Use of fluoroquinolones and third-generation cephalosporins in the emergency department: an 11-year survey

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Fluoroquinolones and third-generation cephalosporins are particularly prone to select bacterial resistance to antibiotics. We aimed to assess the temporal trends of antibiotic use in the emergency department adults unit of an academic hospital between 2002 and 2012. Antibiotic use was converted in defined daily doses (DDD). The total antibiotic consumption tended to decrease, from 53.1±8.5 to 48.6±11.9 DDD/1000 patient visits (estimate decrease per year, −0.9±0.5 DDD/1000 visits, $P=0.07$). Use of third-generation cephalosporins increased significantly, from 9.7% of total antibiotic use to 22.6% (estimate per year, 1.2±0.2%, $P<0.0001$), whereas use of fluoroquinolones decreased from 19.5 to 12.3% (estimate per year, −0.7±0.2%, $P<0.003$). Given their ability to select bacterial resistance, especially extended-spectrum β-lactamases, particular attention should be paid to increasing use of third-generation cephalosporins in the emergency department. *European Journal of Emergency Medicine* **21:442–446 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Antibiotic use is a major determinant of bacterial resistance in community-acquired and hospital-acquired infections. Two classes of antibiotics, fluoroquinolones and third-generation cephalosporins, are specifically prone to promote bacterial resistance, including extended-spectrum β-lactamases in *Escherichia coli*, *Klebsiella* spp. and other gram-negative organisms, resistance of *E. coli* to quinolones and methicillin resistance in *Staphylococcus aureus* [1,2]. Aggregate use of quinolones in US academic hospitals has decreased between 2002 and 2009, and consumption of third-generation and fourth-generation cephalosporins tended to increase in the 2002–2006 period [3,4]. Temporal variations of antibiotic use in the US emergency departments (EDs) have been reported for various infections in adults and children [5–9]. However, global use of fluoroquinolones and third-generation cephalosporins in the ED remains poorly known. Our objective was to assess the consumption of these broad-spectrum agents in the ED during an 11-year period.

Methods

This study was carried out in the ED adults unit of a 3000-bed academic tertiary centre in France. The medical activity of our institution did not change during the period of the study. Monthly use of systemic antibiotics was retrieved from the pharmacy records for the years 2002–2012. Data were converted into defined daily doses (DDD) as recommended by the WHO Collaborating Centre for Drugs Statistics Methodology (*http://www.whocc.no*). Antibacterial agents for systemic use were grouped into 17 classes adapted from the ATC classification: (1) β-lactamase-sensitive penicillins (J01CE), (2) β-lactamase-resistant penicillins (J01CF), (3) amoxicillin (J01CA04) – ampicillin is not commercially available in France, (4) amoxicillin and enzyme inhibitor (J01CR01 and J01CR02), (5) ticarcillin and piperacillin (with or without enzyme inhibitor) (J01CA12, J01CA13, J01CR03, J01CR05), (6) first-generation and second-generation cephalosporins (J01DB, J01DC), (7) third-generation cephalosporins (J01DD) excluding ceftazidime, (8) antipseudomonal cephalosporins including ceftazidime (J01DD02) and fourth-generation cephalosporins (J01DE), (9) carbapenems (J01DH), (10) tetracyclines (J01A), (11) sulphonamides and trimethoprim (J01E), (12) macrolides, lincosamides and streptogramins (J01F), (13) aminoglycosides (J01G), (14) fluoroquinolones (J01M), (15) glycopeptides (J01XA), (16) imidazole derivatives (J01XD) and (17) other antibacterial agents. In addition, fluoroquinolones and third-generation cephalosporins were grouped as broad-spectrum agents. DDDs were ratioed to the number of patient visits (PV) and finally expressed as a percentage of total antibiotic use.

As changes in antibiotic use in the ED may be driven by changing incidences of bacterial infections in the ED,

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and by evolving antibiotic susceptibility of bacteria isolated in the ED, we also surveyed the incidences of *S. aureus* and *E. coli* bacteraemia, along with susceptibility of *E. coli* to ciprofloxacin and to ceftriaxone, and susceptibility of *S. aureus* to methicillin. Monthly numbers of patients who had a blood culture drawn in the ED and that grew *S. aureus* or *E. coli* were retrieved from the hospital laboratory records. Susceptibility of *E. coli* to ciprofloxacin and to ceftriaxone was also obtained for nonduplicate urinary isolates that had been sampled in the ED, as susceptibility of *S. aureus* to methicillin was extracted for blood isolates.

The temporal trend of total antibiotic consumption was assessed using a linear mixed model. The model included a fixed effect for year and random effects for year and month. The temporal trend was considered statistically significant if the estimate of year fixed effect was significantly different from 0. The same model was used to test the temporal trends of use of each antibacterial class ratioed against total antibiotic use to take into account the interyear variability of antibiotic use during the study period. We used the same model to test temporal trends of duration of PV, number of PV and numbers of *S. aureus* and *E. coli* bacteraemia. The χ^2-test for trend was used to test the temporal trend of resistance rates. Statistical analyses were carried out using R-2.15.0 for Windows* (*http://www.r-project.org*).

Results

Characteristics of the emergency department

In 2012, the ED census was 65481. The mean number of visits per month increased from 5106 ± 263 in 2002 to 5457 ± 156 in 2012 (estimate increase per year, 51 ± 17, $P < 0.003$). The mean duration of ED visits (368 min for the entire study period) was roughly stable during the study period.

Antibiotic use

Between 2002 and 2012, the total antibiotic use tended to decrease, from 53.1 ± 8.5 DDD/1000 PV in 2002 to 48.6 ± 11.9 DDD/1000 PV (estimate decrease per year, −0.9 ± 0.5 DDD/1000 PV, $P = 0.07$).

The absolute antibiotic use is reported in Table 1, and consumption expressed as a percentage of the total antibiotic use is shown in Table 2. At the beginning of the study period, as well as at its end, the four most prescribed antibiotic classes were amoxicillin-clavulanic acid, third-generation cephalosporins, fluoroquinolones and aminoglycosides, accounting collectively for more than 70% of the total antibiotic use.

Use of third-generation cephalosporins doubled during the study period, from 9.6 to 22.3% of total antibiotic use, whereas consumption of fluoroquinolones decreased from 19.3 to 11.9%. As a whole, use of broad-spectrum agents,

Table 1 Mean (SD) antibiotic use ratioed to the number of patient visits in the emergency department (defined daily doses per 1000 patient visits)

	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
First-generation and second-generation cephalosporins	0.0 (0.0)	0.0 (0.2)	0.0 (0.0)	0.0 (0.0)	0.2 (0.5)	0.2 (0.3)	0.1 (0.2)	0.0 (0.1)	0.1 (0.1)	0.1 (0.2)	0.0 (0.1)
Third-generation cephalosporins[a]	5.1 (1.7)	6.7 (2.3)	7.3 (3.0)	7.7 (2.1)	7.9 (2.4)	9.5 (2.3)	10.2 (2.2)	9.0 (3.7)	10.2 (2.8)	8.8 (3.0)	10.9 (2.6)
Aminoglycosides	5.9 (5.0)	3.2 (2.4)	3.4 (1.8)	6.2 (3.2)	7.1 (2.7)	9.7 (6.0)	5.6 (2.3)	3.9 (2.1)	5.0 (2.0)	4.3 (2.4)	5.3 (2.1)
Amoxicillin	4.6 (1.7)	4.5 (1.8)	3.5 (1.3)	4.2 (1.7)	3.1 (1.4)	3.9 (1.6)	2.8 (1.3)	3.0 (1.6)	2.7 (0.7)	2.7 (0.9)	2.3 (1.0)
Amoxicillin/ampicillin and EI	17.5 (3.1)	20.0 (3.5)	18.3 (3.5)	18.5 (3.8)	14.2 (2.2)	16.8 (3.6)	16.3 (5.0)	15.4 (3.7)	14.8 (2.0)	14.4 (2.6)	16.0 (4.4)
Antipseudomonal cephalosporins	1.1 (0.9)	1.0 (1.0)	0.9 (0.7)	0.4 (0.4)	0.3 (0.6)	0.2 (0.4)	0.3 (0.3)	0.2 (0.2)	0.2 (0.5)	0.1 (0.2)	0.3 (0.6)
β-Lactamase-resistant penicillins	1.5 (1.9)	1.0 (1.8)	1.7 (2.3)	0.7 (0.8)	1.5 (2.2)	0.8 (1.1)	0.4 (0.7)	0.5 (0.6)	0.7 (1.1)	0.2 (0.3)	0.5 (1.2)
β-Lactamase-sensitive penicillins	1.4 (0.5)	1.6 (0.8)	1.2 (1.0)	1.3 (0.8)	1.4 (0.9)	0.9 (0.7)	1.0 (0.8)	0.7 (0.3)	0.8 (0.9)	0.4 (0.5)	0.3 (0.4)
Carbapenems	0.3 (0.4)	0.0 (0.0)	0.1 (0.2)	0.3 (0.3)	0.3 (0.3)	0.5 (0.6)	0.2 (0.7)	0.2 (0.6)	0.5 (0.5)	0.2 (0.3)	0.3 (0.5)
Fluoroquinolones	10.3 (3.3)	11.5 (3.8)	10.9 (3.3)	13.1 (2.4)	13.7 (3.2)	14.6 (5.2)	11.7 (4.1)	8.9 (2.9)	8.3 (2.1)	7.0 (1.7)	5.8 (1.6)
Glycopeptides	0.8 (1.1)	0.3 (0.7)	0.6 (0.5)	0.7 (0.7)	0.9 (0.8)	0.8 (0.8)	0.8 (0.8)	0.2 (0.7)	0.4 (0.4)	0.2 (0.3)	0.2 (0.3)
Imidazole derivatives	1.0 (0.9)	1.2 (0.6)	1.4 (0.8)	1.6 (0.8)	2.1 (0.9)	2.5 (0.7)	2.8 (1.4)	1.3 (1.5)	1.9 (0.8)	2.0 (0.9)	2.1 (0.6)
Macrolides, lincosamides and streptogramins	3.0 (1.9)	2.8 (1.2)	2.2 (1.0)	3.4 (1.9)	3.4 (1.5)	3.7 (1.7)	3.0 (1.7)	2.2 (1.4)	2.7 (1.8)	2.3 (1.6)	4.0 (1.8)
Other antibacterial agents	0.2 (0.3)	0.1 (0.3)	0.0 (0.1)	0.3 (0.3)	0.1 (0.1)	0.4 (0.7)	0.1 (0.2)	0.1 (0.1)	0.2 (0.3)	0.3 (0.3)	0.3 (0.3)
Sulphamides	0.3 (0.7)	1.0 (1.0)	0.0 (1.4)	0.2 (0.4)	0.2 (0.8)	0.1 (0.2)	0.3 (0.6)	0.4 (0.5)	0.1 (0.3)	0.3 (0.5)	0.0 (0.1)
Tetracyclines	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (2.2)	0.2 (0.4)	0.3 (0.7)	0.0 (0.0)	0.1 (0.3)	0.2 (0.5)	0.2 (0.4)	0.0 (0.0)
Ticarcillin and piperacillin with or without EI	0.1 (0.1)	0.0 (0.2)	0.1 (0.2)	0.7 (0.8)	0.3 (0.4)	0.5 (0.4)	0.6 (0.4)	0.4 (0.2)	0.5 (0.5)	0.7 (0.6)	0.5 (0.5)
Broad-spectrum agents[b]	15.3 (3.9)	18.2 (5.2)	18.2 (5.4)	20.7 (4.0)	21.6 (4.1)	24.1 (6.4)	21.9 (5.6)	17.9 (5.2)	18.5 (3.1)	15.9 (3.3)	16.6 (3.1)
Total antibiotic use	53.1 (8.5)	55.0 (8.4)	51.6 (10.3)	59.3 (10.4)	56.8 (10.8)	65.3 (13.7)	56.3 (11.8)	46.3 (11.9)	49.1 (6.9)	44.1 (6.3)	48.6 (11.9)

EI, enzyme inhibitor.
[a]Excluding ceftazidime.
[b]Include third-generation cephalosporins and fluoroquinolones.

Table 2 Antibiotic use in the emergency department (percentage of total antibiotic use)

	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	Estimate (SD)	*P* value
First-generation and second-generation cephalosporins	0.0 (0.0–8.4)	0.0 (0.0–8.2)	0.0 (0.0–8.7)	0.0 (0.0–7.6)	0.3 (0.0–8.4)	0.3 (0.0–7.4)	0.1 (0.0–8.2)	0.1 (0.0–9.7)	0.1 (0.0–9.2)	0.1 (0.0–10.2)	0.0 (0.0–9.2)	0.01 (0.01)	0.23
Third-generation cephalosporins[a]	9.6 (3.6–21.6)	12.1 (5.3–24.4)	14.1 (6.4–27.2)	13.0 (6.1–24.9)	14.0 (6.6–26.3)	14.5 (7.4–26.0)	18.2 (9.6–31.3)	19.4 (9.8–34.2)	20.8 (11.0–35.2)	20.0 (10.0–35.2)	22.3 (12.1–36.9)	1.21 (0.10)	<0.0001
Aminoglycosides	11.0 (4.5–23.4)	5.8 (1.6–16.6)	6.6 (1.9–18.1)	10.5 (4.4–21.9)	12.5 (5.6–24.6)	14.8 (7.6–26.3)	10.0 (4.0–21.7)	8.5 (2.7–21.4)	10.0 (3.7–22.8)	9.6 (3.2–23.2)	11.0 (4.3–24.1)	0.18 (0.21)	0.40
Amoxicillin	8.6 (3.0–20.4)	8.1 (2.8–19.5)	6.9 (2.0–18.5)	7.1 (2.4–17.7)	5.4 (1.4–15.8)	6.0 (1.9–15.6)	5.1 (1.3–15.5)	6.4 (1.6–18.7)	5.4 (1.3–17.0)	6.0 (1.4–18.6)	4.6 (0.9–16.0)	−0.32 (0.06)	<0.0001
Amoxicillin/ampicillin and EI	33.0 (21.1–47.4)	36.5 (24.2–50.6)	35.6 (23.1–50.3)	31.2 (20.1–44.7)	25.0 (14.9–38.6)	25.8 (16.1–38.4)	28.9 (18.0–42.8)	33.4 (20.6–48.9)	30.1 (18.3–45.1)	32.6 (19.8–48.5)	32.9 (20.5–48.0)	−0.26 (0.33)	0.43
Antipseudomonal cephalosporins	2.2 (0.2–11.8)	1.9 (0.1–11.2)	1.8 (0.1–11.5)	0.7 (0.0–8.8)	0.5 (0.0–8.7)	0.4 (0.0–7.6)	0.5 (0.0–8.9)	0.3 (0.0–10.1)	0.5 (0.0–9.9)	0.2 (0.0–10.3)	0.5 (0.0–10.0)	−0.18 (0.03)	<0.0001
β-Lactamase-resistant penicillins	2.8 (0.3–12.7)	1.8 (0.1–11.1)	3.2 (0.4–13.5)	1.2 (0.0–9.6)	2.6 (0.3–11.9)	1.3 (0.0–9.0)	0.8 (0.0–9.3)	1.1 (0.0–11.3)	1.4 (0.0–11.3)	0.6 (0.0–10.9)	1.0 (0.0–10.8)	−0.18 (0.06)	0.004
β-Lactamase-sensitive penicillins	2.7 (0.3–12.5)	3.0 (0.4–12.7)	2.3 (0.2–12.2)	2.2 (0.2–11.0)	2.5 (0.3–11.8)	1.3 (0.0–9.1)	1.8 (0.1–10.8)	1.4 (0.0–11.8)	1.5 (0.0–11.5)	1.0 (0.0–11.5)	0.6 (0.0–10.1)	−0.21 (0.04)	<0.0001
Carbapenems	0.6 (0.0–9.4)	0.0 (0.0–8.2)	0.2 (0.0–9.0)	0.5 (0.0–8.4)	0.5 (0.0–8.8)	0.7 (0.0–8.1)	0.4 (0.0–8.6)	0.3 (0.0–10.1)	1.0 (0.0–10.6)	0.5 (0.0–10.8)	0.6 (0.0–10.1)	0.03 (0.02)	0.17
Fluoroquinolones	19.3 (10.2–32.9)	21.0 (11.6–34.5)	21.1 (11.4–35.1)	22.0 (12.7–35.1)	24.1 (14.1–37.6)	22.3 (13.3–34.7)	20.7 (11.5–34.0)	19.3 (9.7–34.0)	17.0 (8.2–30.9)	16.0 (7.3–30.8)	11.9 (4.8–25.2)	−0.68 (0.22)	0.002
Glycopeptides	1.6 (0.0–10.9)	0.5 (0.0–9.0)	1.1 (0.0–10.4)	1.2 (0.0–9.6)	1.5 (0.1–10.3)	1.3 (0.0–9.0)	1.3 (0.0–10.1)	0.3 (0.0–10.1)	0.9 (0.0–10.5)	0.4 (0.0–10.6)	0.4 (0.0–9.8)	−0.08 (0.04)	0.04
Imidazole derivatives	1.9 (0.1–11.4)	2.2 (0.2–11.6)	2.6 (0.3–12.7)	2.7 (0.4–11.8)	3.6 (0.7–13.4)	3.8 (0.8–12.6)	5.0 (1.2–15.3)	2.9 (0.3–13.9)	3.8 (0.6–14.8)	4.5 (0.8–16.5)	4.3 (0.8–15.5)	0.24 (0.05)	<0.0001
Macrolides, lincosamides and streptogramins	5.7 (1.5–16.6)	5.1 (1.2–15.6)	4.2 (0.8–15.0)	5.7 (1.6–15.8)	5.9 (1.7–16.5)	5.7 (1.7–15.2)	5.3 (1.4–15.7)	4.7 (0.9–16.4)	5.5 (1.3–17.0)	5.1 (1.0–17.5)	8.2 (2.6–20.6)	0.10 (0.09)	0.23
Other antibacterial agents	0.4 (0.0–9.1)	0.2 (0.0–8.5)	0.0 (0.0–8.7)	0.5 (0.0–8.4)	0.2 (0.0–8.2)	0.5 (0.0–7.9)	0.2 (0.0–8.4)	0.1 (0.0–9.7)	0.5 (0.0–9.9)	0.6 (0.0–10.9)	0.5 (0.0–10.0)	0.02 (0.02)	0.13
Sulphamides	0.5 (0.0–9.3)	1.7 (0.1–10.9)	0.0 (0.0–8.7)	0.3 (0.0–8.1)	0.4 (0.0–8.6)	0.1 (0.0–7.2)	0.6 (0.0–8.9)	0.8 (0.0–10.8)	0.2 (0.0–9.4)	0.7 (0.0–11.1)	0.0 (0.0–9.2)	−0.04 (0.04)	0.39
Tetracyclines	0.0 (0.0–8.4)	0.0 (0.0–8.2)	0.0 (0.0–8.7)	0.0 (0.0–7.6)	0.3 (0.0–8.4)	0.5 (0.0–7.7)	0.0 (0.0–8.0)	0.2 (0.0–9.9)	0.3 (0.0–9.6)	0.4 (0.0–10.6)	0.0 (0.0–9.1)	0.03 (0.04)	0.44
Ticarcillin and piperacillin	0.1 (0.0–8.6)	0.1 (0.0–8.3)	0.3 (0.0–9.1)	1.2 (0.0–9.6)	0.6 (0.0–8.8)	0.8 (0.0–8.3)	1.1 (0.0–9.8)	0.8 (0.0–10.9)	1.0 (0.0–10.6)	1.7 (0.0–12.6)	1.0 (0.0–10.8)	0.12 (0.03)	<0.0001
Broad-spectrum agents[b]	28.9 (17.7–43.2)	33.1 (21.4–47.2)	35.1 (22.7–49.8)	35.0 (23.4–48.6)	38.1 (25.8–52.0)	36.9 (25.5–49.8)	38.9 (26.5–52.9)	38.7 (25.1–54.1)	37.7 (24.6–52.7)	36.1 (22.6–51.9)	34.2 (21.6–49.3)	0.53 (0.21)	0.01

Antibiotic use in DDD/1000 PV were ratioed against total antibiotic use. 95% confidence intervals are provided. Estimates of fixed effect of year should be interpreted as increase (positive value) or decrease (negative value) of monthly antibiotic use.

DDD, defined daily doses; EI, enzyme inhibitor; PV, patient visit.

[a]Excluding ceftazidime.

[b]Include third-generation cephalosporins and fluoroquinolones.

which combined third-generation cephalosporins and fluoroquinolones, increased significantly from 28.9 to 34.2%. Antibiotic use also increased for ticarcillin/piperacillin and for imidazole derivatives, whereas it decreased for five other classes (amoxicillin, antipseudomonal cephalosporins, β-lactamase-sensitive penicillins, β-lactamase-resistant penicillins and glycopeptides).

Bacteraemia incidence and susceptibility to antibiotics

The incidences of *E. coli* and *S. aureus* bacteraemia were, respectively, 1.88 (1.78–1.99) and 0.75 (0.68–0.81) patient/1000 PV. None showed any significant temporal variation during the study period. Frequency of resistance to methicillin among *S. aureus* isolates decreased from 18.2% (8.7–33.2%) in 2002 to 8.2% (2.6–20.5%) in 2012 (P for trend < 0.02).

Susceptibility of *E. coli* to ciprofloxacin among urinary isolates sampled in the ED decreased from 93.4% [95% confidence interval (CI), 90.6–95.4%] in 2002 to 88.8% (95% CI, 86.2–91.0%) in 2012 (P for trend < 0.0001), whereas susceptibility to ceftriaxone decreased from 99.6% (95% CI, 98.2–99.9%) to 95.9% (95% CI, 94.1–97.2%) during the same period (P for trend $<$ 0.0001). Meanwhile, susceptibility of *E. coli* urinary isolates that were isolated in other wards of the institution decreased from 91.2% (89.9–92.3) to 87.4% (86.2–88.6) for ciprofloxacin (P for trend < 0.0001) and from 99.2% (98.7–99.5) to 94.2% (93.3–95.0) for ceftriaxone (P for trend < 0.0001).

Discussion

Our study shows considerable variations in the consumption of broad-spectrum agents during an 11-year period as consumption of third-generation cephalosporins – expressed either in DDD/1000 PV or in percentage of total antibiotic use – almost doubled whereas use of fluoroquinolones decreased. Respiratory and urinary tract infections are the leading diagnoses resulting in antibiotic prescription in the ED [10]. Empirical treatment of community-acquired pyelonephritis is based on either ceftriaxone or a fluoroquinolone in our institution. As *E. coli* isolates became more frequently resistant to fluoroquinolones during the study period, we hypothesize that replacement of fluoroquinolones by ceftriaxone for empirical treatment of pyelonephritis may partly explain these evolutions. Furthermore, third-generation cephalosporins, amoxicillin and amoxicillin-clavulanic acid are commonly used to treat community-acquired lower respiratory tract infections in our ED. Lower respiratory tract infections may have been treated more frequently by third-generation cephalosporins and less frequently by amoxicillin at the end of the study. These hypotheses are under current investigation.

The combined use of fluoroquinolones and third-generation cephalosporins increased worrisomely in our ED during the 11-year period. As both classes of antibiotics are particularly prone to select bacterial resistances, this trend may have increased the subsequent risk of colonization or infection by resistant organisms among patients under antibacterial therapy in the ED.

Conversely, decrease in glycopeptide may be linked to the decreasing resistance of *S. aureus* to methicillin that was observed in our ED as well as in the surrounding community. Finally, inverse trends of consumptions of antipseudomonal cephalosporins and the ticarcillin/piperacillin class should be viewed as a consequence of the replacement of antipseudomonal cephalosporins by the piperacillin/tazobactam combination for empirical treatment of neutropenic patients in our institution.

The main limitation of our study is its monocentric nature. Multicentric studies are needed to assess temporal trends of total antimicrobial use in the ED setting. Furthermore, the design of our study yields no insight into the appropriateness of antibiotic use and reasons for variations of antibiotic use. Further studies are needed to explore these points and to design interventions aiming to reduce consumption of third-generation cephalosporins, without increasing the use of fluoroquinolones or any other broad-spectrum agent.

Conclusion

Our study shows a markedly increased consumption of third-generation cephalosporins in the ED, potentially leading to selection of resistant bacteria in ED patients. Quantitative survey of antibiotic use in the ED is a useful tool to define objectives for antimicrobial stewardship interventions and to assess their efficacy.

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Conflicts of interest

There are no conflicts of interest.

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