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Original article

Evolution of antibiotic treatments for healthcare-associated infections caused by extended-spectrum beta-lactamase-producing *Enterobacteriaceae* in France

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ABSTRACT

Background: Infections caused by extended-spectrum beta-lactamase-producing *Enterobacteriaceae* (ESBLE) remain a public health challenge.
Aim: We traced the evolution of antibiotics prescribed for patients with ESBLE-healthcare associated infections (ESBLE-HAI) between 2012 and 2017, with a specific focus on treatments for lower urinary tract infections (LUTI).
Methods: We used the 2012 and 2017 French point prevalence survey data. Patients with ESBLE-HAI were defined as those diagnosed with at least one *Enterobacteriaceae* with ESBL production. Patients with LUTI caused by ESBLE (ESBLE-LUTI) were defined as those with LUTI as the reported infection site and diagnosed with ESBLE. We only analysed treatments intended for HAI.
Results: In 2017, more than half of treatments for ESBLE-HAIs were β-lactams. While from 2012 to 2017 the proportion of carbapenem treatments decreased from 30% to 25%, penicillin treatments doubled. Among patients treated for ESBLE-LUTI, a larger proportion received a single antibiotic in 2017. The most frequently prescribed antibiotics for these infections were amoxicillin/clavulanic acid, nitrofurantoin and ofloxacin. More than one out of six treatments lasted for more than 7 days. Carbapenem use was halved between 2012 and 2017, and decreases were likewise observed for aminoglycosides.
Conclusion: In accordance with French recommendations, comparison of the two most recent French point prevalence surveys showed an evolution in ESBLE-HAI treatment, especially for ESBLE-LUTI. However, treatment durations remained longer than recommended. Data from the 2022 survey should provide insights on the future evolution of prescription trends.

1. Introduction

Treatments of infections caused by extended-spectrum beta-lactamase-producing *Enterobacteriaceae* (ESBLE) often require carbapenem [1], which can lead to the emergence of carbapenemase-producing *Enterobacteriaceae*. Up until 2016 in France, surveillance data highlighted a worrisomely substantial increase in the incidence of ESBLE-positive samples, from 0.13 per 1000 patient-days (PD) in 2002 to 0.71 in 2016. The trend changed that year, with incidence falling to 0.53 per 1000 PDs in 2019 [2]. This encouraging evolution coincided with decreasing incidence of ESBL-producing *E.coli*. Incidence of the other ESBL-producing *Enterobacteriaceae* (*K. pneumoniae* and *E. cloacae*), which are more commonly acquired in hospitals, seems to have stabilised since 2016. In order to prevent an increase in therapeutic dead-ends [3,4], the French National Strategy 2022–2025 for Infection and Antimicrobial resistance Prevention [5] and the French inter-ministerial roadmap for controlling antimicrobial resistance [6] targeted the fight against ESBLE as a priority. Improved antimicrobial use is a key lever in control of emerging resistant strains. The High Council for Public Health (French acronym HCSP) recommends using the most narrow-spectrum antibiotics available for treatment of infections caused by ESBLE [7].

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The national system of "Surveillance and Prevention of Antimicrobial RESistance in hospital settings" (French acronym SPARES) uses laboratory-based data on consumption volumes by hospital and specialty, without specifying any clinical context [2]. In addition, a point prevalence survey (PPS) of healthcare-associated infections and antimicrobial use in acute care hospitals based on the European protocol is conducted in France every 5 years [8]. It collects data on HAI, including infections caused by ESBLE, and also on the antibiotics (ATB) administered to patients with HAI. A recent study [9] suggested that the 2017 PPS data could help to characterize ATB as intended treatment for the main HAIs.

Our objective was to use the 2017 PPS data to characterize the ATBs prescribed for patients with ESBLE-HAI and to compare the results with those of 2012. We focused on treatments for lower urinary tract infections (LUTI), which are the most frequently reported HAIs [10].

2. Material and methods

2.1. Study population

The Point Prevalence Studies took place in 2012 and 2017 between 15 May and 30 June. While in 2012, all hospitals were invited to participate, in 2017 participating hospitals were randomly selected using a systematic sampling after sorting the hospital list by type and region. Were included: acute care wards, rehabilitation care wards, long-term care wards, and psychiatric wards. All patients having been admitted and not discharged on the day of data collection were included. The complete PPS protocols are available online [11,12].

2.2. Data collection

Data were collected either from standardised data collection forms completed by healthcare professionals or from patient charts. Questionnaires included hospital and patient characteristics (age, sex, risk factors for infections, invasive device exposure). For each patient, the presence of up to two (2017) or up to three (2012) active HAIs on the day of data collection was recorded. The definitions of HAIs were adapted from the European PPS protocol [8,13]. For each HAI, infection site, microorganisms (MO), and MO resistance if relevant, particularly with Enterobacteriaceae, were collected. A HAI could be characterized in any one out of 58 possible locations.

Independently of HAI information, current individual treatment consisted in up to four (2017) or 5 (2012) simultaneously prescribed antimicrobial agents. For each agent, the indication (intended treatment for community-acquired infection, HAI, or surgical or medical prophylaxis), the diagnosis, and the reason for antimicrobial use, if documented in the patient chart, were recorded. Variable diagnosis based on a list of 22 possible clinical indications corresponded to the anatomical site of the infection targeted by the treatment. The start date for antimicrobial treatment and the date and reason for any treatment changes were likewise recorded, when appropriate.

2.3. Case definition and prior results

Patients with ESBLE-HAI were defined as those diagnosed with at least one *Enterobacteriaceae*, with a recorded third-generation cephalosporin-resistant or intermediate phenotype, and recorded ESBL production, either carbapenem-susceptible or resistant. In treatment description, we analysed only those with a prescription context in which the agent was intended for curative treatment of a HAI, and excluded contexts of surgical or medical prophylaxis. Patients with a urinary tract infection (UTI) caused by ESBLE (ESBLE-UTI) were defined as those with UTI who had been diagnosed with ESBLE. Among them, patients treated for ESBLE-LUTI were identified using the variable "diagnosis of the treatment" corresponding to LUTI, with intended treatment for HAI.

The data collection date was the treatment end date.

Patients' treatment records and their infection status were independent, but a previous study [9] confirmed individual-based correspondences between therapeutic indications (diagnosis) and HAI site for the two most frequent therapeutic indications (UTI, and lower respiratory tract infections). For patients with UTI and receiving ATB, the clinical indication associated with the treatment (PPS variable: "diagnosis") was UTI in 94.0% (CI95% [85.7–97.6]) of cases. We consequently interpreted treatments for LUTI with a clinical treatment context in patients with LUTI caused by ESBLE as treatments for EBLSE-UTI.

2.4. Data analysis

Prevalence of patients with ESBLE-HAI per 100 hospitalised patients was estimated using 95% confidence intervals (CI95%). The distribution of patients and infections according to categorical variables was determined in proportions. Treatments were compared between 2012 and 2017 using standardized PPS protocols, which guarantee similarity in data collection. Analyses were performed with STATA 14.2.

3. Results

3.1. Characteristics of patients with ESBLE-HAI

Among the 80,988 patients included in the 2017 PPS, 261 had ESBLE-HAI (prevalence: 0.27% (CI95% [0.23–0.33]). These patients more frequently had McCabe Score 1 or 2, with more infection risk factors than the entire cohort of hospitalised patients (Table 1). They were more frequently hospitalised in acute care wards, particularly in intensive care units (9.6%, CI95% [6.9–13.2] vs 1.7%, CI95% [1.4–2.0]) and in rehabilitation wards (34.8%, CI95% [29.8–40.2] vs 25.8%, CI95% [23.6–28.2]).

3.2. Types of ESBLE-HAI

ESBLE-HAI accounted for 5.5% (CI95% [4.6–6.4]) of all HAIs recorded in the 2017 PPS. The most frequently reported types of infections with ESBLE were urinary tract infections (59.6% CI95% [53.4–65.5]) followed by bloodstream infections, surgical site infections, lower respiratory tract infections, and gastrointestinal infections (Fig. 1). These five types of infection accounted for 93.9% (CI95% [90.6–96.0]) of ESBLE-HAIs.

3.3. Microorganisms isolated from EBSLE-HAI

The most frequently isolated ESBL-producing microorganisms were *Escherichia coli* (52.8% CI95% [46.0–59.6]), *Klebsiella pneumoniae* (26.5% CI95% [20.9–33.1]), and *Enterobacter cloacae* (10.3% CI95% [7.4–14.2]). These three bacteria accounted for 89.7% (CI95% [84.6–93.2]) of all ESBLEs in the 2017 PPS.

By infection type, the main bacteria were *E. coli* in ESBLE-UTI, ESBLE-surgical site infections, and ESBLE-bloodstream infections, and *K. pneumoniae* in ESBLE-respiratory tract infections (Fig. 2).

3.4. ESBLE-HAI treatment in 2012 and 2017

Among patients with ESBLE-HAI in the 2017 PPS, 78.7% (CI95% [71.0–84.7]) received an ATB for HAI compared to 79.3% in the

Table 1
Characteristics of patients enrolled in the 2017 and 2012 PPS, France.

Patient characteristics	2017						2012			
	All hospitalised patients (*n* = 80,988)			Patients with ESBLE-HAI (*n* = 261)			All hospitalised patients (*n* = 300,330)		Patients with ESBLE-HAI (*n* = 696)	
	n	%	[CI95%]	*n*	%	[CI95%]	*n*	%	n	%
Male	38,865	47.4	[46.4–48.4]	149	53.9	[46.2–61.5]	137,196	45.7	366	52.6
Age ≥65 years	44,799	56.7	[54.6–58.8]	182	73.8	[67.6–79.1]	160,681	53.5	486	69.8
McCabe Score 1 & 2[1]	21,635	29.3	[27.4–31.2]	136	56.3	[48.5–63.7]	74,788	29.9	358	61.0
Immunodeficiency	8,811	9.3	[8.5–10.3]	72	24.5	[19.2–30.7]	28,800	10.1	165	24.7
Malignancy	11,323	13.1	[12.2–14.2]	74	28.0	[22.8–33.9]	36,782	13.0	146	22.0
Surgery since admission[2]	14,800	16.9	[15.7–18.2]	95	29.9	[24.3–36.1]	53,183	17.7	204	29.3
Use of at least one invasive device	30,472	32.2	[30.3–34.1]	209	72.1	[65.3–77.9]	94,197	31.4	506	72.7
Use of at least one catheter	28,441	29.7	[27.8–31.6]	193	63.8	[58.0–69.3]	86,159	28.7	458	65.8
Urinary catheter	7,941	8.6	[8.0–9.2]	109	41.6	[35.3–48.3]	24,268	8.1	260	37.4
Mechanical ventilation	1,113	1.0	[0.8–1.3]	25	7.2	[4.9–10.6]	4,460	1.5	79	11.4

ESBLE-HAI: healthcare-associated infection caused by an extended-spectrum beta-lactamase-producing Enterobacteriaceae; PPS: point prevalence survey.
[1] *Classification of underlying medical condition severity; McCabe score 1 = patients with ultimately fatal disease (expected survival between 1 and 5 years); 2 = rapidly fatal disease (expected death within 1 year).*
[2] *Surgery during current hospitalisation.*

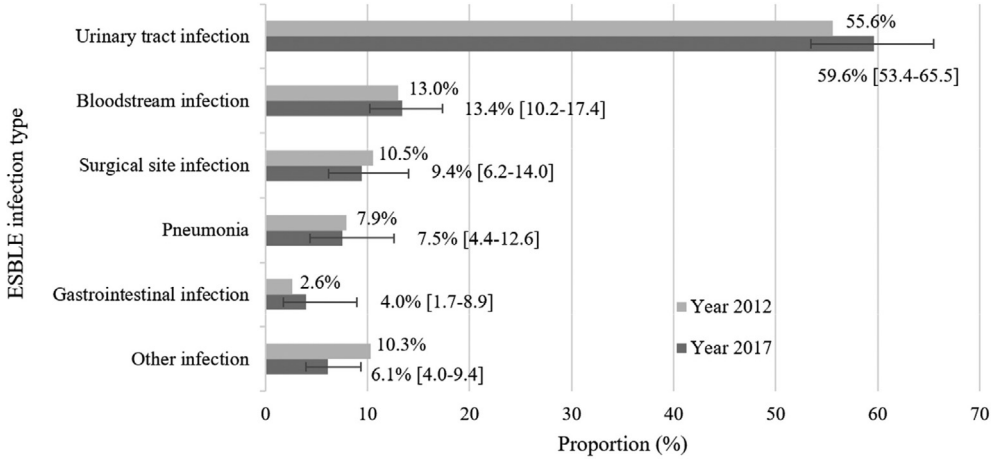


Fig. 1. Distribution of ESBLE-HAI types in the 2017 PPS compared to the 2012 PPS, France. *ESBLE: extended-spectrum beta-lactamase-producing Enterobacteriaceae; PPS: point prevalence survey.*

2012 PPS. Patients received an average of 1.3 (CI95% [1.2–1.4]) ATBs in 2017 versus 1.4 in 2012.

More than half of the treatments were β-lactams (50.4% in 2012 and 57.9% in 2017; Table 2). Among them, carbapenems were the most prescribed ATB, although their proportion decreased (29.7% in 2012 and 24.6% in 2017). There were more treatments with meropenem in 2017 (2.0% in 2012 vs 8.9% in 2017) but fewer with imipenem/cilastatin (22.9% in 2012 vs 9.9% in 2017). Penicillin treatments doubled between 2012 and 2017 (11.8% of ATBs prescribed for ESBLE-HAI in 2012 vs 23.0% in 2017). This was due mainly to a higher proportion of amoxicillin/clavulanic acid (5.2% in 2012 vs 9.8% in 2017) and piperacillin/tazobactam (4.5% in 2012 vs 7.6% in 2017). Prescriptions of third-generation cephalosporins were stable between 2012 (7.4%) and 2017 (7.7%).

Fluoroquinolones were the second most common class (15.3% in 2012 and 13.5% in 2017), with less ciprofloxacin and more levofloxacin prescribed in 2017 than in 2012. Furthermore, fewer aminoglycosides were given in 2017 than in 2012 (2.6% in 2017 vs 9.3% in 2012), particularly amikacin (2.4% vs 7.0%).

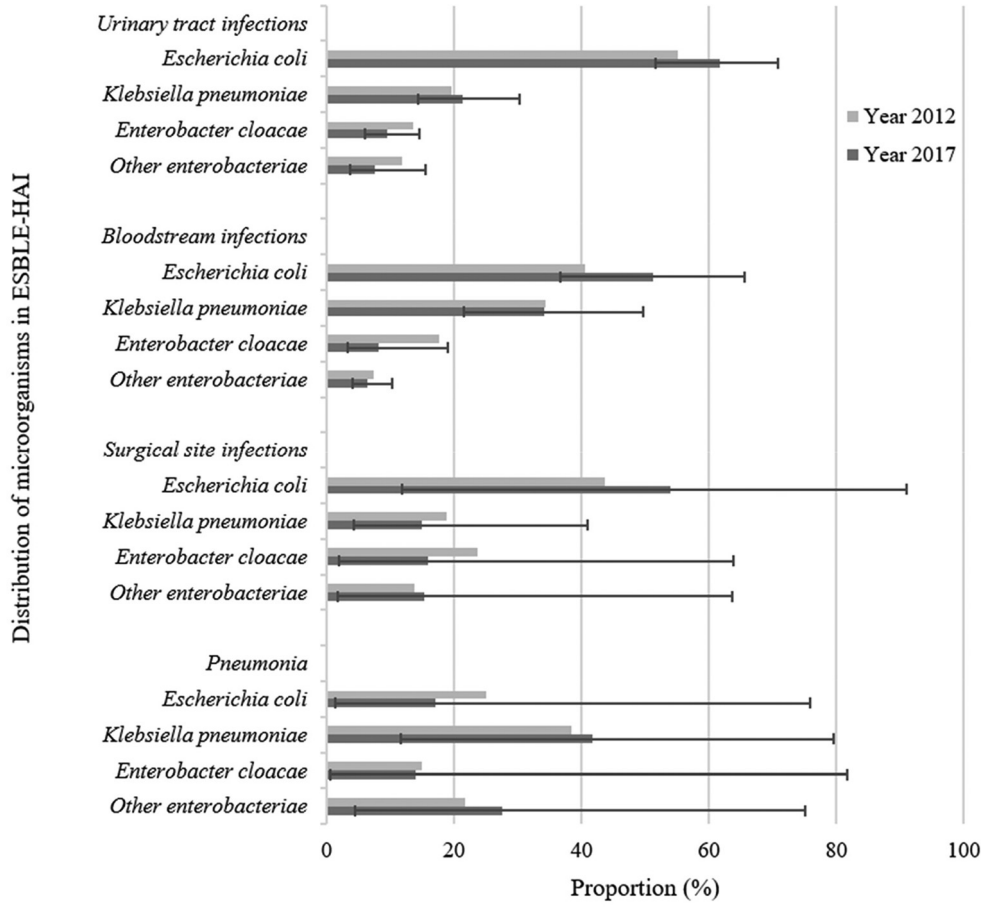
In 2017, the reason for antimicrobial use was documented in patient charts for 92.3% of ESBLE-HAI treatments compared to 90.6% in 2012.

Average treatment duration was 7.5 days (CI95% [6.4–8.6]) in 2017, which was longer than the average of 5.6 days (CI95% [5.0–6.3]) in patients without ESBLE-HAI. Patients with ESBLE-HAI in 2017 were more frequently treated for over 7 days (27.2%, CI95% [22.1–33.1]) than those without ESBLE-HAI (19.2%, CI95% [16.4–22.4]).

3.5. ATB changes

In 2017, the ATB received on the day of the survey was the first to be prescribed in 63.3% (CI95% [56.6–69.5] of treatments. For the remaining 36.7% (CI95% [30.5–43.4]) consisting in second-line ATB, the average time between start of the first ATB prescription and ATB change was 6.0 days (CI95% [5.0–7.0]). Escalation was more frequent than de-escalation for ATBs prescribed for ESBLE-HAI in 2017 (Table 3), except for penicillin. The reason for carbapenem use in 30% of cases was escalation, particularly for imipenem/cilastatin (30.1%, CI95% [17.1–47.2]), and meropenem (25.9%, CI95% [6.2–64.8]).

In comparison, in patients with HAI caused by a non-ESBL-producing *Enterobacteriaceae*, 27.9% (CI95% [24.4–31.7]) of ATB were prescribed as second-line, while average time between the start of the first ATB prescription and ATB change was 5.0 days (CI95% [4.4–5.7]).



ESBLE: extended-spectrum beta-lactamase-producing Enterobacteriaceae; PPS: point prevalence survey

Fig. 2. Distribution of microorganisms isolated in ESBLE-HAI for the four main infection types, in the 2017 PPS compared to the 2012 PPS, France. *ESBLE: extended-spectrum beta-lactamase-producing Enterobacteriaceae; PPS: point prevalence survey.*

3.6. Focus on treatments for ESBLE-LUTI

In the 2017 PPS, 65% (CI95% [59–70]) of patients with EBLSE-HAI had ESBLE-UTI (i.e., 141 patients, prevalence: 0.18% CI95% [0.14–0.23]). Prevalence increased between 2012 and 2017 (0.14% in 2012).

Among these patients, 47.5% in 2012 and 47.5% (CI95% [37.8–57.5]) in 2017 were treated for LUTI with ATBs. Among the 67 patients treated for LUTI with ATBs in 2017, the sex ratio was close to 1 (34 women and 33 men) and among women 6 (24%, CI95% [13–41]) had a urinary tract catheter. Among the 33 men treated for LUTI with ATBs, 12 had a urinary tract catheter (42% CI95% [16–72]).

Most patients received a single ATB, and more frequently in 2017 (98.3% (CI95% [94.1–99.5]) than in 2012 (87.6%). The most frequently prescribed ATBs for patients with ESBLE-LUTI were amoxicillin/clavulanic acid, nitrofurantoin, ofloxacin, ciprofloxacin, and cotrimoxazole (Table 4).

In 2017, average treatment duration for patients with ESBLE-LUTI was 7.0 days (CI95% [5.1–8.9]). More than one out of six treatments (15.6% (CI95% [8.3–27.3]) lasted for more than 7 days.

Pronounced differences in drug consumption were observed between 2012 and 2017. There was a massive decrease in carbapenem use: from 19.0% in 2012 to 8.4% (CI95% [4.1–16.4]) in 2017. From 2012 to 2017, decreases were likewise observed for aminoglycosides (6.2% vs 0.4%, CI95% [0.3–0.7]) and nitrofurantoin (19.5% vs 10.4%, CI95% [7.0–15.0]).

By contrast, increases were observed for penicillin (9.7% in 2012 vs 33.7%, CI95% [25.3–43.2] in 2017), mainly due to amoxicillin/-clavulanic acid (7.5% vs 21.1%, CI95% [13.5–31.4]) and piperacillin/-tazobactam (0.9% in 2012, vs 6.7% CI95% [2.5–16.7] in 2017), and also for fosfomycin trometamol (1.8% vs 7.3 CI95% [2.8–17.9]).

4. Discussion

In our study, patients with ESBLE-HAI had more frequent comorbidities, more infection risk factors, and were older on the average than the cohort of hospitalised patients. They were more frequently hospitalised in intensive care units or rehabilitation wards. This could be linked to longer hospital stays for ESBLE-HAI patients, leading to greater ATB exposure and ESBLE cross-transmission.

Comparison of the two most recent French PPSs highlighted pronounced trends in ESBLE-HAI treatment. These changes are consistent with the French recommendations [7,10,14,15] concerning carbapenem-sparing regimens. Carbapenems were prescribed less often in absolute terms in 2017 (29.7%) than in 2012 (24.6%), a decrease that reflects a shift from imipenem/cilastatin to meropenem. Since 2010, the French HCSP has recommended carbapenem only for severe infections [7]. Nevertheless, it may take several years for prescribers to adopt recommendations, a factor possibly somewhat explaining the differences between 2012 and 2017.

Table 2
Agents and classes of antibiotics prescribed for the treatment of ESBLE-HAI in the 2017 and 2012 PPS, France.

	2017			2012	
Agents and class of antibiotics	n ATB	Prop (%)	CI95%	n ATB	Prop (%)
Beta-lactams	173	57.9	[50.3–65.1]	396	50.4
Penicillin	56	23.0	[17.7–29.4]	93	11.8
amoxicillin/clavulanic acid	*22*	*9.8*	*[6.8–13.9]*	*41*	*5.2*
piperacillin/tazobactam	*21*	*7.6*	*[5.1–11.0]*	*35*	*4.5*
piperacillin	*2*	*0.7*	*[0.1–3.5]*	*3*	*0.4*
amoxicillin	*4*	*2.0*	*[0.7–5.9]*	*5*	*0.6*
temocillin	*4*	*1.5*	*[0.6–4.2]*	*0*	*0.0*
other penicillin	*3*	*1.4*	*[0.3–0.6]*	*9*	*1.1*
First- and second-generation cephalosporins	*5*	2.4	[0.6–0.9]	*11*	*1.4*
Third- and fourth-generation cephalosporins	21	7.7	[5.3–10.9]	58	7.4
cefotaxim	*2*	*0.3*	*[0.1–1.3]*	*4*	*0.5*
ceftriaxone	*8*	*2.4*	*[1.5–3.9]*	*31*	*3.9*
cefixime	*1*	*0.4*	*[0.1–1.8]*	*2*	*0.3*
ceftazidime/avibactam	*2*	*1.0*	*[0.2–5.6]*	*11*	*1.4*
cefepime	*8*	*3.5*	*[1.9–6.6]*	*10*	*1.3*
Carbapenems	90	24.6	[19.7–30.3]	233	29.7
meropenem	*32*	*8.9*	*[5.3–14.6]*	*16*	*2.0*
ertapenem	*15*	*5.9*	*[3.9–8.8]*	*34*	*4.3*
imipenem/cilastatin	*43*	*9.9*	*[7.3–13.2]*	*180*	*22.9*
doripenem	*0*	*0*	–	*3*	*0.4*
Monobactams (*aztreonam*)	1	0.1	[<0.1–1.0]	1	0.1
Fluoroquinolones	36	13.5	[9.2–19.4]	120	15.3
ofloxacin	*12*	*5.2*	*[2.4–11.0]*	*42*	*5.4*
ciprofloxacin	*17*	*5.9*	*[3.8–8.9]*	*60*	*7.6*
levofloxacin	*5*	*1.2*	*[0.4–3.6]*	*5*	*0.6*
norfloxacin	*2*	*1.2*	*[0.3–4.8]*	*13*	*1.7*
Macrolides	1	0.9	[0.1–5.7]	7	0.9
Metronidazole	4	1.7	[0.5–5.7]	20	2.5
Aminoglycosides	12	2.6	[1.4–4.7]	73	9.3
amikacin	*11*	*2.4*	*[1.3–4.6]*	*55*	*7.0*
tobramycin	*1*	*0.1*	*[<0.1–1.0]*	*2*	*0.3*
gentamicin	*0*	*0*	–	*16*	*2.0*
Sulphonamides (*cotrimoxazole)*	9	4.8	[2.5–9.0]	39	5.0
Glycopeptides (*vancomycin*)	13	5.1	[3.4–7.6]	37	4.7
Tetracyclines	4	0.9	[0.3–2.9]	6	0.8
doxycycline	*1*	*0.3*	*[<0.1–2.1]*	*1*	*0.1*
tigecycline	*3*	*0.6*	*[0.2–2.0]*	*5*	*0.6*
Others	31	12.6	[8.2–18.9]	87	11.1
colistin	*5*	*1.0*	*[0.4–2.6]*	*11*	*1.4*
nitrofurantoin	*4*	*3.3*	*[1.5–7.4]*	*46*	*5.9*
fosfomycin trometamol	*4*	*2.5*	*[1.0–6.2]*	*11*	*1.4*
linezolid	*9*	*2.9*	*[1.3–6.3]*	*11*	*1.4*
daptomycin	*5*	*1.2*	*[0.4–3.6]*	*1*	*0.1*
fusidic acid	*0*	*0*	–	*1*	*0.1*
rifampin	4	1.7	[0.5–5.0]	6	0.8
TOTAL	283	*100*	–	785	100.0

ESBLE: extended-spectrum beta-lactamase-producing Enterobacteriaceae; HAI: healthcare-associated infection; PPS: point prevalence survey.

If aminoglycosides were less prescribed in 2017 than in 2012, this may be explained by the recommendations for shorter courses issued by the French Medicine Agency (ANSM) and the French Infectious Diseases Society (SPILF) in mid-2011 [16].

Relatively few third- or fourth-generation cephalosporins were reported in the 2017 PPS (7.7% CI95% [5.3–10.9] vs 7.4% in 2012), notwithstanding the new recommendations for antibiograms given by the French Microbiology Society (CASFM) in 2011, prior to which time, cephalosporins were automatically reported as resistant. According to these recommendations, cephalosporin susceptibility was to be interpreted with the usual breakpoints; as a result, cephalosporins could be considered as a carbapenem-sparing treatment option infections caused by ESBL-producing organisms [15].

Amoxicillin/clavulanic acid and piperacillin/tazobactam use increased slightly. Beta-lactamase inhibitors are at times active against ESBL, particularly in high ATB concentration sites such as the urinary tract. Fluoroquinolone use remained stable.

In 2017, more than one out of four patients received ATB for more than 7 days, which is longer than recommended for common infections. Furthermore, treatment duration in PPS is underestimated, because the data collection date is considered as the treatment end date. Moreover, we are lacking in relevant data about infection severity and evolution. In 2017, the average time for ATB change was 6 days, which seems inappropriately long. This is probably due to ESBLE, as the average treatment duration and average time to change are shorter in patients with HAIs caused by non-ESBL-producing *Enterobacteriaceae*.

For ESBLE-LUTI, the five most frequently prescribed ATBs were amoxicillin/clavulanic acid, ofloxacin, cotrimoxazole, nitrofurantoin, and ciprofloxacin. This is relatively consistent with the guidelines at the time:

- LUTIs are, by definition, non-severe infections.
- LUTIs allow for a wider range of ATBs.
- The following recommendations were issued at the time of the survey [14]:
  - o in highly painful cystitis, fosfomycin trometamol, nitrofurantoin, or fluoroquinolone (the latter has since been removed from the most recent recommendation);

Table 3
Reasons for antibiotic change, by main ATB agents and classes, for the treatment of ESBLE-HAI, 2017 PPS, France.

Antibiotic agent/class	ATB	No change		Therapeutic escalation		Therapeutic de-escalation		Change of administration route		Side effect		Unknown	
	n	*n*	% [CI95%]	*n*	% [CI95%]	*n*	% [CI95%]	*n*	% [CI95%]	*n*	% [CI95%]	*n*	% [CI95%]
Beta-lactams	173	105	59.2 [51.5–66.5]	36	20.4 [15.5–26.4]	20	13.8 [7.8–23.0]	1	0.2 [<0.1–1.8]	2	0.7 [0.1–3.5]	9	5.7 [3.2–9.8]
Penicillin	56	32	52.7 [39.6–65.5]	8	14.3 [9.2–21.5]	9	21.0 [11.4–35.5]	0	0.0	1	1.3 [0.1–12.6]	6	10.7 [5.4–20.1]
amoxicillin/clavulanic acid	*22*	*12*	*48.1 [13.5–84.6]*	*3*	*23.1 [1.3–86.9]*	*3*	*15.5 [8.5–26.5]*	*0*	*0.0*	*1*	*3.0 [1.7–5.34]*	*3*	*10.3 [<0.1–99.1]*
piperacillin/tazobactam	*21*	*15*	*76.1 [64.1–85.0]*	*3*	*7.7 [1.9–26.8]*	*1*	*1.7 [1.7–1.7]*	*0*	*0.0*	*0*	*0.0*	*2*	*14.5 [14.3–14.7]*
Carbapenem	90	55	59.0 [46.6–70.4]	24	31.5 [21.4–43.9]	7	7.3 [3.7–14.0]	1	0.5 [0.1–4.8]	1	0.5 [0.05–4.83]	2	1.1 [0.2–5.4]
imipenem/cilastatin	*43*	*28*	*66.7 [49.2–80.5]*	*13*	*30.1 [17.1–47.2]*	*2*	*3.2 [0.5–17.8]*	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
meropenem	*32*	*21*	*65.0 [31.5–88.2]*	*8*	*25.9 [6.2–64.8]*	*1*	*6.0 [5.7–6.4]*	*2*	*3.1 [0.6–14.3]*	*0*	*0.0*	*0*	*0.0*
Fluoroquinolone	36	19	55.8 [4.6–43.1]	7	20.5 [1.0–17.9]	6	12.7 [4.4–4.6]	1	0.9 [<0.1–0.9]	0	0.0	3	10.0 [0.3–9.3]
Other	101	75	74.7 [65.0–82.5]	12	8.6 [5.4–13.4]	7	6.8 [3.1–14.0]	2	3.0 [0.6–14.0]	2	4.5 [3.1–6.6]	3	2.4 [1.4–4.0]
Total	283	181	63.3 [56.6–69.5]	51	17.1 [12.9–22.5]	29	11.0 [6.9–17.0]	4	1.4 [0.4–4.9]	4	2.2 [1.2–3.8]	14	5.0 [2.9–8.6]

ATB: antibiotic; ESBLE: extended-spectrum beta-lactamase-producing Enterobacteriaceae; HAI: healthcare-associated infection; PPS: point prevalence survey.

Table 4
ATB agents and classes prescribed for the treatment of healthcare-associated lower urinary tract infection caused by ESBLE in the 2017 and 2012 PPS, France.

Antibiotic agent/class	2017			2012	
	n	%	[CI95%]	*n*	%
Beta-lactams	40	49.4	[39.2–59.6]	87	38.5
Penicillin	21	33.7	[25.3–43.2]	22	9.7
amoxicillin	*2*	*2.5*	*[1.2–4.9]*	*3*	*1.3*
mecillinam	*1*	*3.0*	*[0.3–22.1]*	*0*	*0.0*
piperacillin	*1*	*0.4*	*[0.1–3.8]*	*0*	*0.0*
amoxicillin/clavulanic acid	*14*	*21.1*	*[13.5–31.4]*	*17*	*7.5*
piperacillin/tazobactam	*3*	*6.7*	*[2.5–16.7]*	*2*	*0.9*
Second-generation cephalosporin (*cefoxitin*)	1	0.8	[0.2–3.6]	5	2.2
Third- and fourth-generation cephalosporin	7	6.5	[4.0–10.4]	17	7.5
ceftriaxone	*4*	*3.5*	*[2.7–4.5]*	*11*	*4.9*
ceftazidime/avibactam	*0*	*0.0*	–	*2*	*0.9*
cefixime	*1*	*1.1*	*[0.2–6.1]*	*1*	*0.4*
cefepime	*2*	*1.9*	*[0.6–6.0]*	*3*	*1.3*
Carbapenems	11	8.4	[4.1–16.4]	43	19.0
meropenem	*3*	*1.5*	*[0.6–4.1]*	*1*	*0.4*
ertapenem	*3*	*4.8*	*[1.5–14.6]*	*11*	*4.9*
imipenem/cilastatin	*5*	*2.1*	*[1.1–3.8]*	*31*	*13.7*
Fluoroquinolones	16	23.4	[15.7–33.5]	51	22.6
ofloxacin	*5*	*8.9*	*[6.1–12.7]*	*21*	*9.3*
ciprofloxacin	*6*	*8.1*	*[3.8–16.4]*	*16*	*7.1*
norfloxacin	*2*	*3.7*	*[0.8–14.6]*	*12*	*5.3*
levofloxacin	*3*	*2.8*	*[0.6–11.5]*	*2*	*0.9*
Metronidazole	1	0.9	[0.1–7.3]	2	0.9
Aminoglycosides	1	0.4	[0.3–0.7]	14	6.2
amikacin	*1*	*0.4*	*[0.3–0.7]*	*9*	*4.0*
gentamicin	*0*	*0.0*	–	*5*	*2.2*
Sulfonamides (*cotrimoxazole*)	5	7.8	[3.6–16.1]	23	10.2
Glycopeptides (*vancomycin*)	1	0.4	[0.3–0.7]	0	0.0
Tetracyclines (*doxycycline*)	0	0.0	–	1	0.4
Others	7	17.7	[11.1–27.1]	48	21.2
nitrofurantoin	*4*	*10.4*	*[7.0–15.0]*	*44*	*19.5*
fosfomycin trometamol	*3*	*7,3*	[2,8–17,9]	*4*	*1,8*
Total	71	100,0		226	100,0

ATB: antibiotic; ESBLE: extended-spectrum beta-lactamase-producing Enterobacteriaceae; PPS: point prevalence survey.

- in other cases, antibiogram-guided treatment. Drugs that could be active on ESBL were amoxicillin/clavulanic acid, fluoroquinolone, cotrimoxazole, and nitrofurantoin.

In 2017, amoxicillin/clavulanic acid, ofloxacin and ciprofloxacin accounted for half of the ATBs prescribed after a change of ATB in ESBLE-LUTI.

Carbapenems were frequently prescribed in 2012 for ESBLE-LUTI despite being inappropriate for these infections (the PPS data were lacking in information about susceptibility to other ATBs). In 2017, on the other hand, and in accordance with the French recommendations, carbapenems were much less frequently prescribed [14]. A new recommendation published after the 2017 PPS [10] emphasises the need to use carbapenem-sparing regimens. Data from the 2022 PPS should confirm whether or not, as a result, carbapenem prescriptions have continued to decrease.

Single drug regimens increased from 2012 to 2017, which is consistent with a concomitant decrease in aminoglycoside prescriptions. Both the 2011 and 2015 nosocomial UTI recommendations specified that only for severe pyelonephritis or prostatitis were aminoglycosides of interest as short-term combination therapy.

Given the fact that data on HAI and treatments are collected separately, PPS design does not allow them to be directly linked. We overcame this limitation by selecting only ATBs prescribed for HAI treatment, and with a specific focus on LUTI, as previously reported [9]. That said, global description of treatments for ESBLE-

HAI is biased by the few patients having two infections, of which only one is due to an ESBLE (31 patients among the 261). These 31 patients did not influence the results on treatments for ESBLE-LUTI, which were analysed only with a therapeutic indication of LUTI, whether or not the patient had a 2nd infection. On the other hand, these patients could have biased the description of ESBLE-HAI treatments without distinction of infectious site. However, we have shown that the latter are very similar to treatments for ESBLE-LUTI, probably meaning that patients with two infections would have had very little influence on the overall results.

5. Conclusion

In this study, we provide a nationally representative description of antimicrobial use in patients with ESBLE-HAI using data from the two most recent PPSs. We have highlighted an evolution in ATB prescriptions between 2012 and 2017, mainly consistent with the recommendations at that time, especially for ESBLE-LUTI. However, treatment durations remained longer than recommended. Data from future PPSs will be useful to evaluate the evolution of HAI prescription trends. Our results can help to orient future efforts in antimicrobial stewardship. They should nonetheless be interpreted in parallel to the incidence data of drug-resistant infections and ATB prescriptions in hospitals analysed in the framework of the SPARES mission.

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Ethical statement

Analyses were only conducted on aggregated data.

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Conflict of interest

None declared.

Authors' contributions

ML, CoDa, ABC and MCC were involved in conception and design of the study.

ML and CoDa participated in the data curation and conducted the data analysis.

SA, CoDa, CaDu, OB, HB, LS, ABC and MCC participated in the interpretation of the results.

MCC wrote the manuscript.

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