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ORIGINAL ARTICLE

# Stewardship program on carbapenem prescriptions in a tertiary hospital for adults and children in France: a cohort study

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## Abstract

Antimicrobial stewardship programs aim at reducing the overuse of broad-spectrum antibiotics such as carbapenems, but their impact remains unclear. We compared the use of carbapenems between paediatric and adult subjects admitted to a French tertiary hospital and described the intervention of an antibiotic stewardship team (AST). As part of AST routine activity, all adult and paediatric patients receiving carbapenems are identified in real time using a computer-generated alert system and reviewed by the AST. Data associated with carbapenem prescriptions were extracted for 2 years (2014–2015) and were compared between paediatric and adult wards. Prescription appropriateness (i.e. no clinically suitable narrower spectrum alternative to carbapenem for de-escalation) and AST intervention were analysed. In total, 775 carbapenem prescriptions for 291 children and 262 adults were included. Most patients (95%) had a comordity and 52% had known recent carriage of extended-spectrum beta-lactamase producing *Enterobacteriaceae* (ESBLE). Most carbapenem prescriptions came from intensive care units ($n = 269$, 35%) and were initiated for urinary tract ($n = 200$, 27%), sepsis ($n = 181$, 25%), and lung ($n = 153$, 21%) infections. Carbapenems were initiated empirically in 537 (70%) cases, and an organism was isolated in 523 (67%) cases. Among the isolated organisms, 47% ($n = 246$) were ESBLE and 90% ($n = 468$) were susceptible to carbapenems, but an alternative existed in 61% ($n = 320$) of cases according to antibiotic susceptibility testing. Among prescriptions reviewed by the AST, 39% ($n = 255$) were considered non-appropriate and led to either antibiotic discontinuation ($n = 47$, 7%) or de-escalation ($n = 208$, 32%). Non-appropriate prescriptions were more frequent in paediatric wards ($p = 0.01$) and in microbiologically documented infections ($p = 0.013$), and less observed in immunocompromised patients ($p = 0.009$) or with a known ESBLE carriage ($p < 0.001$). Tailored stewardship programs are essential to better control carbapenem use and subsequent antimicrobial resistance.

**Keywords** Carbapenems · Anti-infective agents · Antimicrobial stewardship · Extended-spectrum beta-lactamase Enterobacteriaceae

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**Abbreviations**

| | |
|---|---|
| AST | Antimicrobial stewardship team |
| ESBLE | Extended-spectrum beta-lactamase producing Enterobacteriaceae |
| EUCAST | European Committee on Antimicrobial Susceptibility Testing |
| ICU | Intensive care unit |
| NICU | Neonatal intensive care unit |
| PK/PD | Pharmacokinetics/pharmacodynamics |
| IQR | Interquartile |

## Introduction

Infections with multidrug-resistant bacteria are an emerging threat worldwide. Inappropriate use of antibiotics and subsequent selective pressure might participate in spreading antimicrobial resistance. As observed in other European countries, the incidence of extended-spectrum beta-lactamase producing Enterobacteriaceae (ESBLE) infections has seen a fourfold increase between 2006 and 2016 in France [1, 2]. A significant increase has also been observed in the paediatric community [3]. ESBLE infections can cause failure of classic antibiotic therapy strategies and might require the use of carbapenems, which are considered the most effective antibiotic agents against ESBLE-related infections [4–6].

Facing the increasing prevalence of ESBLE carriage and subsequent risk of ESBLE infection [7–10], carbapenems are sometimes prescribed without any microbiological documentation, particularly in settings at high risk of antimicrobial resistance such as intensive care units (ICU), which might lead to carbapenem overuse [11]. Empirical broad-spectrum antibiotic therapy has critical ecological consequences because of the emergence of bacterial resistance. Indeed, even a short exposure to carbapenem is considered a major risk factor of carbapenem-resistant Gram-negative bacilli intestinal carriage [12].

In France, a twofold increase in carbapenem use has been observed between 2000 and 2015 [13, 19]. Monitoring of over- and inappropriate carbapenem use is, besides regular surveillance of multidrug resistance prevalence, crucial to define corrective actions. Antimicrobial stewardship programs and antimicrobial stewardship teams (AST) were created in many countries, and several studies have shown their effectiveness in reducing inappropriate antimicrobial use and hospital costs on antimicrobials, rates of antimicrobial resistance, and in improving patient care and outcomes [14–20]. However, few data are available regarding the modalities of carbapenem use and the acceptance of AST interventions in paediatric wards [21–24], and no study has compared paediatric and adult carbapenem use.

A review of carbapenem prescriptions with real-time monitoring and intervention of AST was formally implemented in our university hospital in 2013. To better understand carabapenem indications and appropriateness, and the impact of an AST intervention in a large tertiary hospital, we analysed all carbapenem prescriptions over a 2-year period, in both paediatric and adult cases.

## Patients and methods

### Study design and setting

The Necker-Enfants Malades Hospital is a large university hospital in the centre of Paris, France, and includes paediatric and adult wards. This hospital has set an antimicrobial surveillance program for carbapenems together with the Pharmacy Department in 2013. This program is held by the AST, a multisciplinary team consisting of three part-time adult and paediatric infectious disease specialists, a clinical microbiologist, and a pharmacist. In our hospital, AST daily advises physicians (approx. 15 consultations a day), in terms of diagnosis, therapeutics, and prevention, and systematically visits critical settings such as ICUs and Neonatal ICUs (NICUs). AST is informed by the hospital pharmacy of any new carbapenem prescription within the next 24–48 h using a computer-generated alert system. All alerts lead to contact with the prescriber to discuss the case and the relevance of carbapenem use. All clinical, biological, and pharmacological data associated with AST activity are routinely collected in a database.

We retrospectively analysed all carbapenem prescriptions between January 1, 2014, and December 31, 2015. The intervention of the AST was collected and analysed for each prescription. It included carbapenem discontinuation, discontinuation of any other antibiotic therapy, switch to a narrower spectrum antimicrobial, optimal or non-optimal dosing, and consideration of further diagnostic workup.

### Data collection and microbiology

For each carbapenem prescription, the AST collected the following data: patient demographics, pre-existing illness such as cancer or transplant, renal impairment, previous colonization or infection with an ESBLE within the last 3 months (ESBLE carriage), characteristics of the infection which motivated the prescription of carbapenem, and the type of pathogen (if the episode was documented) and its antibiotic susceptibility. ESBLE detection and in vitro susceptibility testing involved a double-disk synergy test between clavulanic acid and extended-spectrum cephalosporin (ceftazidime and ceftriaxone) and the disk diffusion method, respectively, as recommended by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [25].

### Definitions

A carbapenem prescription was defined as a course of carbapenem therapy for a certain indication in a certain continuous time range without disruption (as from the first administration). Patients with carbapenem prescription were either from paediatric wards (~400 beds) that consisted in departments of Medicine (general paediatrics, neurology, endocrinology, gastroenterology, pneumology, dermatology, nephrology, haematology), departments of Surgery, and paediatric and neonatal ICU, or adult wards (~200 beds) that consisted in departments of infectious diseases, nephrology and transplantation, haematology, and adult ICU). Each patient registered at the wards during the daily registration was regarded as one patient day. Treatment duration was defined as number of days with carbapenem exposure. Carbapenem days of therapy (DOT) was calculated and standardized to 1000 patient days [26]. Invasive infection was defined according to the US Centers for Disease Control and Prevention [27]. Sepsis and septic shock were defined according to the international guidelines available at the time of the study [28]. Carbapenem *dosage* and *administration* were considered *optimal* if they followed the local guidelines according to renal function and met requirements on the basis of available pharmacokinetic/pharmacodynamics (PK-PD) evidence for carbapenems, i.e. dosing interval and duration of infusion [29]. Carbapenem prescription was defined as *appropriate* if the members of the AST in charge of the case (at least one resident and one senior infectious disease specialist) considered that, at the time of the prescription review, there was no clinically suitable narrower spectrum alternative to carbapenem antibiotics for de-escalation [30] based on their individual expertise and international and national standards (e.g. documented infections without any alternative to carbapenem, empirical therapy to patients with septic shock and considered to be at high risk for ESBLE) [31]. Microbiologically effective antimicrobial treatment against the causative pathogen was defined as *adequate* [29]. ESBLE carriage was defined as a history of ESBLE rectal colonization or infection in the last 6 months.

### Statistical analysis

Chi-square and Mann-Whitney *U* tests were used to compare the distributions of patients', infections', and prescriptions' characteristics between adult and paediatric carbapenem prescriptions and between appropriate and non-appropriate carbapenem prescriptions, using SPSS v21 (SPSS Inc., Chicago, IL). A $p$ value was considered statistically significant if $< 0.05$ (two-sided). Variables associated with non-appropriate carbapenem prescriptions were analysed using logistic regression. Odds ratios and 95% confidence intervals (95%CI) were estimated in univariate analysis.

### Ethical approval

This study was reviewed and approved by the Necker Hospital Institutional Review Board (Registration number in the registry of the Assistance Publique–Hôpitaux de Paris: 2020 0117181406). All data processing and storage comply with the General Data Protection Regulation (GDPR) and ethical standards of the National Research Committee.

## Results

### Characteristics of patients and prescriptions

In total, 803 carbapenem prescriptions were identified during the study period, 775 of them had available and comprehensive data for further analyses, which concerned 553 patients (291 children and 262 adults). Regarding the 775 included prescriptions, 405 came from paediatric wards and 370 from adult wards (Table 1), with a median patient age of 1.6 [IQR, 0.3–8.8] years and 61.6 [IQR, 46.6–70.2] years, respectively. The male/female sex ratio was 1.1 and did not differ between adult and paediatric wards. The majority of patients under carbapenems had comorbidities (95%), including 57% ($n = 303$) patients with an immune deficiency (i.e. solid organ or haematopoietic stem cell transplantation, malignancy, inherited immune deficiency including sickle cell disease, and immunosuppressive treatment), 22% ($n = 124$) with digestive, neurological, urological, or respiratory chronic disorders, and 11% ($n = 61$) with cardiac failure. Nineteen children (2.4%) were preterm infants. Renal impairment was present in 151 and 41 patients from adult and paediatric wards, respectively.

Documented ESBLE colonization prior to carbapenem prescription was found in 52% of the 747 cases with available data, 55% in paediatric, and 50% in adult wards (Table 1). Patients with immune deficiency had a higher risk of carrying ESBLE prior to carbapenem prescription (56% vs. 44%, $p = 0.009$).

Adult departments of medicine combining nephrology and infectious disease wards were the main prescriptors of carbapenems, followed by paediatric ICUs (Table 1). Imipenem was the most prescribed carbapenem in both paediatric ($n = 205$, 51%) and adult cases ($n = 219$, 59%); but the proportion of molecules was different between adults and children ($p < 0.001$). We did not find any statistically significant difference in treatment duration between adult and paediatric wards, with a median of 7 [IQR, 3–13] and 5 [IQR, 3–10] days, respectively. When the number of days of carbapenem prescription (DOT) was standardized to 1000 patient days, carbapenem use was higher in adult (36.1/1000 patient days) than in paediatric wards (12.4/1000 patient days). The highest standardized carbapenem use was observed in the ICUs, followed

**Table 1** Characteristics of included carbapenem prescriptions ($N = 775$)

| *N* (%), otherwise stated | Total | Paediatric prescriptions | Adult prescriptions | *p** |
|---|---|---|---|---|
| Wards prescribing carbapenems | $n = 775$ | $n = 405$ | $n = 370$ | < 0.001 |
| Departments of medicine | 311 (40) | 88 (22) | 223 (60) | |
| Departments of surgery | 32 (4) | 32 (8) | N/A | |
| Intensive care units | 269 (35) | 199 (49) | 70 (19) | |
| Departments of haematology/immunology | 110 (14) | 33 (8) | 77 (10) | |
| Neonatal intensive care unit | 53 (7) | 53 (13) | N/A | |
| Molecule | | | | < 0.001 |
| Ertapenem | 23 (3) | 6 (1.5) | 17 (5) | |
| Imipenem | 424 (55) | 205 (51) | 219 (59) | |
| Meropenem | 328 (42) | 194 (48) | 134 (36) | |
| Duration, days: median (IQR) | 6 (3–11) | 5 (3–10) | 7 (3–13) | 0.05 |
| Empirical prescription | 537 (70) | 285 (71) | 252 (72) | 0.49 |
| Optimal prescription according to recommendations | $n = 533$ | $n = 283$ | $n = 250$ | |
| Dosage | 469 (88) | 264 (93) | 205 (82) | 0.01 |
| Administration | 481 (90) | 264 (93) | 217 (87) | 0.03 |
| ESBLE screening | $n = 747$ | $n = 391$ | $n = 356$ | |
| Known ESBLE carriage | 392 (52) | 213 (55) | 179 (50) | 0.02 |
| Site of infection | $n = 738$ | $n = 377$ | $n = 361$ | < 0.001 |
| Lower respiratory tract infection | 153 (21) | 96 (26) | 57 (16) | |
| Urinary tract infection | 200 (27) | 73 (19) | 127 (35) | |
| Deep infection | 82 (11) | 48 (13) | 34 (9) | |
| Central nervous system | 10 (1) | 5 (1) | 5 (1) | |
| Superficial infection** | 21 (3) | 8 (2) | 13 (4) | |
| Surgical prophylaxis | 19 (3) | 17 (5) | 2 (1) | |
| Febrile aplasia | 72 (10) | 29 (8) | 43 (13) | |
| Sepsis without identifiable infection | 181 (25) | 101 (27) | 80 (22) | |
| Bacteraemia | 82 (11) | 41 (11) | 41 (11) | 0.84 |
| Septic shock | 66 (9) | 34 (9) | 32 (9) | 0.94 |
| Healthcare-associated infection | 620 (84) | 327 (91) | 293 (78) | 0.16 |

* *p* value of the $Chi^2$ or Mann-Whitney test between paediatric and adult carbapenem prescriptions. ** Surgical site or skin infections

by the units of Haematology/Immunology (Fig. 1). Carbapenems were mainly initiated empirically in both paediatric and adult wards (70% vs. 71%, respectively) (Table 1). Empirical treatment was more frequent in immunocompromised patients (77 vs. 70%, $p = 0.03$), but no difference was observed according to the status of ESBLE carriage or the type of ward. The dosage and administration of carbapenem were more often optimal in paediatric wards (93% vs. 82%, $p = 0.01$, and 93% vs. 82%, $p = 0.03$).

## Characteristics of infections and microbiological data

Among the 738 prescriptions with available data, treatment was mostly initiated for urinary tract infections ($n = 200$, 27%), sepsis ($n = 181$, 25%), and lung infections ($n = 153$, 21%) (Table 1). Septic shock was observed in 9% of the cases ($n = 66$). Healthcare-associated infections represented 84% of the cases and occurred almost exclusively in patients with comorbidities (95%).

Causative pathogens were documented in 523 cases (Table 2). Among documented infections, carbapenems were initiated after documentation in 37% of cases ($n = 196$). *Klebsiella* spp. were the main pathogen involved. ESBLE were identified in 47% of cases ($n = 246$). *Nocardia* spp. and *E. coli* were more frequent in adult wards, while *Klebsiella* spp. and *Pseudomonas* spp. were more observed in paediatric wards. Most of the identified pathogens were susceptible to carbapenems (90%), and there was an alternative to carbapenems in 61% of cases according to antibiotic susceptibility testing (mainly cephamycins and other beta-lactams). No difference in terms of antibiotic treatment adequacy according to antibiotic susceptibility was found between paediatric and adult wards. Among non-documented infections, febrile aplasia (25%) and septic shock (19%) were the main causes

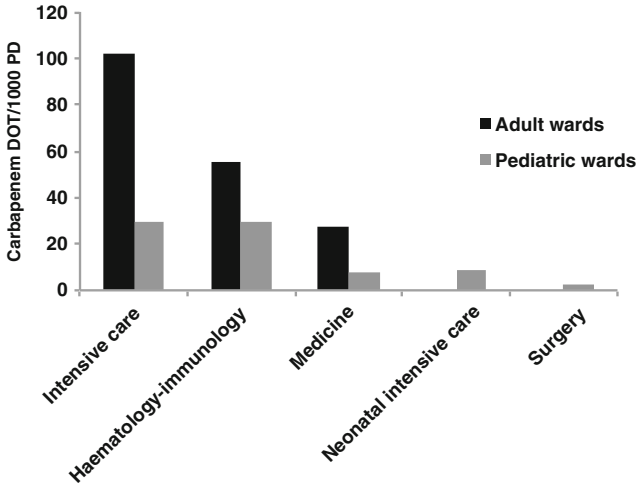


**Fig. 1** Days of carbapenem therapy according to wards. *DOT/1000 PD*, days of therapy per 1000 patient days

of carbapenem initiation, and 38% and 43% of the corresponding patients had a history of ESBLE carriage, respectively.

### AST intervention

Among the 775 prescriptions, 688 (90%) were reviewed by AST and 658 of them had available and comprehensive data for further analyses (Fig. 2 and Table 3). The median response time of AST after carbapenem initiation was 3.5 (range, 0–30) days. Among the 255 (39%) non-appropriate prescriptions, 82% of them had a suitable alternative for de-escalation, such as 3rd generation cephalosporin ($n = 55$), piperacillin-tazobactam ($n = 40$), cotrimoxazole ($n = 17$), cefepime ($n = 15$), fluoroquinolones ($n = 12$), or cefoxitin ($n = 8$). The proportion of non-appropriate prescriptions remained stable between 2014 (38.8%) and 2015 (38.7%).

In univariate analysis, non-appropriate prescriptions were more often observed within paediatric wards compared to adult wards (OR = 1.5; 95%CI = 1.1–2.1) and in documented infections (OR = 1.6; 95%CI = 1.1–2.2). Cases with non-appropriate prescriptions were less likely to have a previous ESBLE carriage (OR = 0.5, 95%CI = 0.4–0.7), an immune deficiency (OR = 0.7, 95%CI = 0.5–0.9), and an infection caused by ESBLE (OR = 0.1, 95%CI = 0.08–0.2) or complicated by septic shock (OR = 0.6; 95%CI = 0.3–0.9) (Table 3). The site of infection was not associated with carbapenem appropriateness ($p = 0.07$).

## Discussion

### Main findings

The increasing use of carbapenems observed worldwide prompt us to better monitor their prescriptions in our hospital. In this study, carbapenems were used more often in adult than paediatric wards and were generally initiated in severely ill patients having serious comorbidities and/or risk factors of drug resistance. Around 50% of patients under carbapenem regimen had a known carriage of ESBLE, which might have been underestimated, as some patients have not been systematically screened for carriage within the first days of hospitalization and rectal swab has false-negative results [32]. Carbapenems were often prescribed empirically (73%)

**Table 2** Documented infections associated with carbapenem prescriptions ($N = 523$)

| Characteristics of documented infections, *N* (%) | Total $n = 523$ | Paediatrics prescriptions $n = 265$ | Adult prescriptions $n = 258$ | *p* |
|---|---|---|---|---|
| Carbapenem treatment initiation following documentation | 196 (37) | 98 (37) | 98 (38) | 0.81 |
| ESBLE | 246 (47) | 124 (47) | 122 (47) | 0.91 |
| Agents | | | | 0.01 |
| *Klebsiella* spp. | 151 (29) | 89 (34) | 62 (24) | |
| *Enterobacter* spp./*Citrobacter koseri* | 104 (20) | 53 (20) | 51 (20) | |
| *E. coli* | 116 (22) | 46 (17) | 70 (27) | |
| *Nocardia* spp. | 12 (2) | 2 (1) | 10 (4) | |
| *Pseudomonas* spp. | 75 (14) | 47 (18) | 28 (11) | |
| Gram-positive cocci | 64(12) | 38 (14) | 26 (10) | |
| Other | 63 (12) | 42 (16) | 21 (8) | |
| Antibiotic therapy | | | | |
| Adequate[#] | 468 (90) | 236 (89) | 232 (90) | 0.65 |
| Existing alternative to carbapenems[#] | 320 (61) | 173 (65) | 147 (57) | 0.15 |

[#] Microbiologically effective according to EUCAST antibiotic susceptibility testing; [*] *p* value of the $Chi^2$ or Mann-Whitney test between paediatric and adult wards

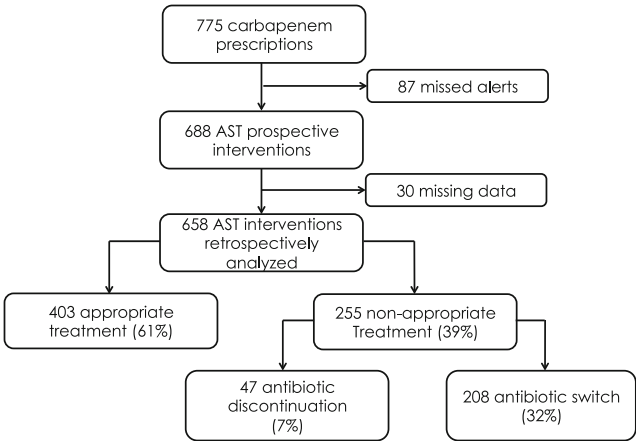


**Fig. 2** Flow chart of carbapenem prescriptions included in the study. *AST*, antibiotic stewardship team

especially for immunocompromised patients. Carbapenem regimens have been prescribed with a proper dosage and/or administration routine in more than 90% of cases. However, more than one-third of prescriptions were considered non-appropriate and have been discontinued following AST recommendation, mostly in paediatric wards.

## Interpretation

Characteristics of our population on carbapenem therapy are consistent with previous studies, as they display comorbidities, carry ESBLE, and are often hospitalized in ICUs [19]. Besides, lung and urinary tract are commonly the major sites of infections, and almost all carbapenem regimens are prescribed for healthcare-associated infections [17, 19]. These observations are consistent with known risk factors for ESBLE carriage and infections, such as hospitalization in ICUs, devices such as central venous cathether, previous hospitalization, and antibiotic therapy [33–35]. However, we observed differences between adult and paediatric wards. First, the highest carbapenem use when standardized to 1000 patient days was observed in adult wards. It may be explained in part by the characteristics of our tertiary hospital whose adult wards (Departments of Infectious diseases, Nephrology and Transplantation, Haematology, and adult ICU) admit almost exclusively immunocompromised patients (85%, vs. 34% in paediatric wards). The higher rate of lower respiratory tract infections and causal pathogens as *K. pneumoniae* or *Pseudomonas* spp. observed in children is clearly related to the high number of patients hospitalized in paediatric ICUs, thus susceptible to ventilator-associated pneumonia. The more frequent use of ertapenem in adult wards is in accordance with current practice in adults, as it can be administered once a day [36]. We observed a sub-optimal dosage and administration routine more often in adult wards, which might be explained by a higher frequency of kidney failure in adults and subsequent difficulties to provide optimal dosage [37]. However, no measurement of serum carbapenem concentration was assessed in our study to confirm this hypothesis.

In our study, only one-third of carbapenem prescriptions were initiated after microbiological documentation; the major rate of empirical carbapenem initiation observed in both adult and paediatric wards by the prescribers reveals their reluctance of narrower spectrum antimicrobial agents for antibiotic initiation despite the absence of ESBLE colonization, most of the time because of the patients' underlying severe diseases, especially innate or acquired immune deficiency. This suggests poor adherence to predictive tools for ESBLE infections and subsequent recommendations for empirical carbapenem prescription [38, 39]. Among the documented infections, 61% of pathogens were susceptible to other antibiotics according to antibiotic susceptibility testing. Beta-lactam/beta-lactamase inhibitors were showed to be an acceptable alternative in some studies, even in febrile aplasia/neutropenia [40–43]. A recent study suggests that, regarding definitive therapy for infections caused by 3rd generation cephalosporin-resistant Enterobacteriaceae, overall mortality might be lower for patients receiving carbapenems compared with those receiving piperacillin-tazobactam [5]. These discrepancies prompt us to consider the studied population, the primary outcome, and the type of infections in such studies, as treatment success also depends on PK/PD properties, the site of infection, and antibiotic diffusion [44–46]. Carbapenems might be preferable for deep-seated documented infections with ESBLE, and alternatives might be easier to find in community-onset ESBLE infections and urinary tract infections [3]. All these data suggest the need for a consensual strategy to help clinicians for empirical therapy, especially during healthcare-associated infections in patients with severe underlying diseases.

In our tertiary hospital, the AST aims at improving infectious disease management and contain non-appropriate carbapenem prescriptions. This study revealed that more than one-third of carbapenems prescriptions were considered non-appropriate by the AST and its intervention led to either discontinuation or de-escalation of carbapenem. Most of these non-appropriate prescriptions were documented (76%). These data confirm the potential impact of carbapenem stewardship, through a strategy combining diagnostic and therapeutic advices during systematic visits of AST in all wards and post-prescription review with rapid feedback [17, 18]. Development of AST in hospitals shows a better control antibiotic prescriptions and help physicians to improve health care and consider alternative antibiotics [14, 15] [HAS, 2019 #57]. It implies, together with clinical experience, getting all data needed to assess and reduce the antibiotic spectrum, complying to guidelines, and considering the microbial ecology of the patient and wards, predictive PK-PD, benefit-to-risk ratio for the patient, and the cost. Recent implementation of antibiotic

**Table 3** Univariate analysis of factors associated with non-appropriate carbapenem prescriptions following AST review ($N = 658$)

| Factors (%) | *N* | Appropriate | Non-appropriate | Odds ratio (95% CI) | *p* |
|---|---|---|---|---|---|
| Prescription characteristics | | | | | |
| Paediatric prescriptions | | | | | |
| Yes | 348 | 197 (57) | 151 (43) | 1.5 (1.1–2.1) | 0.01 |
| No | 310 | 206 (67) | 104 (33) | Reference | |
| Empirical prescription | | | | | |
| Yes | 452 | 273 (60) | 179 (40) | 1.0 (0.7–1.5) | 0.80 |
| No | 174 | 107 (61) | 67 (39) | Reference | |
| Wards prescribing carbapenems | | | | | 0.07 |
| Departments of medicine | 259 | 165 (64) | 94 (36) | 0.9 (0.39–1.2) | |
| Departments of surgery | 29 | 15 (52) | 14 (48) | 1.4 (0.7–3) | |
| Department of haematology/immunology | 88 | 61 (69) | 27 (31) | 0.7 (0.4–1.1) | |
| Neonatal intensive care unit | 47 | 22 (47) | 25 (53) | 1.7 (1.1–3.2) | |
| Intensive care units | 235 | 140 (60) | 95 (40) | Reference | |
| Patient characteristics | | | | | |
| Comorbidities | | | | | |
| Yes | 615 | 375 (61) | 194 (39) | 1.4 (0.6–3.2) | 0.39 |
| No | 29 | 20 (69) | 9 (31) | Reference | |
| Immune deficiency | | | | | |
| Yes | 370 | 243 (66) | 127 (34) | 0.7 (0.5–0.9) | 0.009 |
| No | 274 | 152 (56) | 122 (44) | Reference | |
| Known carriage of ESBLE | | | | | |
| Yes | 331 | 226 (68) | 105 (32) | 0.5 (0.4–0.7) | < 0.001 |
| No | 308 | 162 (53) | 146 (47) | Reference | |
| Infection characteristics | | | | | |
| Documented infection | | | | | |
| Yes | 464 | 270 (58) | 194 (42) | 1.6 (1.1–2.2) | 0.01 |
| No | 194 | 133 (69) | 61 (31) | Reference | |
| Septic shock | | | | | |
| Yes | 63 | 46 (73) | 17 (27) | 0.6 (0.3–0.9) | 0.04 |
| No | 595 | 357 (60) | 238 (40) | Reference | |
| Healthcare-associated infection | | | | | |
| Yes | 548 | 337 (62) | 211 (39) | 1.08 (0.7–1.7) | 0.74 |
| No | 98 | 62 (63) | 37 (36) | Reference | |

stewardship programs is described to be associated with a significant decrease of carbapenem prescriptions [15, 21–23, 47, 48].

Our data also reveal that despite a lower DOT/1000 patient days, hospitalization in a paediatric ward, and NICU in particular, is associated with non-appropriateness. However guidelines for carbapenem use are common for both types of wards in our hospital. Children, neonates in particular, are known to be more exposed to antibiotics with a less proportion with confirmed infection [49, 50]. This might be explained by a more challenging interpretation of clinical symptoms, risk factors, and biomarkers in children. Children are also often considered "vulnerable" by clinicians, and decision of a de-escalation may be difficult to make [23]. Our study highlights that, despite common stewardship targets, tailored stewardship interventions considering the patients' specificities and issues, as well as clinicians' practice, perceptions, and attitudes, are a pre-requisite for their success [51].

## Limitations

The major limit of this study is the lack of exhaustiveness for data collection by the AST compared to pharmacy alerts, which might be due to a lack of time dedicated to carbapenem surveillance, and the subsequent need of a retrospective review of the database. The surveillance and data collection was prospective, but all data were retrospectively reviewed for the study, leading to missing data. For example, we could

not assess how often carbapenems were part of a en "escalation" strategy. We also observed that the median time to intervention of AST was longer than expected (> 48 h); these findings highlight that dedicating the necessary human resources to AST is also paramount for a fully successful prescription-control program. Finally, this study could not clearly measure the impact of a carbapenem stewardship program, as there was no comparator; we could not exclude that clinicians would have modified carbapenem therapy even without the intervention of the AST. Besides, we did not evaluate any correlation between AST intervention and changes in prevalence of antibiotic resistance; indeed, there are still concerns that reduction in consumption of some classes of antibiotics can result in an increase in other classes with possible similar deleterious ecological effects, and the impact of a reduction of treatment duration is still unclear [30, 52].

## Conclusion

Carbapenem therapy was generally initiated in severely ill patients or with risk factors of drug resistance. However, more than one-third of carbapenem prescriptions were considered non-appropriate by the AST, mostly in paediatric wards, with an indication for discontinuation or de-escalation. This work resulted in the implementation of local guidelines for carbapenem prescriptions. The study suggests that AST intervention is essential to better control paediatric antibiotic use and subsequent antimicrobial resistance.

**Authors' contribution** JT, MP, JRZ, and OL conceived the study. JP, PP, JFC, and JT designed the study. JP, PP, BP, JFC, and JT collected and were responsible for the data. PF and JRZ participated to data analysis. P, PP, BP, OL, JFC, and JT participated in patient care, investigation, and data collection. JT and JFC performed the statistical analysis. EB performed the microbiology analyses. JP and JT wrote the first draft of the manuscript. All authors drafted the manuscript for important intellectual content, contributed to the revision of the final version of the manuscript, and approved the final version submitted.

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**Data availability** Data will be made available on reasonable request.

## Compliance with ethical standards

**Competing interests** P.F. has received research grants (to his institution) from the French National Agency for AIDS Research (ANRS) and honoraria and travel grants from ViiV Healthcare, Bristol-Myers Squibb, Janssen Cilag, Gilead Sciences, Pfizer, Medtronic, and MSD France for participation in advisory boards, educational programs, and conferences, outside the submitted work. All other authors report no potential conflicts.

**Ethical approval, consent to participate, and consent for publication** Participants provided informed consent for the anonymous use of their clinical and biological data for biomedical research (For paediatric patients, informed consent was provided by parents/guardians). This study was reviewed and approved by the Necker Hospital Institutional Review Board (Registration number in the registry of the Assistance Publique – Hôpitaux de Paris: 2020 0117181406). All data processing and storage comply with the General Data Protection Regulation (GDPR) and ethical standards of the National Research Committee.

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