Fighting the spread of AmpC-hyperproducing Enterobacteriaceae: beneficial effect of replacing ceftriaxone with cefotaxime

P. Grohs¹*, S. Kerneis¹–⁵, B. Sabatier¹,², M. Lavollay¹,⁴, E. Carbonnelle¹,⁴, H. Rostane¹, C. Souty⁵, G. Meyer³,⁴,⁷, L. Gutmann¹,⁴ and J. L. Mainardi¹–⁴

¹Service de Microbiologie, AP-HP, Hôpital Européen Georges Pompidou, Paris F-75015, France; ²Unité Mobile de Microbiologie Clinique, AP-HP, Hôpital Européen Georges Pompidou, Paris F-75015, France; ³Comité des Anti-infectieux, AP-HP, Hôpital Européen Georges Pompidou, Paris F-75015, France; ⁴Faculté de Médecine Paris Descartes, 15 Rue de l’Ecole de Médecine, Paris F-75006, France; ⁵UMR-S 707, INSERM, Université Pierre et Marie Curie, Paris F-75012, France; ⁶Service de Pharmacie, AP-HP, Hôpital Européen Georges Pompidou, Paris F-75015, France; ⁷Service de Pneumologie, AP-HP, Hôpital Européen Georges Pompidou, Paris F-75015, France

*Corresponding author. Department of Microbiology, AP-HP Hôpital Européen Georges Pompidou, 20-40 rue Leblanc, 75908 Paris cedex 15, France. Tel: +33-1-56-09-38-44; Fax: +33-1-56-09-24-46; E-mail: patrick.grohs@egp.aphp.fr

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Objectives: Considering the hypothesis that the high biliary elimination of ceftriaxone could be responsible for the selection of Enterobacteriaceae harbouring high-level AmpC β-lactamase (HL-CASE), the use of ceftriaxone was discontinued in our hospital in 2006 and replaced with cefotaxime.

Methods: Antibiotic consumption, expressed as defined daily dose (DDD)/1000 patient-days (PD), and HL-CASE incidence, expressed as the number of patients carrying HL-CASE/1000 PD, were compared between the pre-intervention period (Period 1, 2001–05) and the post-intervention period (Period 2, 2006–12) using an interrupted time series analysis.

Results: The incidence of HL-CASE increased significantly from 0.32 to 0.69/1000 PD during Period 1 (coefficient = 0.082, P < 0.01). A significant inflection of the slope in the incidence curve occurred in Period 2 (coefficient = -2.061, P = 0.05), mainly owing to the stabilization of the HL-CASE incidence of Enterobacteriaceae harbouring chromosomally inducible cephalosporinase (Period 1, 0.27 to 0.64/1000 PD; Period 2, 0.58 to 0.61/1000 PD) and especially for Enterobacter cloacae (Period 1, 0.09 to 0.30/1000 PD; Period 2, 0.26 to 0.27/1000 PD). This deceleration was observed despite a significant increase in the slope of cefotaxime consumption over Period 2 (coefficient = 2.97, P < 0.01).

Conclusion: Despite the disadvantages of using cefotaxime compared with ceftriaxone (administration three times daily versus once a day), the ecological benefits of this substitution seem sufficiently convincing to preferentially use cefotaxime. Control of HL-CASE incidence is crucial to limiting carbapenem use and preventing the selection of carbapenemase-producing Enterobacteriaceae.

Keywords: antibiotics, bacterial resistance, cephalosporins

Introduction

The use of third-generation cephalosporins (3GCs) as the standard antibiotic regimen for the treatment of Enterobacteriaceae infections is called into question by the continuing spread of resistance to these molecules.¹ Resistance to 3GCs is mediated primarily by the production of extended-spectrum β-lactamase (ESBL) and AmpC β-lactamase (CASE), which can result either from overexpression of the chromosomal ampC gene or by the acquisition of a plasmid-mediated AmpC enzyme [high-level CASE (HL-CASE)].¹,² Because infections caused by these 3GC-resistant Enterobacteriaceae have significant human and economic costs,³ a continuous surveillance system for 3GC-resistant Enterobacteriaceae incidence has been implemented in our university hospital since 2001.

In 2005 we were alerted to a significant increase in HL-CASE incidence, from 0.32/1000 patient-days (PD) in 2001 to 0.69/1000 PD in 2005. Most of the HL-CASE Enterobacteriaceae were Enterobacter cloacae and harboured the chromosomally inducible CASE gene. These isolates were encountered in all wards of the hospital, had different antimicrobial resistance patterns, and epidemiological investigations did not show any evidence of cross-transmission (P. Grohs and G. Meyer, unpublished data). Since antibiotic selection pressure contributes to the emergence of antibiotic-resistant Gram-negative bacteria,⁴,⁵ with a link between 3GC use and the selection of HL-CASE Enterobacteriaceae,⁶,⁷ we investigated our hospital’s antimicrobial consumption from 2001 to 2005.

During this period, global antibiotic consumption decreased, whereas 3GC consumption increased by 50% (see Table 1 and
Table 1. Enterobacteriaceae incidence and antibiotic consumption

<table>
<thead>
<tr>
<th>Incidence densities (number of patients)</th>
<th>Pre-intervention period</th>
<th>Post-intervention period</th>
<th>Trend in pre-intervention period (b1)</th>
<th>Change in level (b2)</th>
<th>Change in slope (b3)</th>
<th>P value</th>
<th>P value</th>
<th>P value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient days (PD)</td>
<td>163671</td>
<td>190829</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence densitiesa (number of patients)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H. alvei</td>
<td>0.57 (93)</td>
<td>0.96 (184)</td>
<td>0.75 (145)</td>
<td>0.69 (135)</td>
<td>0.88 (180)</td>
<td>0.97</td>
<td>0.035</td>
<td>0.04 to 0.11</td>
<td>0.01</td>
</tr>
<tr>
<td>E. coli</td>
<td>0.32 (52)</td>
<td>0.53 (102)</td>
<td>0.56 (108)</td>
<td>0.59 (113)</td>
<td>0.69 (140)</td>
<td>0.76</td>
<td>0.001</td>
<td>0.00 to 0.18</td>
<td>0.01</td>
</tr>
<tr>
<td>Inducible AmpC</td>
<td>0.27 (45)</td>
<td>0.45 (86)</td>
<td>0.58 (114)</td>
<td>0.64 (130)</td>
<td>0.74 (142)</td>
<td>0.74</td>
<td>0.031</td>
<td>0.00 to 0.13</td>
<td>0.01</td>
</tr>
<tr>
<td>E. coli</td>
<td>0.09 (14)</td>
<td>0.18 (35)</td>
<td>0.21 (41)</td>
<td>0.26 (51)</td>
<td>0.32 (52)</td>
<td>0.32</td>
<td>0.05</td>
<td>0.00 to 0.18</td>
<td>0.01</td>
</tr>
<tr>
<td>No AmpC</td>
<td>0.01 (1)</td>
<td>0.02 (4)</td>
<td>0.02 (4)</td>
<td>0.04 (8)</td>
<td>0.07 (15)</td>
<td>0.07</td>
<td>0.014</td>
<td>0.00 to 0.18</td>
<td>0.01</td>
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<tr>
<td>Antimicrobial consumption*</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>all antibiotics</td>
<td>976</td>
<td>803</td>
<td>796</td>
<td>817</td>
<td>750</td>
<td>708</td>
<td>750</td>
<td>710</td>
<td>777</td>
</tr>
<tr>
<td>all aminopenicillins</td>
<td>311</td>
<td>325</td>
<td>399</td>
<td>421</td>
<td>381</td>
<td>365</td>
<td>378</td>
<td>361</td>
<td>355</td>
</tr>
<tr>
<td>all 3GCs</td>
<td>37.4</td>
<td>34.3</td>
<td>45.6</td>
<td>55.3</td>
<td>55.5</td>
<td>44.3</td>
<td>55.3</td>
<td>51.5</td>
<td>56.5</td>
</tr>
<tr>
<td>ceftriaxone</td>
<td>15.3</td>
<td>18.0</td>
<td>16.0</td>
<td>21.5</td>
<td>6.3</td>
<td>6.3</td>
<td>2.2</td>
<td>2.2</td>
<td>3.0</td>
</tr>
<tr>
<td>cefotaxime</td>
<td>6.8</td>
<td>5.0</td>
<td>7.3</td>
<td>6.1</td>
<td>5.9</td>
<td>8.1</td>
<td>20.5</td>
<td>28.1</td>
<td>25.8</td>
</tr>
<tr>
<td>cefoperazone</td>
<td>5.3</td>
<td>6.9</td>
<td>5.5</td>
<td>7.5</td>
<td>7.6</td>
<td>6.0</td>
<td>6.0</td>
<td>11.1</td>
<td>17.1</td>
</tr>
</tbody>
</table>

a Incidence densities are expressed as the number of patients (duplicates excluded) carrying resistant strain reported/1000 PD.

b 3GC-resistant Enterobacteriaceae, i.e. harbouring HL-CASE and/or ESBL.

c Strains harbouring chromosomal AmpC cephalosporinase.

d Strains without chromosomal AmpC cephalosporinase.

e Antibiotic consumption is expressed as DDD/1000 PD.
Figure 1a). Concomitantly, Muller et al.\(^8\) reported a specific correlation between ceftriaxone use and the development of resistance in \textit{E. cloacae} isolates. These authors suggested that the pharmacokinetic properties of ceftriaxone, in particular its high biliary elimination, could be involved in the selection of \textit{E. cloacae} HL-CASE producers in the digestive flora.\(^6\) This attractive hypothesis was the basis for a change in antibiotic use in our institution, and in 2006 the Anti-Infectious Committee (COMAI) decided to replace ceftriaxone with cefotaxime. In this work we report the impact of this substitution on the incidence of HL-CASE Enterobacteriaceae.

**Methods**

This retrospective observational study was conducted at the Hôpital Européen Georges Pompidou, a French 830 bed acute-care teaching hospital with 23 wards (11 medical wards, 7 surgical wards and 5 intensive care units) that admits an average of 30000 patients each year. Two periods of antibiotic consumption and HL-CASE incidence were compared: 2001 to 2005 (pre-intervention period=Period 1) and 2006 to 2012 (post-intervention period=Period 2); corresponding to the periods of ceftriaxone and cefotaxime use, respectively. Defined daily dose (DDD)/1000 PD was the international unit used to monitor antibiotic consumption.\(^7\) Only diagnostic samples collected from inpatients were included in the study. Antimicrobial susceptibilities were determined by the disc diffusion method on Mueller–Hinton agar (MH; Bio-Rad, Marne-la-Coquette, France) according to European guidelines.\(^9\) An isolate was categorized as an HL-CASE producer when its phenotype displayed the following three features: (i) resistance to 3GCs; (ii) absence of synergy between any 3GCs and clavulanic acid; and (iii) at least a 5 mm increase in the inhibition diameters for the 3GCs, read on an MH versus MH + clavulanic acid (250 mg/L). For each patient, HL-CASE isolates of the same species and displaying the same antimicrobial pattern during the calendar year were labelled as duplicates and were excluded from analysis. Finally, HL-CASE incidence was expressed as the number of patients carrying HL-CASE/1000 PD. To assess the impact of the switch from ceftriaxone to cefotaxime (referred to as the ‘intervention’) on the incidence of HL-CASE, we used an interrupted time series analysis, as previously described.\(^11,12\)

Briefly, the time series was divided into pre- and post-intervention segments, and the level and trend of the pre-intervention segment served as the control for the post-intervention segment. In the linear regression autoregressive error model, the incidence of HL-CASE (per 1000 PD) was expressed as:

\[
\text{Incidence}_t = \beta_0 + \beta_1 \text{time}_t + \beta_2 \text{period}_t + \beta_3 \text{time after intervention}_t + e_t
\]

where ‘time’ is a continuous variable indicating the time in years from the start of the study period, ‘period’ is a qualitative variable being 0 pre-intervention and 1 post-intervention and ‘time after intervention’ is a continuous variable indicating the number of years after the intervention (0 before 2005, 1 in 2006, 2 in 2007, etc.). \(\beta_0\) estimates the baseline incidence of HL-CASE, \(\beta_1\) the pre-intervention trend in incidence, \(\beta_2\) the change in level of the incidence after the intervention and \(\beta_3\) the change in trend of the incidence after the intervention. The model was corrected for auto-correlation (e). Level and trend for the pre-intervention period represent a baseline for the post-intervention segment. Because the change in trend after the intervention was significant, we decided to keep all variables in the final model, as \(\beta_3\) can be interpreted as the interaction between time and period.\(^11\) Statistical analyses were carried out using R 2.4.0 statistical software.\(^11\)

**Results and discussion**

In the pre-intervention period, we observed an increase in the consumption of aminopenicillins (amoxicillin and amoxicillin/clavulanic acid, \(\beta_1 = 23.60, P<0.01\)), which represent about half the total antibiotic use in our hospital, and 3GCs (\(\beta_1 = 5.72, P<0.01\), although the overall antibiotic use decreased for the same period (\(\beta_1 = -43.80, P=0.01\), Figure 1a and Table 1). Since aminopenicillins combined with clavulanate can induce Enterobacteriaceae cephalosporinase expression,\(^16\) and 3GC use has been associated with 3GC-resistant Enterobacteriaceae,\(^7,8\) the increasing consumption of these drugs during the pre-intervention period could be involved in the rise of HL-CASE-producing Enterobacteriaceae. Starting in 2006, the replacement of ceftriaxone by cefotaxime was rapidly implemented as illustrated in Figure 1(a), leading to minimal numbers of ceftriaxone prescriptions since 2007. Conversely, a significant increase in the slope of cefotaxime consumption occurred over Period 2 (\(\beta_3 = 2.97, P<0.01\)), from 18.1 DDD/1000 PD in 2006 to 37 DDD/1000 PD in 2012. Finally, the stabilization of aminopenicillin consumption during the post-intervention period suggests that the change in HL-CASE incidence could be due mainly to the replacement of ceftriaxone by cefotaxime.
As shown by the results of the regression analysis (Table 1), a significant increase in the incidence of HL-CASE occurred over the pre-intervention period ($\beta_1 = 0.082, P < 0.01$). In the post-intervention period, there was no significant change in the incidence ($\beta_2 = -0.076, P = 0.37$); however, a significant decrease in the slope was observed ($\beta_3 = -0.06, P = 0.05$), suggesting that progression of the incidence of HL-CASE was slowing. In detail, the inflexion was mainly due to stabilization in the incidence of HL-CASE Enterobacteriaceae harbouring chromosomally inducible CASE, in particular of E. cloacae (Figure 1b). No significant change in slope was observed for HL-CASE Escherichia coli incidence, although a rise in the incidence of this species has been observed in recent studies, explained by mechanisms different from those encountered in E. cloacae, including mutations in the promoter region of the chromosomally non-inducible ampC gene and acquisition of plasmid-mediated HL-CASE. Unfortunately, our hospital the increasing incidence of patients carrying 3GC-resistant Enterobacteriaceae during the post-intervention period, due to the presence of ESBL and various HL-CASE mechanisms, from 0.97/1000 PD in 2006 to 1.83/1000 PD in 2012 (Table 1), led to a significant increase in the slope of carbapenem consumption ($\beta_1 = 2.99, P = 0.01$), which was 6 DDD/1000 PD in 2007 and 25.5 DDD/1000 PD in 2012 (Table 1).

Conclusions

This study suggests that the replacement of ceftriaxone by cefotaxime could stabilize the incidence of HL-CASE resulting from chromosomally inducible CASE Enterobacteriaceae. Despite the disadvantages of using cefotaxime compared with ceftriaxone (administration three times daily versus once a day), the ecological benefits of this substitution seem sufficiently convincing to preferentially use cefotaxime. The long-term objective of reducing HL-CASE incidence is also to enable the limitation of carbapenem use and hence prevent the selection of carbapenem-producing Enterobacteriaceae.

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Transparency declarations

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References