analyses were undertaken by controlling for pneumonia severity index (PSI) score and study site. To avoid overfitting, fewer than 10 explanatory variables per number of subjects or number of outcomes were introduced.

Effectiveness results
Comparison between guideline groups (i.e. between cases treated before guideline revision and cases treated after revision).

Overall, 636 cases (91%) were treated according to the guidelines, with a non significant increase in adherence between the early and recent periods (89 to 92%; p=0.20).

In the early cohort, 26 (10.4%) guideline-adherent cases died, but no deaths occurred in the guideline-discordant group, (p=0.09). In the recent cohort, 34 (8.8%) guideline-adherent cases died and 4 (12.5%) guideline-discordant cases died, (p=0.52).

Overall, in guideline-adherent patients, there was no difference in mortality between early and recent guidelines cohorts, (p=0.59).

Analysis by empirical antibiotic regimen.

The number of deaths was 17 (7%) with quinolone monotherapy, 12 (5%) with cephalosporin monotherapy, 17 (18%) with cephalosporin plus macrolide, 1 (4%) with macrolide monotherapy and 14 (24%) with an anaerobic regimen. These differences were statistically significant across all groups, (p<0.0001).

To assess the specific impact of different empirical antibiotic regimens, multivariable modelling of mortality was performed. After controlling for other confounding factors, patients receiving empirical cephalosporin plus a macrolide, or coverage for anaerobics, had significantly higher mortality.
When cephalosporin monotherapy was used as the reference, the mortality odds ratio was 2.7 (95% confidence interval, CI: 1.2 - 6.4; p=0.02) for cephalosporin plus macrolide, and 2.7 (95% CI: 1.2 - 6.5; p=0.001) for the anaerobic regimen.

**Clinical conclusions**
There were no statistically significant differences in mortality rates between cases treated with the old guidelines and those treated with revised guidelines, which included respiratory quinolones. However, when considering antibiotic therapy group, patients treated with cephalosporin plus macrolide, or an anaerobic regimen, had significantly higher mortality rates. However, the authors reported that these associations were due to PSI scores providing incomplete prognostic information.

**Measure of benefits used in the economic analysis**
The authors did not derive a measure of health benefit. The analysis was, in effect, a cost-consequences study.

**Direct costs**
The direct costs of the hospital were included in the analysis, and only those of the antibiotics were actually included. These represented hospital drug acquisition prices. The authors did not include nursing time, intravenous equipment, or preparation costs. Discounting was not relevant, as all the costs were undertaken during a short time, and hence was not performed. The costs and the quantities were not reported separately. The study reported the average costs. The price year was 2000.

**Statistical analysis of costs**
The costs were treated stochastically. The costs of guideline groups were compared with t-tests or Mann Whitney U-tests. Differences between antimicrobial regimens were analysed using analyses of variance or Kruskall-Wallis tests. Multivariable analyses were also undertaken.

**Indirect Costs**
The indirect costs were not included in the study.

**Currency**
Canadian dollars (Can$).

**Sensitivity analysis**
Sensitivity analyses were not performed.

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

**Cost results**
Comparison between guideline groups (i.e. between cases treated before guideline revision and cases treated after revision).

In the early cohort, the median antibiotic cost was Can$84.00 (quartiles: $50.01 - 148.68) for guideline-adherent cases and Can$91.18 (quartiles: 49.23 - 185.44) for guideline-discordant cases, (p=0.64). In the recent cohort, the median antibiotic cost was Can$63.00 (quartiles: 30.58 - 107.96) for guideline-adherent cases and Can$85.56 (quartiles: 29.42 - 174.82) for guideline-discordant cases, (p=0.23). Overall, in guideline-adherent patients, the antibiotic costs were significantly lower in the recent cohort than in the early cohort, (p<0.0001).
Analysis by empirical antibiotic regimen.

The median antibiotic cost was Can$49.65 (quartiles: 24.00 - 79.00) for quinolone monotherapy, Can$72.12 (quartiles: 43.14 - 104.28) for cephalosporin monotherapy, Can$156.96 (quartile: 98.08 - 256.58) for cephalosporin plus macrolide, Can$27.02 (quartiles: 13.40 - 46.91) for macrolide monotherapy and Can$176.56 (quartiles: 98.01 - 288.48) for the anaerobic regimen. These differences were statistically significant across all groups, (p<0.0001).

To assess the specific impact of different empirical antibiotic regimens, multivariable modelling of antibiotic costs was performed. After control for other confounding factors, patients receiving empirical cephalosporin plus a macrolide had significantly higher antibiotic costs, while those receiving quinolone monotherapy incurred significantly lower antibiotic costs. When cephalosporin monotherapy was used as the reference, the antibiotic cost-difference was Can$91.35 (95% CI: 61.42 - 128.33; p<0.001) for cephalosporin plus macrolide and -Can$19.19 (95% CI: -11.41 - -25.85; p<0.0001) for quinolone monotherapy.

Synthesis of costs and benefits
The costs and benefits were not combined.

Authors' conclusions
The use of recent empirical treatment guidelines for community-acquired pneumonia (CAP), including respiratory quinolones, was associated with favourable outcomes, lower drug costs and simpler antibiotic regimens. The association between mortality and certain empirical antibiotic combinations suggested that the pneumonia severity index (PSI) provided incomplete prognostic information.

CRD COMMENTARY - Selection of comparators
The reason for the comparators used was given. Earlier guidelines had represented current practice in the authors’ setting. You should decide if the comparator represents current practice in your own setting.

Validity of estimate of measure of effectiveness
The analysis was based on a retrospective cohort study that was undertaken in two different time periods. This type of study design was appropriate for the study question, as the two different guidelines were introduced in different time periods. However, these studies have important limitations. For example, external factors changing over time (such as management changes, clinical practice, environmental or seasonal changes) might explain differences in the outcomes rather than the intervention. The study sample appears to have been representative of the study population, but over 40% of potentially eligible cases were not reviewed. The patient groups in each guideline were shown to be comparable, whereas patients in the antibiotic treatment groups were not. The antibiotic therapy groups differed in terms of age, time to first antibiotic, pneumonia severity and residence (i.e. long-term care). The authors undertook appropriate statistical analyses to account for these potential confounding factors.

Validity of estimate of measure of benefit
The authors did not derive a summary measure of health benefit. The analysis was, in effect, a cost-consequences study. The comments in the ‘Validity of estimate of measure of effectiveness’ field (above) therefore apply.

Validity of estimate of costs
The authors did not report the perspective adopted in the economic analysis. They only included antibiotic costs in their analysis, which represented hospital drug acquisition prices. Therefore, this cost analysis was very limited. The costs and the quantities were not reported separately, which will limit the generalisability of the authors’ results. Appropriate statistical analyses of the costs were undertaken to determine statistically significant differences in the costs, and also to control for bias and confounding factors. Discounting was unnecessary since all the costs were incurred during a short time. The price year was reported, which will aid future inflation exercises.
Other issues
The authors reported that prospective trials assessing guideline adherence impact on clinical outcomes had not been performed. However, observational studies of previous guidelines for CAP treatment had generally not shown adherence to produce significant improvements in clinical outcomes. The issue of generalisability to other settings was not addressed. The authors do not appear to have presented their results selectively and their conclusions reflected the scope of the analysis. The authors reported a number of further limitations to their study. First, it might have been underpowered to detect an association between guideline adherence and mortality. Second, the association between certain antibiotic therapies and mortality might relate to the presence of an unknown confounder. The authors reported that, given the higher illness severity in patients receiving the "high risk" antibiotic combinations, it was likely that other confounding factors were the cause. Hence, the authors reported that the non-randomised nature of their study was an important limitation.

Implications of the study
The findings of the present study supported the use of recent empirical treatment guidelines for CAP, including respiratory quinolones, on the basis of improved health outcomes, lower cost and simplicity in application. The authors believed, however, that prospective studies are needed to identify other potentially prognostic factors of CAP.

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