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Major article

Empirical therapies among adults hospitalized for community-acquired upper urinary tract infections: A decision-tree analysis of mortality, costs, and resistance

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Background: Poor outcomes occur when patients with serious infections receive antibiotics to which the organisms are resistant.
Methods: Decision trees simulated in-hospital mortality, costs, incremental cost-effectiveness ratio per life year saved, and carbapenem resistance according to 3 empirical antibiotic strategies among adults hospitalized for community-acquired (CA) upper urinary tract infections (UTIs): ceftriaxone (CRO) plus gentamicin (GM) in the intensive care unit (ICU), imipenem (IMP), and individualized choice (IMP or CRO) based on clinical risk factors for CA- extended-spectrum β-lactamase (ESBL).
Results: The estimated prevalence of CA-ESBL on admission was 5% (range, 1.3%-17.6%); 3% and 97% were admitted to the ICU and medical ward (MW), respectively. In the ICU, CRO plus GM was dominated; IMP was cost-effective (incremental cost-effectiveness ratio: €4,400 per life year saved compared with individualized choice). In the MW, IMP had no impact on mortality and was less costly (−€142 per patient vs CRO, −€38 vs individualized choice). The dominance of IMP was consistent in sensitivity analyses. Compared with CRO, colonization by carbapenem-resistant pathogens increased by an odds ratio of 4.5 in the IMP strategy.
Conclusion: Among the ICU patients, empirical IMP therapy reduces mortality at an acceptable cost. Among MW patients, individualized choice or CRO is preferred to limit carbapenem resistance at a reasonable cost.

Poor outcomes occur when patients with serious infections caused by extended-spectrum β-lactamase (ESBL)–producing organisms are treated with antibiotics to which the organisms are resistant.[1-3] Carbapenems, which are not affected by ESBLs, are considered the drugs of choice for treating severe infections caused by ESBL producers. However, carbapenem-resistant *Enterobacteriaceae*, which produce plasmid-encoded carbapenemases (eg, *Klebsiella pneumoniae carbapenemase*, New Delhi Metallo-Beta-Lactamase, oxacillinase-48), are a potential major global health problem.[4] Therefore, the individual benefit of selecting an appropriate empirical antibiotic therapy should be balanced against the ecologic impact of using last-line antibiotics and costs, in particular for the treatment of upper urinary tract

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infection (UTI), which is frequent and associated with a low mortality.

In our study we developed a decision analytic model to evaluate the effectiveness, ecologic impact, and cost-effectiveness of different empirical antibiotic therapies administered to patients hospitalized for UTIs.

METHODS

Target population

The target cohort for our decision model comprised adults presenting at an emergency department who required hospitalization for UTI. Within the case mix of subjects hospitalized for UTI, mortality varies from <1% for community-acquired UTI admitted to the medical wards (MWs)[5] to 20% for patients with community-acquired UTI admitted in the intensive care units (ICUs).[6,7] Therefore, in our analysis, the 2 populations (ICU vs MW) were separated. In the target population, we estimated that 3% and 97% of UTI patients were hospitalized in the ICU and MW, respectively (Supplemental Appendix 1; Fig 1). We excluded patients who were discharged from the emergency department from our analysis.[8]

Decision model

We used the standard computer program TreeAge Pro 2008 (TreeAge Software, Williamstown, MA) to construct 2 decision trees to model the effects of 3 different empirical antibiotic treatment strategies on an hypothetical cohort according to the initial severity of the infection (Supplemental Appendix 2; Fig 2).

Comparators

Three initial, intravenously administered empirical treatment strategies that are in accordance with current Infectious Diseases Society of America treatment[9] and French guidelines for patients with UTI requiring hospitalization were explored. They include the following: (1) ceftriaxone (CRO) plus a single dose of gentamicin in the ICU; (2) imipenem (IMP); and (3) an individualized empirical strategy based on a patient's clinical risk factors, restricting IMP use to patients at risk for harboring ESBL-producing *Escherichia coli*. We used the predictive score developed and validated by Tumbarello et al,[10] with a threshold of ≥3 points in ICU patients (sensitivity, 93%; specificity, 62%) and ≥6 points in MW patients (sensitivity, 63%; specificity, 95%) considered to have significant clinical risk factors for harboring ESBL-producing *E coli*. Briefly, the score contains 2 major risk factors (3 points, namely prior hospitalization <12 months and admission from another health care facility) and 4 minor risk factors (2 points, namely a Charlson comorbidity score ≥4, β-lactam or quinolone use <3 months, urinary catheter <30 days, and age ≥70 years). Different thresholds were used for ICUs and MWs to reduce inappropriate treatment by increasing the sensitivity in ICUs and to reduce IMP exposure by increasing the specificity in MWs. Positive and negative predictive values were computed from the sensitivity, specificity, and information on the community-acquired extended spectrum betalactamase prevalence in the target population, using Bayes' theorem. Other alternative drugs such as those combined with β-lactamase inhibitors conferring a potential anti-ESBL activity were not considered because they are not recommended.

Data and assumptions

Table 1 presents the base-case probability estimates and the ranges tested in the sensitivity analyses.

The data sources used to derive the probability estimates and costs of care in the decision tree included data published until October 1, 2014, including systematic reviews and meta-analyses (Supplemental Appendix 2), data collected in the COLIBAFI cohort[11] and the OUTCOMEREA,[7] and data from French hospital databases from the *Etude Nationale des Coûts* (http://www.atih.sante.fr/) with code 11M04 for kidney and urinary tract infections (corresponding to code 590 of the ICD-9-CM classification) and code 18M07 for septicemia (corresponding to code 038 of the ICD-9-CM classification). In the absence of available data, expert opinions were also used. We obtained direct costs of drugs in euros (2012 €, multiply by 1.11 to convert to US$) from the pharmacy and billing departments at Caen University Hospital.

In the ICU, when the bacteria responsible for UTI were resistant to CRO but susceptible to gentamicin in the CRO strategy, we considered the empirical treatment was appropriate.[12] We considered that urine samples were systematically collected and that de-escalation of empirical therapy was always performed after 48 hours (ie, switch to CRO in the IMP strategy if the bacteria responsible for the UTI were sensitive to CRO).

Prevalence of ESBL infections

We reviewed the studies conducted after 2011 in different countries and continents that reported the rates of ESBL-positive *E coli* isolates collected from patients hospitalized for UTI. *E coli* was chosen because it is a major pathogen in UTI. The prevalence varied from 1.3%[13] to 17.6%[14] in these studies. Sensitivity analyses were conducted within this range.[13-20] The case-base analysis model used a fixed prevalence of ESBL-positive *E coli* isolates of 5%, which corresponds to the weighted rates of ESBL-positive *E coli* isolates collected from patients suffering from UTI.

Measurement of effectiveness

It is already known that inappropriate treatment of ESBL-related severe sepsis leads to higher mortality,[1] and we used a relative risk estimate of 1.5[2] for the hypothetical cohort admitted in the ICU in our case-base analysis (Table 1). Less well studied is the impact of inappropriate treatment of ESBL-related nonsevere UTIs, and we therefore conducted a systematic review and meta-analysis (Supplemental Appendix 3). As shown in Figure 1 and based on 8 other studies[15,17,21-26] conducted among patients admitted in the MW with UTIs, we failed to demonstrate any differences in mortality associated with inappropriate empirical therapy (absolute difference, 0.00; 95% confidence interval, −0.02 to 0.02), without evidence of publication bias. We therefore applied a relative risk estimate of 1.0 for the cohort admitted in the MW in our case-base analysis (Table 1).

Outcomes

We analyzed 3 outcomes for each treatment strategy (Supplemental Appendix 4): effectiveness (probability of survival until discharge and life expectancy), risk of colonization by carbapenem-resistant pathogens, and expected health care costs.

Sensitivity analyses

To assess the robustness of our results, we subjected each probability estimate in our model to a univariate sensitivity analysis. We evaluated the effect of varying the value of each probability estimate within a plausible range on the outcomes of interest, incremental life expectancy, and incremental cost-effectiveness. In addition, costs varied to cover other alternatives in the strategy (doripenem, ertapenem, and meropenem in the IMP