Carbapenem use in French hospitals: A nationwide survey at the patient level

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ABSTRACT

The objective of this study was to evaluate the characteristics of carbapenem use in French healthcare settings in order to guide future actions. Healthcare facilities voluntarily participated in a nationwide cross-sectional survey in 2011. Medical data and reasons for carbapenem treatment (CPR) and discontinuation were recorded for all patients treated with carbapenems. A total of 2338 patients were recorded by 207 facilities. The median duration of CPR was 8 days, and 31.4% of patients received CPR for >10 days. An antibiotic consultant was involved in the initial choice of CPR in 36.8% of cases. CPR was chosen on an empirical (EP) basis for 1229 patients (52.6%), mainly because of severe sepsis (48.6%) or a perceived risk of bacterial resistance (33.7%). Among EP patients, de-escalation was more frequent in the case of intervention of an antibiotic consultant (35.1%) than without intervention (22.9%) ($P < 0.01$). Among the 1109 patients receiving CPR initially based on bacteriological results, 607 (54.7%) had ESBL-producing Enterobacteriaceae and 397 (35.8%) had Gram-negative bacilli susceptible to at least one β-lactam other than carbapenems or to fluoroquinolones. Among the latter, de-escalation was performed in 59 cases (14.9%). The intervention of an antibiotic consultant did not favour de-escalation in this group. In conclusion, carbapenems are frequently used for treating suspected or confirmed multidrug-resistant bacteria, and overall CPR duration is long. De-escalation is frequently not implemented despite isolates being susceptible to other drugs. More frequent antibiotic consultant intervention may help to decrease carbapenem use in the case of EP treatment.

1. Introduction

In most part of the world, Gram-negative bacilli (GNB) are the most frequent micro-organisms isolated both from community and nosocomial infections. Among these bacteria, resistance to extended-spectrum cephalosporins (ESCs) has increased over the last decade [1]. In addition, the emergence of CTX-M-type extended-spectrum β-lactamases (ESBLs) has modified the epidemiology of ESC resistance in Enterobacteriaceae since the dissemination of ESBL enzymes has occurred in the community as well as in healthcare settings [2].

The consequence of increasing ESC resistance has been a significant rise in the use of antibiotics active against multidrug-resistant (MDR) bacteria, mainly carbapenems. Increased carbapenem use has been followed by an increase in carbapenem-resistant *Pseudomonas aeruginosa* and Enterobacteriaceae [1]. The use of carbapenems in intensive care units has been associated with the emergence of imipenem-resistant GNB in the commensal flora, even after a short treatment duration [3]. In addition, new mechanisms of resistance to carbapenems have emerged in the last decade [4]. Therefore, it is in our interest to limit the use of carbapenems to well-defined indications.

We have previously reported a rather high proportion (7.8%) of carbapenem use among patients treated by antibiotics in French hospitals [5]. Hence, a better understanding of the characteristics of carbapenem prescriptions should help to develop comprehensive recommendations for carbapenem use. Therefore, a cross-

sectional survey of carbapenem use at the patient level, including the reasons for carbapenem prescribing, was designed.

2. Methods

2.1. Study design

French healthcare settings collaborating with the French Society of Infectious Diseases (SPILF) (http://www.infectiologie.com) and the French National Observatory for Epidemiology of Bacterial Resistance to Antibiotics (ONERBA) (http://www.onerba.org) were asked to participate on a voluntary basis in an observational study of inpatients receiving a carbapenem-containing regimen during a 3-month period (October–December 2011).

2.2. Data collection

Healthcare settings had to record data for ≥10 consecutive inpatients treated by a carbapenem in all wards of the facility, or all inpatients if <10 cases were eligible during the study period. Data collected included prior history of hospitalisation and antibiotic treatment in the previous 3 months, ward hospitalisation and antibiotic received since admission and before the first carbapenem administration.

Data regarding carbapenem treatment (CPR) included the site of infection, empirical versus targeted treatment, reasons for carbapenem initial choice and cessation as recorded by the prescriber, treatment duration, and re-assessment after 2–3 days and 7–10 days. De-escalation was defined as replacement of a carbapenem by

another antibiotic. Microbiological data were the results of culture of clinical samples processed by the local laboratory, including species identification, antimicrobial susceptibility test (AST) results, and testing for production of ESBLs by Enterobacteriaceae following the 2011 recommendations of the French Committee for Antibiogram of the French Society for Microbiology (http://www.sfm-microbiologie.org). In order to assess alternative antibiotics to carbapenems, all GNB from patients with polymicrobial infections were considered as a whole for evaluating antibiotic susceptibilities. Empirical therapy was defined as CPR in patients without documented infection or initiated before the availability of AST results for bacteria isolated from clinical samples.

2.3. Statistical analysis

Data were collected using a standardised website questionnaire. Continuous variables were expressed as median and range and were compared using the Kruskal–Wallis test. Categorical variables were expressed as number and proportions, and the χ^2 test or Fisher's exact test were used as appropriate for comparisons. Statistical analysis was performed using STATA (StataCorp, College Station, TX) and $P < 0.05$ was deemed statistically significant.

3. Results

3.1. Facilities

A total of 251 healthcare facilities (41 teaching hospitals, 175 non-teaching or private hospitals and 35 rehabilitation or long-term care facilities) participated in the study

covering 74 (73.3%) of the 101 French departments. They represented 17.7% and 4.8% of acute-care and rehabilitation or long-term care facilities, respectively, and 23% of all French healthcare beds. All but one facility had appointed an antibiotic specialist (AB) consultant. A total of 231 facilities (92.0%) reported controlled access to carbapenems; 195 (77.7%) undertook systematic re-assessment of prescription at 48–72 h and 109 (43.4%) after 7–10 days. Among all facilities, 44 did not record any CPR during the 3-month study period, 102 recorded <10 patients receiving CPR and 105 recorded ≥10 CPR patients.

3.2. Treatment

The 207 facilities included 2338 patients (62.3% male) receiving at least one CPR (Table 1), mainly imipenem (*n* = 2051; 87.7%) and ertapenem (*n* = 173; 7.4%).

The median age of the patients was 67.0 years (0.1–100.0 years) and 24.5% were aged >80 years. A total of 1485 (63.5%) and 1210 (51.8%) patients had a history of prior hospitalisation and antibiotic treatment, respectively; 1637 patients (70.0%) had a history of one of both of these. A total of 1525 patients (65.2%) already received an antibiotic course (86.7% β-lactams) other than a carbapenem since admission and before CPR.

Moreover, 26 patients (1.1%) had CPR on admission, 389 (16.6%) on the day of admission and 975 (41.7%) >10 days after hospital admission. Among the latter, 856 (87.8%) had already been treated by antibiotics since admission (Table 2).

Initial CPR choice was empirical (EP) for 1229 patients (52.6%) and was based on bacteriological results (BR) for the remaining 1109 (47.4%). Among patients from the EP group, 1062 (86.4%) had a prior history of hospitalisation and/or antibiotic use. In the EP group, CPR choice was based on the severity of illness (48.6%) or a perceived risk of resistance to ESCs (33.7%), and 17.7% for other criteria or no reason mentioned. AB consultants were less likely to be consulted for CPR initiation in the EP than in the BR group (32.6% vs. 41.5%; $P < 0.001$).

The median duration of CPR was 8 days (1–188 days) and it was longer for the BR group (9 days) than for the EP group (6 days) ($P < 0.001$). Patients receiving CPR for >10 days ($n = 735$; 31.4%) were mainly treated for urinary tract infections (26.1%), pulmonary infections (22.3%) and intra-abdominal infections (11.3%). Among the 141 patients (19.2%) with other infections, 53 (7.2%) had bone and joints infections and 5 (0.7%) had endocarditis. There was no statistical difference in the CPR duration for patients treated for the three main infections with or without AB consultants.

For 1643 patients (70.3%), the carbapenem was combined with at least one antibiotic, and this proportion was higher in the EP group (74.9%) than in the BR group (65.1%) ($P < 0.001$). However, only 59.8% of the patients received an antibiotic combination active against GNB. The carbapenem was associated with an aminoglycoside in 932 cases (56.7%) and with a fluoroquinolone in 431 cases (26.2%). The median treatment duration with the combined antibiotics was longer in the BR group than in the EP group, either for aminoglycosides (3 days vs. 2 days; $P < 0.001$) or for fluoroquinolones (11 days vs. 7 days; $P < 0.001$).

3.3. Bacteriology

In the EP group, 208 patients (16.9%) did not have any microbiological sample drawn and 385 (31.3%) had samples yielding no growth; thus, 5936 (48.3%) of the EP patients had no positive microbiological results and 636 (51.7%) had documented infections. Patients without a positive result were not more likely to be treated for <7 days with a carbapenem than other patients (58.7% vs. 61.0%; *P* = 0.40). An AB consultant was involved in the CPR choice in 31.4% of the cases for patients without a positive result and in 39.3% of cases for the others (*P* = 0.006).

Among the 1745 patients with positive bacteriological culture, 480 (27.5%) had more than one bacterial species isolated from their clinical samples (Table 3). Overall, 1309 patients (75.0%) harboured Enterobacteriaceae, including 773 (59.1%) ESBL-producing Enterobacteriaceae (ESBL-EB).

Among the EP patients from whom a GNB was isolated, 365 (72.4%) of the 504 with available AST results had isolates susceptible to one drug among ESCs, piperacillin/tazobactam (TZP) and fluoroquinolones (Table 3). De-escalation was performed in 177 (48.5%) of these cases and it was more frequent after (59.2%) than without (39.2%) the intervention of an AB consultant (*P* < 0.01). Among the 597 patients in the EP group for whom CPR choice was based on the severity of illness, 261 (43.7%) had negative microbiological results. Among the remaining 336, 254 had GNB with available AST results, of whom 90 (35.4%) had isolates resistant to all β-lactams but carbapenems. Among the 414 patients in the EP group for whom CPR choice was based on a perceived risk of multidrug resistance, 128 (30.9%) had no

positive cultures. Among the remaining 286, 228 had GNB with available AST results, of whom 89 (39.0%) had isolates resistant to all β-lactams but carbapenems.

Among the 933 BR patients with available AST results for GNB, 397 (42.6%) had isolates susceptible to one drug among ESCs, TZP and fluoroquinolones (Table 3).

Among the latter, de-escalation was performed in 59 cases (14.9%). The frequency of de-escalation was not different according to the intervention of an AB consultant: 16.6% in case of intervention versus 12.8% without intervention (P = 0.37).

4. Discussion

We conducted the first countrywide study of carbapenem use at the patient level in a large sample of French hospitals. More than one-half of the CPR was initiated on an empirical basis, including nearly one-half for severe sepsis and one-third for a perceived risk of multidrug resistance. When the CPR choice was based on bacteriological results, an alternate drug was available in more than one-third of cases. Overall, almost one-third of CPR lasted >10 days. Finally, a large part of CPRs were used to treat suspected or confirmed MDR isolates.

This study underlined the long duration of antibiotic treatment in France. There is a lack of data regarding the appropriate duration of antibiotic treatment in most infections. As a consequence, a large majority of guidelines give a range of days for the recommended treatment duration, which does not help in treatment shortening. However, a large majority of the patients in this study treated for >10 days had

urinary, pulmonary or intra-abdominal infections for which a few studies are now suggesting that antibiotic treatment duration could be shortened [6].

In the present study, one-third of empirical CPR was initiated in relation to a perceived risk of antibiotic resistance. Such a strategy is widely accepted because low adequacy of initial antibiotic treatment has been linked to an increase in morbidity and mortality in severe sepsis. The dramatic increase in gastrointestinal carriage of ESBL-producing Enterobacteriaceae in the community reinforces this strategy [2]. The fact that ESBL-EB infections remain infrequent among colonised patients [7,8] and that widespread screening for ESBL-EB carriage could lead to inappropriate use of carbapenems [9] should question this strategy in the context of carbapenem resistance emergence.

We reported that 16.9% of EP patients did not have any microbiological sample drawn and that 31.3% had sterile microbiological samples. Hence, approximately one-half of the patients receiving empirical CPR in French healthcare settings were without positive bacteriological results, suggesting that the use of a carbapenem was based on a perception of the risk of resistance. Of interest, CPR duration was similar among patients without and those with microbiological results. These results contradict with the fact that all facilities declared having an AB consultant and that a large majority declare controlling carbapenem dispensing and having a systematic re-assessment of prescription, strategies that have been proven to be efficient [10].

In cases where empirical use of large-spectrum antibiotics is considered as good practice, de-escalation is a required partner. In this study, de-escalation was clearly

not systematic. Indeed, CPR was continued for >3 days in 66.2% of patients treated empirically and in 89.0% for the others. However, the efficacy of alternatives to carbapenems against ESBL-EB is controversial, and carbapenems have remained the drugs of choice. However, this needs to be re-evaluated now that carbapenemase-producing Enterobacteriaceae have emerged. β-Lactams combined with inhibitors appeared suitable alternatives for treating ESBL-producing *Escherichia coli* bacteraemia [11,12]. Nevertheless, generalisation of the latter observational studies is difficult because source of infection, severity of illness and antibiotic dosage may play a major role in treatment outcome [13]. In addition, it has been suggested that the minimum inhibitory concentration (MIC) of β-lactams combined with inhibitors may be of interest only for bloodstream infections with non-urinary tract sources [14]. Finally, the choice of antibiotics based on MIC levels is not implementable when considering empirical treatment. Hence, carbapenems will remain the initial choice for empirical treatment of serious life-threatening infections when MDR organisms are suspected [12]. In such cases, and as shown in this study, AB consultants may help in achieving de-escalation. Hence, antimicrobial stewardship programmes should place the de-escalation issue as a priority [10].

This study has some limitations. First, alternatives to carbapenems were defined solely on AST results. We did not consider other parameters involved in the antibiotic choice, such as primary site and severity of infection, bacterial load and antibiotic MIC. Second, we did not consider ertapenem as de-escalation, in contrast to other studies. However, there is no consensus regarding the definition of de-escalation [15] and only a small number of patients received ertapenem as second carbapenem, which is likely not to impact the results. Third, the study was performed

before the implementation of the new European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines recommending interpreting the susceptibility of ESBL-EB to ESCs based on MICs results, and not as systematically non-susceptible (http://www.eucast.org/clinical_breakpoints/). Finally this study was performed at the end of 2011. It is possible that changes regarding carbapenem use have occurred meanwhile, especially in a context of increase of ESBL-EB and of the emergence of carbapenemase-positive Enterobacteriaceae. Recent national data show that carbapenem use has increase since 2011 in France, suggesting that little has been implemented to reduce consumption.

In conclusion, CPR is widely used as first-line treatment of patients suspected of harbouring resistant bacteria. National and international recommendations for sparing carbapenems appear to not be being widely adopted. Decreasing overall treatment duration and implementing de-escalation by systematic re-evaluation on Day 3 should be a priority of antibiotic stewardship programmes. Finally, gathering more evidence on the cost effectiveness of alternatives to carbapenems will help in the near future to spare carbapenems.

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Table 1

Characteristics of 2338 patients treated by carbapenems according to the type of treatment initiation [a]

Variable	Total (*n* = 2338)	Treatment initiation		*P*-value
		Empirical (*n* = 1229)	Bacteriological results (*n* = 1109)	
Ward				
Medicine	796 (34.0)	334 (27.2)	462 (41.7)	<0.001
Oncology/haematology	254 (10.9)	178 (14.5)	76 (6.9)	<0.001
Paediatrics	56 (2.4)	27 (2.2)	29 (2.6)	0.59
Surgery	435 (18.6)	210 (17.1)	225 (20.3)	0.04
ICU	638 (27.3)	422 (34.3)	216 (19.5)	<0.001
Rehabilitation/long-term care	159 (6.8)	58 (4.7)	101 (9.1)	<0.001
Type of infection				
Intra-abdominal	308 (13.2)	197 (16.0)	111 (10.0)	<0.001
Pulmonary	630 (26.9)	393 (32.0)	237 (21.4)	<0.001
Urinary tract	623 (26.6)	169 (13.8)	454 (40.9)	<0.001
Febrile neutropenia	136 (5.8)	122 (9.9)	14 (1.3)	<0.001
Bacteraemia	78 (3.3)	30 (2.4)	48 (4.3)	0.02
Ocular	46 (2.0)	45 (3.7)	1 (0.1)	<0.001
Skin and soft tissue	130 (5.6)	61 (5.0)	69 (6.2)	0.21

Others	311 (13.3)	146 (11.9)	165 (14.9)	0.04
Unknown	76 (3.3)	66 (5.4)	10 (0.9)	<0.001
Antibiotic since admission and before CPR	1525 (65.2)	758 (61.7)	767 (69.2)	<0.001

ICU, intensive care unit.

[a] Data are given as *n* (%).

Table 2

Characteristics of the 2338 carbapenem treatment (CPR) regimens according to the type of treatment initiation [a]

Variable	Total (*n* = 2338)	Treatment initiation		*P*-value
		Empirical (*n* = 1229)	Bacteriological results (*n* = 1109)	
CPR administration within 2 days of admission	726 (31.1)	448 (36.5)	278 (25.1)	<0.001
AB consultant for CPR initial prescription	861 (36.8)	401 (32.6)	460 (41.5)	<0.001
Reason of initial CPR choice				
Local recommendations	89 (3.8)	76 (6.2)	13 (1.2)	<0.001
Severe sepsis	820 (35.1)	597 (48.6)	223 (20.1)	<0.001
Risk of ESC resistance	414 (17.7)	414 (33.7)	–	–
AST results	792 (33.9)	–	792 (71.4)	–
Others	87 (3.7)	51 (4.1)	36 (3.2)	–
No reason mentioned	136 (5.8)	91 (7.4)	45 (4.1)	–
CPR duration				
0–3 days	538 (23.0)	416 (33.8)	122 (11.0)	<0.001
4–7 days	626 (26.8)	320 (26.1)	306 (27.6)	0.40
8–10 days	439 (18.8)	188 (15.3)	251 (22.6)	<0.001
>10 days	735 (31.4)	305 (24.8)	430 (38.8)	<0.001
Reason of CPR cessation				
Scheduled end of treatment	1162 (49.7)	456 (37.1)	706 (63.7)	<0.001
De-escalation	352 (15.1)	283 (23.0)	69 (6.2)	<0.001
Death	188 (8.0)	130 (10.6)	58 (5.2)	<0.001
Others	472 (20.2)	280 (22.8)	192 (17.3)	0.001
Unknown	164 (7.0)	80 (6.5)	84 (7.6)	0.31
Other antibiotics combined with CPR				
All antibiotics	1643 (70.3)	921 (74.9)	722 (65.1)	<0.001

Only antibiotics active against GNB	1398 (59.8)	760 (61.8)	638 (57.5)	0.03
Aminoglycosides	932/1643 (56.7)	499/921 (54.2)	433/722 (60.0)	0.02
Fluoroquinolones	431/1643 (26.2)	261/921 (28.3)	170/722 (23.6)	0.03

AB, antibiotic specialist; ESC, extended-spectrum cephalosporin; AST, antibiotic susceptibility test; GNB, Gram-negative bacilli.

[a] Data are given as *n* (%).

Table 3

Bacteriological results for the 2338 patients treated by carbapenems according to the type of treatment initiation [a]

Variable	Total (*n* = 2338)	Treatment initiation	
		Empirical (*n* = 1229)	Bacteriological results (*n* = 1109)
At least one sample drawn	2130 (91.1)	1021 (83.1)	1109 (100)
Sterile samples	385 (16.5)	385 (31.3)	–
Positive sample	1745 (74.6)	636 (51.7)	1109 (100)
Polymicrobial samples	480 (20.5)	199 (16.2)	281 (25.3)
Sample with ≥1 GNB	1624 (69.5)	539 (43.9)	1085 (97.8)
Enterobacteriaceae	1309 (56.0)	417 (33.9)	892 (80.4)
ESBL-positive isolates	773/1309 (59.1)	166/417 (39.8)	607/892 (68.0)
Pseudomonas aeruginosa	374 (16.0)	136 (11.1)	238 (21.5)
Others	84 (3.6)	49 (4.0)	35 (3.2)
GNB susceptible to:			
ESC or TZP (*n* = 1422)	544/1422 (38.3)	311/500 (62.2)	233/922 (25.3)
Fluoroquinolones (*n* = 1552)	553/1552 (35.6)	263/512 (51.4)	290/1040 (27.9)
β-Lactams or fluoroquinolones (*n* = 1437)	762/1437 (53.0)	365/504 (72.4)	397/933 (42.6)
Gentamicin or amikacin (*n* = 1554)	1342/1554 (86.4)	450/507 (88.8)	892/1047 (85.2)

GNB, Gram-negative bacilli; ESBL, extended-spectrum β-lactamase; ESC, extended-spectrum cephalosporin; TZP, piperacillin/tazobactam.

[a] Data are given as *n* (%).