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ARTICLE

Increasing use of third-generation cephalosporins for pneumonia in the emergency department: may some prescriptions be avoided?

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Abstract Third-generation cephalosporins are used to treat inpatients with community-acquired pneumonia. Some of these prescriptions may be avoided, i.e. replaced by agents less likely to promote ESBL-mediated resistance. Our objectives were to assess the recent trend of third-generation cephalosporins use for pneumonia in the emergency department, and the proportion of avoidable prescriptions. This was a retrospective study of patients treated for community-acquired pneumonia in an emergency department, and subsequently hospitalized in non ICU wards. Third-generation cephalosporin prescriptions were presumed unavoidable if they met both criteria: (i) age≥ 65 yr or comorbid condition, and (ii) allergy or intolerance to penicillin, or failure of penicillin first-line therapy, or treatment with penicillin in three previous months. Prescriptions were otherwise deemed avoidable. The proportion of patients treated with a third generation cephalosporin increased significantly from 13.9 % (6.9–24.1 %) in 2002 to 29.5 % (18.5–42.6 %) in 2012 (OR=1.07 [1.01–1.14] , *P*=0.02). This increase was independent from other factors associated with the prescription of a third-generation cephalosporin (immunocompromising condition, antibacterial therapy in three previous months, fluid resuscitation and REA-ICU class). Treatment with third-generation cephalosporin was avoidable in 118 out of 147 patients (80.3 % [72.7–86.2 %]). On day 7 after admission in the ED, treatment with third-generation cephalosporins was stopped or de-escalated in, respectively, 17 % and 32 % of patients. Antibiotic stewardship programs should be implemented to restrict the third-generation cephalosporins use for pneumonia in the emergency department.

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Introduction

Third-generation cephalosporins, amoxicillin-clavulanate and fluoroquinolones are the most frequently prescribed antibiotics in European patients hospitalized with community-acquired pneumonia [1]. In US emergency departments (ED), ceftriaxone is the most commonly prescribed antibiotic for pneumonia, accounting for 20 % of ED visits [2]. Furthermore, consumption of third-generation cephalosporins in French hospitals doubled between 2000 and 2010 [3]. Bacterial resistance mediated by extended-spectrum β-lactamases (ESBL) has recently emerged as a major threat for treatment of community-acquired enterobacterial infections [4]. Two classes of antibacterial agents, fluoroquinolones and third-generation cephalosporins, are specifically prone to promote ESBL-mediated resistance [5–10]. Hence, these antibiotics should be used cautiously [11, 12]. Conversely, ESBL-mediated resistance seems less likely to occur after exposure to amoxicillin-clavulanate [6, 10]. For hospitalized patients with community-acquired pneumonia with no need for intensive care treatment, the European Respiratory Society and the European Society for Clinical Microbiology and Infectious Diseases (ESCMID/ERS) recommend as an initial empirical treatment either a β-lactam (aminopenicillin, aminopenicillin/β-lactamase inhibitor, cefotaxime, ceftriaxone or penicillin G) possibly combined with a macrolide, or a respiratory fluoroquinolone [13]. The Infectious Diseases Society of America and American Thoracic Society

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(IDSA/ATS) recommend for patients hospitalized in non ICU wards either a respiratory fluoroquinolone, or a β-lactam—preferred agents including cefotaxime, ceftriaxone, and ampicillin—plus a macrolide [14]. However, circumstances under which a third-generation cephalosporin should be preferred to an aminopenicillin or an aminopenicillin/β-lactamase inhibitor combination are not detailed [13, 14]. Hence, considering their respective ability to select bacterial resistances, criteria are needed to help physicians to choose between an aminopenicillin, combined or not with β-lactamase inhibitor, and a third-generation cephalosporin. Such criteria may help to restrict use of third-generation cephalosporins in pneumonia.

The recent trend of third-generation cephalosporins use in patients with pneumonia is poorly known in the ED, as well as the proportion of prescriptions that could be avoided. Our objectives were to test whether the proportion of patients with pneumonia who are treated in the ED with a third generation cephalosporin has increased during recent years, and to estimate the proportion of avoidable prescriptions.

Methods

Patients

The study was retrospectively conducted in a 3000-bed academic centre between 2002 and 2012. Eligible patients were selected from the institution database using the following criteria: age of 15 years or more, and admission from the ED to any acute medical ward (except intensive and intermediate care units), with a principal diagnosis of pneumonia according to the 10th International Classification of Diseases at hospital discharge. Patients transferred from another acute care hospital to the ED were not eligible. Among 7,258 eligible patients, 100 cases were randomly selected per year using a computer-generated random sequence, and screened for inclusion. Patients were included if the diagnosis of pneumonia was mentioned on the ED chart's conclusion and if an antibacterial agent was administered in the ED. Patients were excluded if any other acute infectious disease was diagnosed or suspected in the ED chart's conclusion.

Medical records of the whole hospital stay were abstracted to collect data on demographics, history, physical examination, coexisting illnesses, laboratory results, radiographic findings and treatment.

Avoidable prescriptions of third-generation cephalosporins

The third-generation cephalosporin class was restricted to ceftriaxone and cefotaxime, and included neither oral or antipseudomonal cephalosporins. As stated above, ESCMID/ERS and IDSA/ATS guidelines do not mention how to select between a third-generation cephalosporin and an aminopenicillin—with or without a β-lactamase inhibitor—for treating hospitalized patients with community-acquired pneumonia with no need for intensive care treatment [13, 14]. French national guidelines for pneumonia treatment specify that third-generation cephalosporins should be restricted as a first-line therapy to patients with higher age or comorbid condition [15]. Therefore, we considered that third-generation cephalosporin was not avoidable if prescribed for patients with (i) comorbid condition or age≥65 years, and (ii) either allergy or intolerance to penicillin, failure of aminopenicillin, or treatment with aminopenicillin in the three previous months. The prescription of third-generation cephalosporin was otherwise deemed avoidable.

Antibacterial therapy on day 7

Patients who were treated by a third-generation cephalosporin in the ED and who were alive on the seventh day after admission in the ED were classified in one of following classes according to the treatment given on day 7: (i) ongoing treatment with third-generation cephalosporin, (ii) no antibacterial therapy, (iii) de-escalation, (iv) other. De-escalation was defined as antibacterial therapy with amoxicillin, amoxicillin-clavulanate, telithromycin or pristinamycin, neither combined with a third-generation cephalosporin or a fluoroquinolone. For patients discharged before day 7, we considered the discharge prescription form.

Statistical analysis

Based on previous pilot studies in our ED, we hypothesized that the prescription rate of third-generation cephalosporin increased from 12 % in 2002 to 34 % in 2012. In order to compare these two proportions, the required sample size was established to 84 patients by year, considering a 5 % level of significance and a power of 90 %. Taking into account cases that would not fulfill inclusion criteria or meet exclusion criteria, we screened 100 patients per year. Continuous data were described using medians (1st and third quartiles). Proportions were described using estimated value [95 % confidence interval]. The association between antibiotic use and year was tested using logistic regression. All variables with a P value<0.2 in univariate analysis were included for multivariate analysis, and were selected using a backward procedure. All statistical tests were two-tailed, and P value≤0.05 was considered statistically significant. Statistical analyses were performed using R software, version 2.15.0, ISBN 3-900051-07-0 (http://CRAN.R-project.org).

Results

Baseline characteristics

Among 1,100 eligible patients, medical records were not available in 52 cases, and 11 patients finally proved to be admitted from the ED to an intensive care unit or intermediate unit after analysis of medical records. Inclusion criteria were not met for 293 patients: no diagnosis of pneumonia in the ED (n=257), and no antibacterial therapy administered in the ED (n=36). Twelve patients were excluded because another acute infectious disease was diagnosed or suspected in the ED chart's conclusion. Finally, 732 patients were included. Baseline characteristics are reported in Table 1. Subsequent admission from a medical ward to the ICU was noted for 2.5 % [1.5–3.9 %] of patients. Blood culture was drawn from 510 patients, and grew bacteria in 10.0 % [7.6–13.0 %]. *Streptococcus pneumoniae* was the most frequent pathogen (28 among 51 patients). Amoxicillin-clavulanate, third-generation cephalosporins and fluoroquinolones were the most frequently prescribed antibiotics in the ED during the study period (Table 1).

Secular trends in treatment with third-generation cephalosporins in the ED

The proportion of patients treated with a third generation cephalosporin in the ED increased from 13.9 % [6.9–24.1 %] in 2002 to 29.5 % [18.5–42.6 %] in 2012 (Fig. 1). Univariate logistic regression showed that this trend was significant (OR=1.07 [1.01–1.14] , P=0.02). Meanwhile, use of macrolides also increased (OR=1.25 [1.12–1.40], P=0.0001), whereas decreased use was observed for amoxicillin-clavulanate (OR=0.95 [0.91–1.00, P=0.05) and fluoroquinolones (OR=0.89 [0.84–0.95], P=0.0008). No significant trend was observed for amoxicillin (OR=1.03 [0.95–1.12], P=0.47) and for treatment by third-generation cephalosporin and/or fluoroquinolone (OR=1.00 [0.95–1.05], P=0.96).

ED physicians may prefer a third-generation cephalosporin when treating patients with comorbid conditions, severe infection or previously exposed to antibacterial agents. Therefore, we also tested the association between third-generation cephalosporin treatment and alcoholism, disabling health condition, immunocompromising condition, chronic neurological disease, previous pneumonia, antibacterial therapy in three previous months, fluid resuscitation in the ED, vasopressor use in the ED, ventilatory support in the ED, do-not-resuscitate order, secondary admission to ICU, death during the hospital stay, pneumonia severity index class≥4 and REA-ICU class. Along with year, univariate logistic regression showed that seven variables were significantly linked with administration of third-generation cephalosporin in the ED: immunocompromising condition (OR, 3.00 [1.81–4.94]),

Table 1 Patients baseline characteristics

Characteristic	Description	Value
Demographic data	Age (years)	78 (65–85)
	Male	55.9 % [52.2–59.5 %]
	Nursing home resident	20.1 % [17.3–23.2 %]
	Length of hospital stay (days)	6 (4–11)
Comorbid conditions	Congestive heart failure	16.9 % [14.3–19.9 %]
	Coronary artery disease	19.3 % [16.5–22.3 %]
	Alcohol abuse	7.5 % [5.8–9.7 %]
	Chronic liver disease	3.0 % [1.9–4.6 %]
	Immunocompromising conditions[a]	10.4 % [8.3–12.9 %]
	Neoplastic disease	14.3 % [11.9–17.1 %]
	Chronic lung disease	24.6 % [21.5–27.9 %]
	Cerebrovascular disease	13.1 % [10.8–15.8 %]
	Other chronic neurologic conditions	19.1 % [16.4–22.2 %]
	Diabetes mellitus	13.3 % [10.9–16.0 %]
	Renal disease	6.8 % [5.2–9.0 %]
	History of multiresistant bacteria	0.5 % [0.2–1.5 %]
Severity	Pneumonia severity index (class)	
	I	0
	II	18.7 % [16.0–21.8 %]
	III	19.0 % [16.2–22.1 %]
	IV	40.1 % [37.1–44.4 %]
	V	21.6 % [18.7–24.8 %]
	REA-ICU class	
	I	53.1 % [49.4–56.8 %]
	II	35.4 % [31.9–39.0 %]
	III	7.0 % [5.3–9.1 %]
	IV	4.5 % [3.2–6.3 %]
	Do not resuscitate order	6.4 % [4.8–8.5 %]
	In-hospital mortality	9.7 % [7.7–12.1 %]
Antibacterial therapy in the emergency department (ED)	Antibacterial agent (patients, %)	
	Third generation cephalosporin	20.1 % [17.3–23.2 %]
	Amoxicillin	8.7 % [6.9–11.1 %]
	Amoxicillin-clavulanate	63.8 % [60.2–67.3 %]
	Fluoroquinolone	15.6 % [13.1–18.4 %]
	Macrolide	6.2 % [4.6–8.2 %]
	Aminoglycoside	1.6 % [0.9–2.9 %]
	Imidazole derivative	2.3 % [1.4–3.8 %]
	Other agent	2.5 % [1.5–3.9 %]
	Third-generation cephalosporin and/or fluoroquinolone	35.7 % [32.2–39.3 %]
	Number of antibacterial agents par patient	
	1	80.6 % [77.5–83.4 %]
	2	18.0 % [15.4–21.1 %]
	3	1.4 % [0.7–2.6 %]
	Delay in antibiotic administration (h:min)	4:47 (2:54–7:17)

Percentages are shown with 95 % confidence intervals. Quantitative variables are expressed as median (first and third quartile)

[a] Immunocompromising conditions were: immunocompromising treatment including corticosteroid therapy (>10 mg/day) for at least 1 month, antineoplastic chemotherapy in six previous months, history of splenectomy or AIDS, cachexia

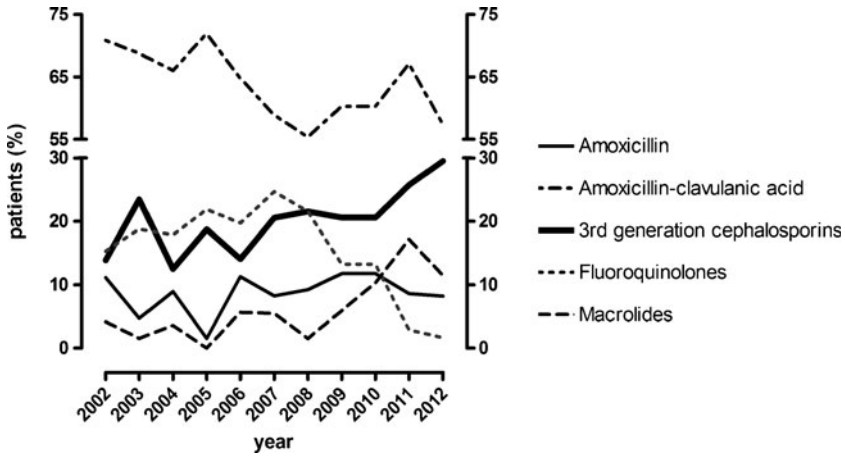

Fig. 1 Trends in antibacterial therapy for community-acquired pneumonia in the emergency department (ED)

antibacterial therapy in three previous months (OR, 2.84 [1.52–5.20]), fluid resuscitation in the ED (OR, 3.55 [2.12–5.88]), do-not-resuscitate order (OR, 2.18 [1.13–4.05]), death during the hospital stay (OR, 1.78 [1.01–3.04]), and pneumonia severity index class≥4 (OR, 1.88 [1.27–2.84]), REA-ICU class (OR, 1.55 [1.26–1.91]). Five variables, including year, remained independently associated with the third-generation cephalosporin treatment in multivariate logistic regression (Table 2).

Avoidable prescriptions of third-generation cephalosporins

Among 147 patients treated with a third-generation cephalosporin in the ED, 29 prescriptions were not avoidable, because they were associated with allergy or intolerance to penicillins (n=11), failure of aminopenicillin therapy (n=13) or treatment with aminopenicillin in three previous months (n=5), all in patients aged>65 years or with any comorbid condition. Therefore, treatment with third-generation cephalosporin was classified as avoidable in 118 out of 147 patients (80.3 % [72.7–86.2 %]).

Median duration of treatment with third-generation cephalosporins was 3 (1–8) days, and accounted for 50 % [47–52 %] of total duration of antibacterial therapy. One hundred thirty-four (134) patients treated with a third-generation cephalosporin in the ED were alive on the seventh day after admission in the ED. Among these patients, status of antibacterial therapy at day 7 was: on-going treatment with third-generation cephalosporin in 32 % [24–41 %], no antibacterial therapy in 17 % [11–25 %], de-escalation in 32 % [24–41 %], and other in 19 % [13–27 %]. Among 43 patients who were de-escalated at day 7, blood culture and sputum culture were positive in, respectively, 3 and 0 cases. Treatment with third-generation cephalosporin was more frequently de-escalated in patients classified as avoidable prescription than in patients classified as unavoidable prescription (40 % [30–50 %] vs 4 % [0–20 %], χ^2 test, P value<0.001).

Table 2 Factors independently associated with third-generation cephalosporin use for community-acquired pneumonia in the ED

Variable	Odds ratio	P value
Year	1.01 [1.00–1.02]	0.02
Immunocompromising condition[a]	1.20 [1.10–1.32]	<0.0001
Antibacterial therapy in three previous months	1.21 [1.08–1.36]	0.001
Fluid resuscitation	1.22 [1.11–1.35]	<0.0001
REA-ICU class	1.06 [1.02–1.10]	0.002

[a] Immunocompromising conditions were: immunocompromising treatment including corticosteroid therapy (>10 mg/day) for at least 1 month, antineoplastic chemotherapy in six previous months, history of splenectomy or AIDS, cachexia

Discussion

Our results show that third-generation cephalosporins use for treating pneumonia dramatically increased between 2002 and 2012 in our ED. At the end of the study, the proportion of patients treated with a third-generation cephalosporin was roughly similar to those observed in US and European EDs [1, 2]. Treatment with a third-generation cephalosporin was de-escalated in 32 % of cases. Considering the whole series, the frequency of de-escalation (5.8 %) was quite similar to what has been observed in a multicentric study [1]. In the majority of cases, de-escalation was not guided by microbiological results. These findings retrospectively suggest that it was not necessary to use agents with such a large antibacterial spectrum as third-generation cephalosporins in these patients. Furthermore, according to restrictive criteria, we retrospectively considered that 80.3 % of third-generation cephalosporin prescriptions were avoidable, and could have been replaced by an agent with a more narrow spectrum such as amoxicillin or amoxicillin-clavulanate. This is far higher than the actually observed rate of de-escalation during hospital stay, hence suggesting that third-generation cephalosporins use may be significantly restricted during or after the ED visit.

This study has three main limitations. First, it is a retrospective study. However, this design would hardly alter the assessment of prescriptions, as every drug prescription is written in the patient's medical records in our institution. Second, its monocentric nature prevents us from extrapolating our conclusions. A multicentric study would improve the scope of our results. Third, there is no general agreement about criteria for selecting a third-generation cephalosporin or an agent covering a more narrow spectrum such as amoxicillin or amoxicillin-clavulanate, when treating patients with pneumonia. For example, it may be discussed whether penicillin therapy in three previous months justifies a third-generation cephalosporin rather than an aminopenicillin combined or not with β-lactamase inhibitor. Conversely, some may prefer ceftriaxone to amoxicillin-clavulanate in severely ill patients of whom admission to the ICU has been discarded due to advanced age or comorbidity, although there is no evidence that ceftriaxone is more effective than amoxicillin-clavulanate in community-acquired pneumonia [16, 17]. Furthermore, the distinction between community-acquired and health-care associated pneumonia remains debated in Europe [18]. According to the IDSA/ATS guidelines, pneumonia in a non ambulatory nursing home resident should be treated as a healthcare-associated pneumonia with risk factor for multidrug resistant bacteria, i.e. with an antipseudomonal and antistaphylococcal regimen [14, 19]. Conversely, ESCMID/ERS and French guidelines do not recommend specific therapy for nursing home residents, except in case of aspiration pneumonia [13, 15]. Given that third-generation cephalosporins were more frequently de-escalated among patients with avoidable prescription than in patients with unavoidable prescription, our results suggest that our pre-specified criteria for avoidable prescription may be acceptable. However, evidence-based criteria are needed to help physicians to choose between antibiotics that cause such different collateral effects on bacterial resistance.

In conclusion, third-generation cephalosporins are increasingly used in the emergency department to treat pneumonia. Most of these prescriptions are avoidable. Antibiotic stewardship programs should be implemented in emergency departments to restrict use of third-generation cephalosporins.

Conflict of interest The authors declare that they have no conflict of interest.

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