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High variability among Emergency Departments in 3rd-generation cephalosporins and fluoroquinolones use for community-acquired pneumonia

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Abstract
Objective Fluoroquinolones and 3rd-generation cephalosporins that are prescribed for pneumonia may be avoided and replaced by a penicillin in some cases. We aimed to determine if the proportion of patients treated for pneumonia with a cephalosporin, a fluoroquinolone or both varies among Emergency Departments (EDs), and to estimate the proportion of avoidable prescriptions.
Methods This was a retrospective study of patients treated for pneumonia in eight French EDs, and subsequently hospitalized in non-ICU wards. Third-generation cephalosporins or respiratory fluoroquinolones were presumed unavoidable if they met both criteria: (1) age ≥65 years or comorbid condition; and (2) allergy or intolerance to penicillin, or failure of penicillin, or previous treatment with penicillin, or for fluoroquinolones only, suspected legionellosis.
Results We included 832 patients. Thirty-four percent (95 % CI, 31–38 %) of patients were treated with a cephalosporin, a respiratory fluoroquinolone or both (range among EDs 19–44 %). Four EDs were independent risk factors for prescription of a cephalosporin, a fluoroquinolone or both [adjusted OR, 2.27 (1.64–3.15)], as were immune compromise [aOR 2.54 (1.56–4.14)], antibacterial therapy started before arrival in the ED [aOR 3.32 (2.30–4.81)], REA-ICU class III or IV [aOR 1.93 (1.15–3.23)], PSI class V [aOR 1.49 (1.00–2.20)], fluid ressuscitation [aOR 3.98 (2.49–6.43)] and non-invasive ventilation in the ED [aOR, 7.18 (1.7–50.1)]. Treatment with a cephalosporin, a fluoroquinolone or both was avoidable in 67 % (62–73 %) of patients.
Conclusion Cephalosporins and fluoroquinolones use in pneumonia is highly variable among EDs. The majority of these prescriptions are avoidable. Antibiotic stewardship programs should be implemented to restrict their use in EDs.

Keywords Community-acquired pneumonia · Antibiotic prescription · Prudent use · Cephalosporins · Fluoroquinolones · Emergency department

Introduction

Fluoroquinolones and 3rd-generation cephalosporins play a major role in promoting bacterial resistance. These agents are specifically prone to promote extended-spectrum β-lactamases (ESBL)-mediated resistance in

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Enterobacteriaceae, which may decrease efficacy of usual therapy of urinary tract and intra-abdominal infections [1–5]. Hence, these antibiotics should be used cautiously [6, 7]. Conversely, ESBL-mediated resistance seems less likely to occur after exposure to amoxicillin–clavulanate [2, 5]. To our knowledge, there is no proof that 3rd-generation cephalosporins are associated with better outcome in pneumonia than amoxicillin–clavulanate [8–10]. 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 [11]. The Infectious Diseases Society of America and American Thoracic Society (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 [12]. However, circumstances under which a 3rd-generation cephalosporin or a fluoroquinolone should be preferred to an aminopenicillin or an aminopenicillin/β-lactamase inhibitor combination are not detailed [11, 12]. We have recently proposed criteria to determine when a 3rd-generation cephalosporin should be preferred to a penicillin, and when it should not [13]. Using these criteria, we estimated in a monocentric study that 80 % of 3rd-generation cephalosporin prescriptions for community-acquired pneumonia in Emergency Department (ED) patients subsequently hospitalized in non-ICU wards were avoidable, i.e., could be replaced by a penicillin [13].

Third-generation cephalosporins and fluoroquinolones are widely used to treat patients with community-acquired pneumonia [14–18]. As described for total antibiotic use in the community, the literature suggests marked geographical differences in hospital antibiotic prescriptions for community-acquired pneumonia [19]. Indeed, recent studies have shown that the proportion of patients treated for community-acquired pneumonia with a 3rd-generation cephalosporin or a respiratory fluoroquinolone ranged between 40 and 70 %, while the proportion of patients treated with a penicillin monotherapy ranged between 5 and 24 % [14–16]. A high variability of the proportion of patients treated for pneumonia by a combination therapy has also been reported among hospitals [16, 18]. However, it is not known whether, and to what extent, the proportion of patients treated with a cephalosporin, a fluoroquinolone or both varies among EDs.

Our objective was to determine if the proportion of patients treated in ED for pneumonia with a cephalosporin, a fluoroquinolone or both shows interhospital variability. We also aimed to estimate the proportion of avoidable prescriptions of these antibacterial agents.

Methods

Setting, patients and study design

The study was retrospectively conducted in eight Emergency departments in western France. Eligible patients were selected from the institutional databases using the following criteria: age of 18 years or more, admission in the ED between January 2013 and December 2013, transfer from the ED to any acute medical ward (except intensive and intermediate care units), and main 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 3396 eligible patients, we randomly selected cases in whom inclusion and exclusion criteria were subsequently searched, using a computer-generated random number list. 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.

Methods and measurements

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

Outcomes

Antibacterial therapy was assessed as previously described [13]. Antibacterial agents administered in the ED and in medical wards were classified in one of the following classes: amoxicillin, amoxicillin–clavulanate, 3rd-generation cephalosporins (exclusively including ceftriaxone and cefotaxime), respiratory fluoroquinolones (exclusively including levofloxacin and moxifloxacin), other fluoroquinolones, macrolides, pristinamycin, aminoglycosides, imidazole derivatives and other antibiotics.

As stated above, ESCMID/ERS and IDSA/ATS guidelines do not mention how to select between a 3rd-generation cephalosporin, a respiratory fluoroquinolone and an aminopenicillin—with or without a β-lactamase inhibitor—for treating inpatients hospitalized in non-ICU wards for community-acquired pneumonia [11, 12]. French national guidelines for pneumonia treatment specify that 3rd-generation cephalosporins and antipneumococcal fluoroquinolones should be restricted as a first-line therapy to patients with higher age or comorbid condition [20]. Therefore, we considered that 3rd-generation cephalosporin was

not avoidable if prescribed for patients with (1) comorbid condition or age ≥65 years, and (2) either allergy or intolerance to penicillin, failure of aminopenicillin or treatment with aminopenicillin in 3 previous months. The prescription of 3rd-generation cephalosporin was otherwise deemed avoidable. Likewise, we considered that respiratory fluoroquinolone was not avoidable if prescribed for patients with (1) comorbid condition or age ≥65 years, and (2) either allergy or intolerance to β-lactams, suspected legionellosis, failure of aminopenicillin, or treatment with aminopenicillin in three previous months.

Antibacterial therapy on day 7 was assessed in patients who were alive on day 7 after admission in the ED. Patients who were treated in the ED by a 3rd-generation cephalosporin or a respiratory fluoroquinolone were classified in one of the following classes according to the treatment given on day 7: (1) on-going treatment with a cephalosporin, a fluoroquinolone or both (2) no antibacterial therapy (3) de-escalation and (4) other. De-escalation was defined as antibacterial therapy with amoxicillin, amoxicillin–clavulanate, macrolide, telithromycin or pristinamycin, neither combined with a 3rd-generation cephalosporin or any fluoroquinolone. Patients who were treated in the ED with a penicillin (i.e., amoxicillin or amoxicillin/clavulanate) and neither with 3rd-generation cephalosporin or fluoroquinolone were classified as follows: (1) on-going treatment with penicillin, (2) no antibacterial therapy, (3) broadening of spectrum and (4) other. Broadening of spectrum was defined as therapy with a cephalosporin, a fluoroquinolone or both. For patients discharged before day 7, we considered the discharge prescription form.

Statistical analysis

Based on a previous study conducted in one of the participating EDs, we hypothesized that the prescription rate of 3rd-generation cephalosporins was 30 % [13]. We estimated that 900 patients were necessary to obtain a 95 % confidence interval precision of 3 % for the prescription rate of 3rd-generation cephalosporins. Considering that one eligible case out of three would not fulfill inclusion criteria or meet exclusion criteria, and that 12 % of medical charts would not be available, we planned to screen 1344 eligible cases for inclusion, i.e., 168 cases per ED, in order to include 900 cases.

Continuous data were described using medians (1st and 3rd quartiles). Proportions were described using estimated value (95 % confidence interval). As we planned to include the same number of patients for each ED, whereas the number of eligible cases in each ED actually differed, descriptive statistics of our sample was not exactly representative of the study population. Hence, to extrapolate some results to the study population, we weighted the results of each ED by its number of eligible cases. Unless otherwise stated, data were not extrapolated. Risk factors for 3rd-generation cephalosporin or fluoroquinolone treatment were tested using logistic regression. All variables with a P value <0.2 in univariate analysis were included for multivariate analysis. For inclusion of multilevel variables in the multivariate analyses (i.e., ED, REA-ICU class and Pneumonia Severity Index class), we grouped values that showed non-different ORs in univariate analysis using Wald tests for linear hypotheses (contrast tests). Then, variables were selected using an automated backward procedure at level 5 % with the R glm and MASS package stepAIC functions. No confounding variable was forced in the models. 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 1344 eligible patients (median number per ED, 398 [320–573]), medical records were not available in 14 cases, seven patients were not admitted from the ED to an acute medical ward, one patient was not admitted from the ED and two patients were admitted in 2012. Inclusion criteria were not met for 463 patients: no diagnosis of pneumonia in the ED (n = 338), and no antibacterial therapy administered in the ED (n = 125). Twenty-five patients were excluded because another acute infectious disease was diagnosed or suspected in the ED chart's conclusion. Finally, 832 patients were included [median (range) number per ED, 100 (89–138)]. Baseline characteristics are reported in Table 1. Subsequent admission from a medical ward to the ICU was noted for 1.2 % [0.6–2.3 %] of patients. Blood culture was drawn from 563 patients (68 % [64–71 %]), and grew bacteria in 38 patients. *Streptococcus pneumoniae* was the most frequent pathogen (15 patients). Urinary pneumococcal antigen and urinary *Legionella* antigen were positive in 44 among 288 patients (15 % [11–20 %]) and 0 among 313 patients, respectively. Amoxicillin–clavulanate and 3rd-generation cephalosporins were the most frequently prescribed antibiotics in the ED (Table 1). The proportions of patients treated by these antibiotics as extrapolated to the study population were similar (Supplementary file). Median duration of antibacterial therapy was 11 (8–13) days. Amoxicillin–clavulanate was recommended by local guidelines for initial therapy of community-acquired pneumonia in patients with comorbid condition or age ≥65 years in all EDs. Respiratory fluoroquinolones and 3rd-generation cephalosporins were also

Table 1 Patients baseline characteristics

Characteristic	Description	Value
Demographic data	Age (years)	82 (69–88)
	Male	54 % (51–57 %)
	Nursing home resident	28 % (25–31 %)
	Length of hospital stay (days)	8 (5–12)
Comorbid conditions	Congestive heart failure	15 % (12–17 %)
	Coronary artery disease	13 % (11–15 %)
	Alcohol abuse	6 % (4–7 %)
	Chronic liver disease	2 % (1–3 %)
	Immunocompromising conditions	11 % (9–13 %)
	Neoplastic disease	16 % (14–19 %)
	Chronic lung disease	24 % (21–27 %)
	Cerebrovascular disease	15 % (13–18 %)
	Other chronic neurologic conditions	25 % (22–28 %)
	Diabetes mellitus	18 % (15–21 %)
	Renal disease	9 % (8–12 %)
	History of multiresistant bacteria	1 % (0–2 %)
Severity	Pneumonia Severity Index class	
	I	0
	II	17 % (14–19 %)
	III	17 % (15–20 %)
	IV	42 % (39–46 %)
	V	24 % (21–27 %)
	REA-ICU Class	
	I	48 % (45–52 %)
	II	40 % (37–44 %)
	III	9 % (7–11 %)
	IV	2 % (1–3 %)
	Do not ressuscitate order	7 % (6–9 %)
	In-hospital mortality	10 % (8–12 %)
Antibacterial therapy in the ED	Antibacterial agent (patients, %)	
	Amoxicillin–clavulanate	59 % (56–63 %)
	3rd-generation cephalosporin	31 % (28–34 %)
	Macrolide	10 % (8–12 %)
	Respiratory fluoroquinolone	7 % (5–9 %)
	Amoxicillin	5 % (4–7 %)
	Imidazole derivative	3 % (2–4 %)
	Aminoglycoside	2 % (1–3 %)
	Other antibacterial agent	1 % (1–2 %)
	Non-respiratory fluoroquinolone	1 % (0–2 %)
	Pristinamycin	1 % (1–2 %)
	3rd-generation cephalosporin, respiratory fluoroquinolone or both	34 % (31–38 %)
	Antibacterial agent per patient, *N*	
	1	82 % (79–84 %)
	2	17 % (14–20 %)
	≥3	1 % (1–3 %)
	Delay in antibiotic administration (min)	265 (163–415)

Percentages are shown with 95 % confidence intervals. Quantitative variables are expressed as median (1st and 3rd quartile)

Table 2 Inter-hospital variability of proportions of patients treated in the ED with a 3rd-generation cephalosporin, a respiratory fluoroquinolone or both

Centre	Patients treated (%)			Limitation in use as first-line therapy[a]	
	3rd-generation cephalosporin	Respiratory fluoroquinolone	3rd-generation cephalosporin, respiratory fluoroquinolone or both	3rd-generation cephalosporin	Respiratory fluoroquinolone
A	22 % (15–31 %)	17 % (10–25 %)	29 % (21–39 %)	Limitation	Limitation
B	14 % (8–22 %)	5 % (2–12 %)	19 % (12–28 %)	No limitation	No limitation
C	38 % (30–47 %)	15 % (10–23 %)	45 % (37–54 %)	No limitation	Limitation
D	35 % (26–46 %)	0 % (0–5 %)	35 % (26–46 %)	No limitation	Limitation
E	26 % (17–36 %)	4 % (1–12 %)	30 % (21–41 %)	Limitation	Limitation
F	41 % (32–51 %)	6 % (3–13 %)	42 % (33–52 %)	No limitation	Limitation
G	25 % (17–35 %)	1 % (0–6 %)	26 % (18–36 %)	No limitation	No limitation
H	42 % (31–53 %)	2 % (0–9 %)	44 % (33–55 %)	No limitation	No limitation

[a] Local guidelines for community-acquired pneumonia in a patient with comorbid condition or age ≥65 years, to be hospitalized in medical ward

Table 3 Predictive factors for treatment with a 3rd-generation cephalosporin in the ED: multivariate analysis

Characteristic	Variable	Adjusted OR	*P* value
Comorbid condition	Immunocompromising condition	2.25 (1.37–3.70)	0.001
	Antibacterial therapy started before ED visit	2.82 (1.94–4.13)	<0.001
Severity	REA-ICU class[a]		
	II	1.58 (1.11–2.25)	0.011
	III or IV	2.92 (1.72–4.94)	<0.001
	Fluid ressuscitation in the ED	4.56 (2.85–7.37)	<0.001
	Non-invasive ventilation in the ED	9.26 (2.18–63.76)	0.007
Centre	C or D[b]	1.95 (1.31–2.92)	0.001
	F or H[b]	3.60 (2.40–5.42)	<0.001

[a] The REA-ICU class I was the reference

[b] EDs A, B, E and G were the reference

recommended with some limitation in 2 and 5 EDs, respectively, and without restriction in other EDs (Table 2).

Frequency and predictive factors of treatment with a 3rd-generation cephalosporin or a fluoroquinolone in the ED

Proportions of patients treated in the ED with a 3rd-generation cephalosporin or a respiratory fluoroquinolone showed high variability among EDs, from 14 to 42 % for 3rd-generation cephalosporin, from 0 to 15 % for respiratory fluoroquinolone, and from 19 to 44 % for cephalosporin, fluoroquinolone or both (Table 2). Third-generation cephalosporins were less frequently administered in EDs where they are recommended with limitations (24 % [18–30 %]) than in EDs where there is no limitation (33 % [29–37 %], $P = 0.02$). Respiratory fluoroquinolones were more frequently administered in EDs where they are recommended with limitations (9 % [6–12 %]) than in EDs where there is no limitation (4 % [2–7 %], $P = 0.02$). Proportions of patients treated in the ED with a cephalosporin, a respiratory fluoroquinolone or both did not differ significantly between EDs where both classes are recommended with limitations (30 % [24–37 %]) and those where there is no limitation (36 % [32 − 40 %], $P = 0.14$). Predictive factors for treatment with a cephalosporin, a respiratory fluoroquinolone or both were tested among comorbid conditions, history, severity markers and EDs. Multivariate analysis showed that treatment with 3rd-generation cephalosporin was associated with immunocompromising condition, antibacterial therapy started before the ED visit, REA-ICU class II and class III or IV, fluid ressuscitation, non-invasive ventilation in the ED, and 4 EDs (Table 3). Multivariate analysis showed that treatment with respiratory fluoroquinolone in the ED was associated with a history of pneumonia (adjusted OR 2.35 (1.22–4.40), $P = 0.009$), antibacterial therapy started before the ED visit [adjusted OR 2.98 (1.62–5.39), $P < 0.001$], REA-ICU class IV [adjusted OR

Table 4 Predictive factors for treatment with a 3rd-generation cephalosporin, a respiratory fluoroquinolone or both, in the ED: multivariate analysis

	Variable	Adjusted OR	*P* value
Comorbid condition and history	Immunocompromising condition	2.54 (1.56–4.14)	<0.001
	Antibacterial therapy started before ED visit	3.32 (2.30–4.81)	<0.001
Severity	REA-ICU class III or IV[a]	1.93 (1.15–3.23)	0.013
	Pneumonia Severity Index class V	1.49 (1.00–2.20)	0.048
	Fluid ressuscitation in the ED	3.98 (2.49–6.43)	<0.001
	Non-invasive ventilation in the ED	7.18 (1.7–50.1)	0.017
Centre	C or D or F or H[b]	2.27 (1.64–3.15)	<0.001

[a] The REA-ICU classes I–II were the reference

[b] EDs A, B, E and G were the reference

7.18 (2.03–22.78), $P = 0.001$] and ED A or C [adjusted OR 6.86 (3.81–12.87), $P < 0.001$]. In multivariate analysis, we found that seven parameters were associated with a cephalosporin, a respiratory fluoroquinolone or both in the ED: immune compromise, antibacterial therapy started before ED visit, Pneumonia Severity Index class V, REA-ICU class III or IV, fluid ressuscitation and non-invasive ventilation in the ED, and four EDs (Table 4).

EDs were included in these analyses after pseudonymization. De-pseudonymization revealed that the two EDs where 3rd-generation cephalosporins are recommended with some limitation in pneumonia (centres A and E) were among the four EDs that had been selected as reference (adjusted OR = 1) for treatment with 3rd-generation cephalosporins in the multivariate logistic regression (Table 3). Among the five EDs where fluoroquinolones are recommended with some limitation, only two had been selected as reference for treatment with a fluoroquinolone in the multivariate logistic regression (EDs A and C), and the three others were at risk for fluoroquinolone treatment (EDs D, E and H). Finally, the two EDs where both respiratory fluoroquinolones and 3rd-generation cephalosporins are recommended with some limitation (centres A and E) were among the four EDs that had been selected as reference for treatment with a cephalosporin, a respiratory fluoroquinolone or both (Table 4).

Avoidable prescriptions of 3rd-generation cephalosporin or respiratory fluoroquinolone in the ED

Among 255 patients treated with a 3rd-generation cephalosporin in the ED, the 3rd-generation cephalosporin was not avoidable for 76 patients, because it was associated with allergy or intolerance to penicillins ($n = 25$), failure of aminopenicillin therapy ($n = 46$) or treatment with aminopenicillin in three previous months ($n = 21$), all in patients aged >65 years or with any comorbid condition. Therefore, treatment with 3rd-generation cephalosporin was classified as avoidable in 179 out of 255 patients [70 % (64–76 %)]. The extrapolation of this proportion to the study population was [70 % (64–76 %)].

Among 58 patients treated with a respiratory fluoroquinolone in the ED, the respiratory fluoroquinolone was not avoidable for 26 patients, because it was associated with allergy or intolerance to penicillins ($n = 9$), failure of aminopenicillin therapy ($n = 11$), treatment with aminopenicillin in three previous months ($n = 8$), or suspected legionellosis ($n = 3$), all in patients aged > 65 years or with any comorbid condition. Hence, treatment with respiratory fluoroquinolone was classified as avoidable in 32 among 58 patients [55 % (42–68 %)]. The extrapolation of this proportion to the study population was 52 % (39–65 %).

Among 285 patients treated in the ED with a 3rd-generation cephalosporin, a respiratory fluoroquinolone or both, these antibacterial agents were not avoidable for 93 patients, because of allergy or intolerance to penicillins ($n = 31$), failure of aminopenicillin therapy ($n = 52$), treatment with aminopenicillin in 3 previous months ($n = 28$), or suspected legionellosis ($n = 3$), all in patients aged >65 years or with any comorbid condition. Hence, treatment with a 3rd-generation cephalosporin, a respiratory fluoroquinolone or both was classified as avoidable in 192 among 285 patients [67 % (62–73 %)]. The extrapolation of this proportion to the study population was [67 % (62–73 %)].

Subsequent antibacterial therapy in medical wards

Among patients treated with a 3rd-generation cephalosporin, a respiratory fluoroquinolone or both in the ED, the median duration of treatment with these agents was 8 (3–11) days, and accounted for 71 % (69–73 %) of the total duration of antibacterial therapy. Among patients treated with penicillin (amoxicillin or amoxicillin–clavulanate) in the ED, the median duration of treatment with penicillin (amoxicillin or amoxicillin–clavulanate) was 9 (6–11) days, and accounted for 81 % (80–82 %) of the total duration of antibacterial therapy. The difference between these proportions was highly significant (χ^2 test, $P < 0.0001$).

Table 5 Antibacterial therapy on day 7

Treatment on day 7	*N*	%
Patients treated in the ED with a 3rd-generation cephalosporin, a respiratory fluoroquinolone or both		
No antibacterial therapy	38	15 % (11–20 %)
3rd-generation cephalosporin, fluoroquinolone or both	145	56 % (49–62 %)
De-escalation	73	28 % (23–34 %)
Other	4	2 % (0–4 %)
Total	260	
Patients treated in the ED with a penicillin[a]		
No antibacterial therapy	54	11 % (9–14 %)
Penicillin	339	70 % (66–74 %)
Spectrum broadening	76	16 % (13–19 %)
Other	13	3 % (2–5 %)
Total	482	

As percentages were rounded, sums may not equal 100 %. De-escalation was defined as antibacterial therapy with amoxicillin, amoxicillin–clavulanate, macrolide, telithromycin or pristinamycin, neither combined with a 3rd-generation cephalosporin or any fluoroquinolone. Broadening of spectrum was defined as therapy with a cephalosporin, a fluoroquinolone or both. The class "Other" encompasses all other situations

[a] Amoxicillin or amoxicillin–clavulanate (combinations with 3rd-generation cephalosporin or fluoroquinolone were excluded)

784 patients were alive on day 7. Among 260 patients treated in the ED with a 3rd-generation cephalosporin, a respiratory fluoroquinolone or both, 111 [43 % (37–49 %)] were either de-escalated or without antibacterial therapy on day 7 (Table 5). The extrapolation of this proportion to the study population was 46 % (40–52 %). The proportion of patients treated with a penicillin (amoxicillin or amoxicillin–clavulanate) in the ED and still treated with a penicillin on day 7 (70 %) was higher than the proportion of patients treated in the ED with a 3rd-generation cephalosporin, a respiratory fluoroquinolone or both, and still receiving one of these antibiotics on day 7 (56 %, $P < 0.0001$). Of note, the number of patients treated in the ED with a cephalosporin, a fluoroquinolone or both and de-escalated on day 7 ($n = 73$) was roughly similar to the number of patients treated in the ED by a penicillin in whom spectrum was subsequently broadened ($n = 76$). Microbiological tests identified no causative bacterium in 81 % (70–89 %) of patients initially treated with a 3rd-generation cephalosporin, a respiratory fluoroquinolone or both and subsequently de-escalated. Finally, we confronted the classification of ED prescriptions as avoidable or unavoidable treatment with the observed antibacterial therapy on day 7. The proportion of patients treated in the ED with a 3rd-generation cephalosporin, a respiratory fluoroquinolone or both, and subsequently de-escalated was higher among patients for whom the prescription was classified as avoidable [35 % (28–43 %)] than among patients for whom it was classified as unavoidable [14 % (8–23 %)], *P* value <0.001).

Discussion

Our multicentric study shows that 34 % of patients with community-acquired pneumonia are treated in the ED with a 3rd-generation cephalosporin, a fluoroquinolone or both in western France EDs. This proportion is similar to what has been shown in European hospitals, and is much lower than reported in Vietnamese hospitals [14, 16]. Interestingly, patterns of antibacterial therapies in this series strongly differ from treatments in US EDs, where aminopenicillins, cephalosporins and fluoroquinolones were prescribed in 5–10 %, in ~25 % and in ~45 % of ED visits, respectively [15].

Furthermore, our study shows that the proportion of patients treated for pneumonia with a 3rd-generation cephalosporin or a fluoroquinolone may be dramatically lowered, as 67 % of these prescriptions were avoidable, i.e., they could have been replaced by an aminopenicillin. This result is supported by the high prevalence (28 %) of de-escalation in patients treated in the ED with a 3rd-generation cephalosporin, a respiratory fluoroquinolone or both, which was mostly done without bacterial isolation. The pneumococcal urinary antigen test was performed in less than half of these series patients. Using this test more frequently may incite doctors to replace a cephalosporin or a fluoroquinolone with amoxicillin, which is recommended to treat pneumococcal pneumonia in France. However, as described for urine culture in urinary tract infections, clinicians do not de-escalate antibacterial therapy according to the pneumococcal urinary antigen test result as often as they could [21–25].

We have recently reported an increased use of 3rd-generation cephalosporins for pneumonia between 2002 and 2012 in one ED involved in this study [13]. This increase was independent of other conditions that may justify to use a 3rd-generation cephalosporin rather than an aminopenicillin, and suggested a drift in antibiotic use. This issue, combined with the high proportion of patients treated by a cephalosporin or a fluoroquinolone in this series, is of concern, as older age—a risk factor for carriage and infection by ESBL producing bacteria—was frequent in our series [3, 4].

Of note, 3rd-generation cephalosporins were far more frequently prescribed than fluoroquinolones in our study. Considering the increasing use of 3rd-generation cephalosporins and the decreasing use of fluoroquinolones in France between 2000 and 2013, we hypothesize that the awareness of antibiotic collateral damage is more common

among French physicians for fluoroquinolones than for cephalosporins [26]. Here, we show striking differences in 3rd-generation cephalosporin and fluoroquinolone use between EDs of a small region (maximal distance between EDs, 230 km). The reason why ED physicians prescribe more or fewer 3rd-generation cephalosporin or fluoroquinolone in pneumonia remains unclear. There was no obvious link between antibiotic use in the ED and either affiliation to a university, type of provided care or number of eligible cases (data not shown). Furthermore, as patient characteristics were thoroughly taken into account through multivariate analyses, we consider that inter-ED variability of antibiotic use is not only explained by differences of patient profiles. Hence, these differences between EDs suggest that treatment of community-acquired pneumonia with a 3rd-generation cephalosporin or a fluoroquinolone is also a matter of prescription habits at the ED level, and reinforce our hypothesis that these antibacterial agents may be less prescribed. Furthermore, we hypothesize that EDs where 3rd-generation cephalosporins and fluoroquinolones are more frequently prescribed for pneumonia have higher rates of avoidable prescriptions of 3rd-generation cephalosporin or fluoroquinolone. Nevertheless, we included too few EDs in this study to test this hypothesis.

Our results question the influence of local guidelines on the rate of cephalosporin and fluoroquinolone prescriptions. Multivariate analysis showed that the two EDs where 3rd-generation cephalosporins and fluoroquinolones are recommended with some limitation were at the lowest risk for treatment with at least one of these antibiotics. However, other EDs where local guidelines included no limitation were also at the lowest risk for treatment with these agents. Furthermore, there was a limitation for fluoroquinolones in local guidelines of the EDs that were at risk for fluoroquinolone prescription. These results support the fact that local guidelines are not sufficient to reduce prescriptions of cephalosporins and fluoroquinolones, and highlight the necessity to implement antibiotic stewardship programs that proved to be effective in reducing the use of these agents [27].

Need for antibiotic stewardship in the ED has been highlighted [28]. Due to the high variability of antibiotic use among EDs participating to this study, if antibiotic stewardship programs aiming at decreasing the use of 3rd-generation cephalosporins and fluoroquinolones in community-acquired pneumonia were to be implemented, they should be tailored to each ED.

This study had three limitations. First, it is a retrospective study. This design would hardly alter the assessment of prescriptions, as every drug prescription was written in the patient's medical records of participating centres during the study period. However, it may have impacted the assessment of covariates. Second, the number of patients treated with a fluoroquinolone was too low to draw any robust conclusion. Third, there is no general agreement on criteria for selecting a 3rd-generation cephalosporin, a fluoroquinolone or an aminopenicillin, when treating patients with pneumonia. For example, it may be discussed whether a penicillin therapy in the three previous months justifies a 3rd-generation cephalosporin or a respiratory fluoroquinolone rather than an aminopenicillin combined or not with a β-lactamase inhibitor. Conversely, although there is no evidence that ceftriaxone is more effective than amoxicillin–clavulanate in community-acquired pneumonia, some clinicians may prefer a 3rd-generation cephalosporin to amoxicillin–clavulanate in severely ill patients, even if they are not admitted in an ICU [8, 9]. However, given that therapies with a 3rd-generation cephalosporin, a fluoroquinolone or both were more frequently de-escalated among patients with avoidable prescription than in patients with unavoidable prescription, our results suggest that our prespecified criteria for avoidable prescription may be acceptable. Furthermore, our criteria for selecting a 3rd-generation cephalosporin or a respiratory fluoroquinolone rather than a penicillin were compatible with the British Thoracic Society guidelines, which recommend levofloxacin or 3rd-generation cephalosporins when penicillins or macrolides are contra-indicated [29]. However, evidence-based criteria are needed to help physicians to choose between antibiotics that cause so different collateral effects on bacterial resistance [30].

In conclusion, our multicentric study shows that the proportion of patients treated for community-acquired pneumonia with a 3rd-generation cephalosporin, a respiratory fluoroquinolone or both is highly variable among EDs. Combined with the fact that most of these prescriptions are avoidable, this result suggests that the choice of antibacterial therapy in the ED is influenced by prescription habits. These should be altered to decrease the use of cephalosporins and fluoroquinolones in pneumonia, in order to slow the emergence of antibiotic-resistant bacteria.

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

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