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Evaluation of the Appropriate Use of Carbapenems Regarding Patients Taken in Hand by Intensive Care Unit in the Marrakech University Hospital Center

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Abstract:

Introduction: Carbapenems are antibiotics of last resort used to treat infections with multi-resistant bacteria. The objective of this study is to analyze the prescriptions of carbapenems (CBP) and evaluate the conformity of the probabilistic prescription of these molecules.

Materials and methods: This is a prospective study over from 1 August 2016 to 31 December 2016.

Results: 100 prescriptions of an antibiotic of the carbapenem class were collected. Percentage of prescriptions for CBP was highest in neonatal intensive care (36%) and adult intensive care (34%). The main indication for prescribing CBP to the different intensive care services was sepsis and septic shock (45%). This prescription was probabilistic in 67% of cases. Nosocomial infection motivated the prescription of CBP in 76% of cases. 27 percent of CBP prescriptions were made to treat a documented infection to a C3G-resistant by production of ESBL. Imipenem was predominantly prescribed in neonatal intensive care unit and adult surgical intensive care unit. Erapenem was prescribed in 28% of Cases in medical intensive care unit and 20% in pediatric intensive care unit. Imipenem was prescribed in accordance with the standards in 88% of cases, ertapenem in 10% of prescriptions and meropenem in 2% of prescriptions. Doses were compliant for 87 prescriptions.

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Conclusion: The conformity rate has yet to be re-evaluated and improved. The appointment of a referent in antibiotics is essential to supervise the prescription of these broad spectrum antibiotics and limit their use.

Keywords: Good use of carbapenems –Intensive care unit - Multi - resistant bacteria - Probabilistic anti biotherapy.

Introduction:

In recent years, the use of carbapenems (CBP), broad-spectrum antibiotics, active in particular on enterobacteria producing beta-lactamases extended spectrum (EBLSE), is increasing [1]. One of the hypotheses of this rise is the increase in the incidence of EBLSE [2].This very worrying epidemiological situation raises fears that carbapenems will be too widely used, far beyond the only cases of clinical infections documented at EBLSE, resulting in the emergence of new resistance and the appearance of enterobacteria. productrices de carbapénémase. These resistances are at the origin of failures exposing to therapeutic impasses [3,4].

In order to improve the quality of care, we decided to analyze the prescriptions of carbapenems made in intensive care and evaluate the good use of these molecules during the prescription of empiric antibiotic therapy in patients in charge of resuscitation at the Mohammed VI University Hospital in Marrakech.

Material and methods:

This is a prospective observational and descriptive study over a period of 6 consecutive months from August 1, 2016 to December 31, 2016.The study was conducted at the intensive care unit of Mohamed VI University Hospital in Marrakech. The intensive care units have 47 hospital beds, including 24 medical and surgical adult resuscitation beds, 12 pediatric resuscitation beds and 11 neonatal resuscitation beds.

We included in this study all adult, child and newborn patients who received at least one dose of carbapenems during their stay.

The carbapenems evaluated were Tienam® (Imipenem), Invanz® (Ertapenem) and Meronem® (Meropenem), these molecules are marketed and available in Morocco.

The data was collected from the medical records of the hospitalized patients in the neonatal resuscitation, pediatric resuscitation, and medical and surgical resuscitation departments of the adult in Mohamed VI University Hospital. These data were entered on an index card that included anamnestic, clinical, bacteriological, therapeutic and evolutionary variables.

The data collected were:

Demographics data: age, sex, hospital death, services of origin.

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Types of infections: primary focus (urinary, bronchopulmonary ...), mode of acquisition (community, care-related or nosocomial) and types of infections treated.

Type of prescriptions: documented or probabilistic, the molecule prescribed, the dosage, the duration of the intra-hospital treatment, the previous treatment, the prescription in association or not.

Clinical indication: motivating treatment with carbapenems

Microbiological data: microorganism (s) found, infectious sites, types of possible resistance, **Antibiogram of the organism (s):** related to the prescription of carbapenems.

Evolution of the infectious episode: Improvement - Stationary - Death.

The compliance analysis was based on the recommendations of the "Antibioguide®" standard [5]. This reference is based on the national recommendations for the good use of carbapenems and the recommendations in force (AMM).

These documents include the recommendations of good use of carbapenems according to the rules of good practice of the Society of infectious pathology of French language (SPILF).

CBPs are antibiotics with a high ecological risk. Their use probabilistic treatment is conceivable that in the presence of bacilli risk factors for multidrug-resistant Gram-negative and must be re-evaluated on microbiological results between 48 and 72 hours [5-6].

The compliance of the indication for a carbapenem was evaluated according to the recommendations of good use of CBP [5]. Two choices were reported with respect to indication, duration of treatment and dosage: Compliant, Non-Compliant.

Results:

Over the study period, 100 prescriptions of an antibiotic of the carbapenem class were collected.

Patients were predominantly male (64%) with a sex ratio of 1.7.

The average age was 40 years in surgical and adult medical resuscitation, 4 years, 6 months, 7 days in pediatric resuscitation and 6 days in neonatal resuscitation.

The majority of CBP prescriptions were found in neonatal resuscitation (36%) and adult resuscitation (34%).Figure 1 illustrates the distribution of carbapenem prescriptions according to the resuscitation services of the University Hospital of Marrakech.

The localization of the infections was as follows: pulmonary (31%), abdominal (10%) and urinary (8%).

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The most frequent indications were sepsis and septic shock with (45%), followed by nosocomial pneumonitis (31%) and intra-abdominal infections (10%).Figure 2 shows the part of the various indications found, any molecule carbapenems.

A probabilistic prescription by CBP was found in 67% of cases. Figure 3 represents the distribution of documented infections that motivated the prescription of a carbapenem molecule.

In 76% of cases, CBP was used to treat a nosocomial infection, in 24% a community infection.

Microbiological documentation motivating the prescription of CBP was found in 33% of cases: hemocultures (41%), protected distal samples (17%) and urine samples (14%).

On the bacteriological samples taken, 74 bacteria were isolated. The most frequently found germs are shown in Table I. These were the following Gram-negative bacilli: 32 Klebsiella pneumoniae, 17 Acinetobacter baumannii, 7 E. coli and 5 Pseudomonas aeruginosa. Within isolated Enterobacteria, (40%) were resistant to C3G by productionde BLSE.

All isolates of K. pneumoniae were resistant to C3G by ESBL production, 71% of isolated E. coli strains were resistant to C3G by ESBL production, and all strains of Acinetobacter baumannii isolated were multiresistant.

Imipenem (84%) and ertapenem (13%) were the two most prescribed antibiotics. Imipenem was predominantly prescribed in neonatal resuscitation, found in all prescriptions of neonatology and in 87.5% of CBP prescriptions in adult surgical resuscitation.

Erapapenem was prescribed in 28% of cases in medical resuscitation and 20% in pediatric resuscitation.

As for meropenem, it was prescribed in 10% of cases and only in pediatric resuscitation.

74% of patients were treated with a combination of antibiotics and 26% with monotherapy. Table II shows the number of treatment associations most frequent according to the intensive care unit at the University Hospital of Marrakech. The treatments prescribed in combination with CBP were amikacin (47%), vancomycin (18%), colistin (6%) and tigecycline (3%).

63% of the total prescriptions of carbapenems were made in the second line of treatment. When CBPs were used in the second line, the main antibiotics used in the first line were: C3G + Gentamicin (43%), AMX-CLAVULANIC ACID (8%) and fluoroquinolones in (6%) cases.

A re-evaluation in the first 72 hours after the initiation of carbapenem treatment was found in 90% of cases.

The average dosage was 1.5 to 2g / l in medical and surgical resuscitation, for neonatal (20mg / kg / 8h) and pediatric (18mg / kg / 8h) resuscitation.

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The average duration of treatment was 9 days in neonatal and pediatric resuscitation; (11.6 days) in surgical resuscitation and 6 days in medical resuscitation.

The average length of stay in intensive care unit was 16 days.

The evolution was favorable in 74% of the cases, (3%) stationary and one death was found in (23%) of the cases.

Table III summarizes the main results obtained for each of the parameters studied. It summarizes the prescribing practices of carbapenems in the intensive care unit of Mohammed VI University Hospital in Marrakech.

The analysis of the compliance of the prescriptions of the notified CBP with the indication, the duration of treatment and the dosage showed very reassuring results:

• The indication of antibiotic therapy was considered compliant in 90% of cases. In 10% of cases, these were non-compliant prescriptions (infections without ESBL risk factor or severity criteria).

• The dosage administered was non-compliant for 3 prescriptions of CBP.

• The average duration of treatment was considered compliant for all CBP prescriptions.

• With respect to the reassessment at 72h, 81 of the prescriptions were compliant.

Discussion:

The percentage of prescribing CBP was high in neonatal resuscitation; this can be explained by several risk factors: the high prevalence of nosocomial infections in neonatology, the high frequency of outbreaks of epidemic multidrug-resistant, the invasive nature of the care procedures, the alteration of the immune defense mechanisms and the fragility of the terrain of these patients.

Studies conducted in 2011 and 2012 on the prescribing of CBP [7-8] reported that infections motivating the prescription of a carbapenem molecule were pulmonary infections (45% and 26%) and mainly nosocomial infections (31%). The main indication of the prescription of a carbapenem to the various intensive care units of the University Hospital of Marrakech was sepsis and septic shock.

This prescription was probabilistic in 67% of the cases. This value is close to data reported in several French establishments 60%, 71% and 52% [7-9].

Nosocomial infection motivated the prescription of CBP in 76% of cases. A French study conducted in 2010 reports a 76% prescription similar to this study [10].

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27% of CBP prescriptions were made to treat a documented infection with a C3G resistant strain by ESBL production. This number is close to data reported in literature [9].

The prescription of a CBP molecule was followed by a favorable evolution in 74% of the cases and for 23% of prescriptions, one death was notified. These values were similar in terms of mortality data Besançon study [7], healing (47.5%), relapse (27.3%) and deaths (20.2%).

Imipenem was predominantly prescribed in neonatal resuscitation and in adult surgical resuscitation. Imipenem and meropenem are used primarily for the treatment of Nosocomial infections suspected or proven resistant gram-negative bacilli, including nosocomial pneumonias, postoperative and nosocomial peritonitis, late super infections of necrotizing pancreatitis, bronchopulmonary infections of cystic fibrosis, febrile neutropenia, sepsis and bacillus infections Gram negative catheter or implantable chamber [5].

Erapapenem was prescribed in 28% of cases in medical resuscitation and 20% in pediatric resuscitation. In clinical practice, ertapenem is potentially useful in the treatment of urinary tract infections (off-label), intra-abdominal and pelvic infections, community-acquired pneumonia, and infections of the skin and soft tissues in diabetic patients [5-11].

Given its spectrum, ertapenem should only be used in nosocomial infections at high risk of multidrug-resistant organisms after microbiological documentation [5].

This study found that 74% of patients were treated with a dual therapy combining a CBP molecule with another molecule (Colistin, Amikacin, Tigecycline). Despite a low overall level of evidence, a combination of antibiotics is also recommended for the most severe or fragile patients, especially when they are at risk of BMR infection [12].

The indication of the prescription of a carbapenem molecule was found to compliant with the standard in 90% of cases. Imipenem was prescribed in accordance with the standards in 88% of cases, ertapenem in 10% of prescriptions and meropenem for 2% of prescriptions. This compliance rate is close to that found by two studies conducted at the French institutions level at AP-HP (75%) and Besançon (71.7%).

The percentage of non-compliance of prescriptions was 10%:

• 5% of probabilistic prescriptions for imipenem in the absence of risk factors for multidrug-resistant bacteria [5].

• 5% of probabilistic prescriptions by ertapenem without bacteriological documentation. Due to its lack of activity on Pseudomonas spp and Acinetobacterspp, ertapenem can be used in nosocomial infections at high risk of multidrug-resistant organisms only after microbiological documentation [5]

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This rate of non-compliance is much lower than the values found in the literature. Indeed, for the Besançon study [7], 28% of indications were non-compliant. It is the same with the AP-HP [9] which found a rate of non-compliance to 25%.

Once the primary criteria were defined, the compliant prescriptions for the indication were analyzed according to secondary criteria: dosage, duration of treatment, re-evaluation of treatment.

Overall compliance (the compliance of the indication and secondary criteria) was found for 78% prescriptions out of 100.

An analysis of the secondary criteria was carried out for the requirements for which conformity could be established for the main criteria.

The dosages were consistent for 87 CBP prescriptions. The three non-compliant prescriptions were mainly found in burn patients. This is explained by the higher volume of distribution for these patients [13]. These dosages are not comply with the standards but are justified by the pharmacokinetic changes found in these burn patients.

Indeed, high dosages should be used at the beginning of treatment, when the inoculum is the most important, in case of severe sepsis, as well as in all situations where the volume of distribution is increased (resuscitation patients, haematology, burns ....) [14].

The median duration of carbapenem treatment reported in the literature varies between 4 and 7 days in the literature [15, 16]. This study reports a mean duration of treatment with a CBP is 9 days in neonatal and pediatric resuscitation and 6 days in adult intensive care. The duration of treatment was compliant for all CBP prescriptions. According to the recommendations for the good use of carbapenems, the duration of treatment should be as short as possible, especially since the indications justifying a prolonged treatment of more than seven to ten days are exceptional and a relationship exists between the duration of treatment by CBP and the risk of emergence of resistant strains [5, 15, 16].

In regard to the reassessment at 72 hours, 81 of the prescriptions were compliant. The re-evaluation would allow shorter treatment times, consumptions and better bacteriological adaptation [17]. In order to limit the consumption of carbapenems and therefore the selection pressure exerted by these antibiotics on the commensal flora, it is recommended whenever possible after bacteriological documentation to seek a therapeutic alternative to carbapenems depending on the site infected and after discussion between microbiologists and clinicians. Given the new CA-SFM recommendations for critical concentrations (C3G and Aztreonam), based on PK / PD data (Pharmacokinetics / Pharmacodynamics), there are possible alternatives to the use of carbapenems. Betalactamine-beta-lactamase inhibitor combinations are also possible alternatives. In all cases, the site and microbiological data (CIM) must always be readjusted and taken into account [18].

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It is recommended to limit the presumptive prescription of carbapenems in the community to patients who accumulate risk factors for infection with ESBL enterobacteria and who have a serious infection. In the nosocomial context, the prescription cannot be systematic: it will of course depend on the clinical situation and the risk factors for multi-resistant bacteria infection.

Knowledge of the ecology of the establishment and the service is primary. The choice between molecules within this class should be based on the spectrum of action, and pharmacokinetic and pharmacodynamic data. Whatever the mode of prescription, it is important to take into account the collective risks linked to overconsumption of this therapeutic class.

Conclusion:

Carbapenems are valuable molecules that must be preserved effectively. In practice, this implies that their use must comply with four rules that are part of the general framework of the proper use of carbapenems [5]:

• Carbapenems should be prescribed only when there is a risk of infection with resistant Gram-negative bacilli.

• De-escalation for a narrower spectrum molecule must be made or at least discussed.

• The duration of treatment should be as short as possible to limit the risk of emergence of resistant strains.

• Adequate dosages, particularly at the initial stage of infection during which the inoculum is highest, should be used.

This study analyzed the CBP requirements in intensive care and noted a reassuring compliance rate based on recommendations for the good use of carbapenems. This rate still needs to be reassessed and improved. The appointment of a referent in antibiotic therapy is essential to supervise the prescription of these broad-spectrum antibiotics and limit their use

Conflict of Interest:

The authors declare no potential conflicts of interest, financial or otherwise.

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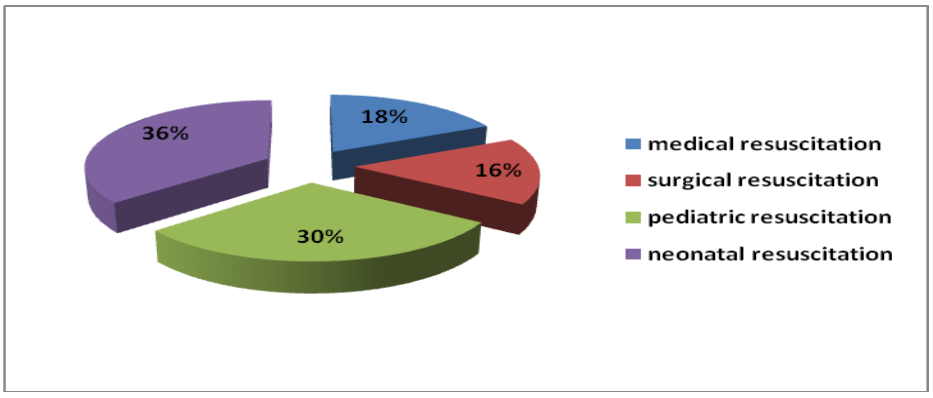

Figure 1: Distribution of carbapenem prescriptions according to resuscitation services at the University Hospital of Marrakech (n = 100)

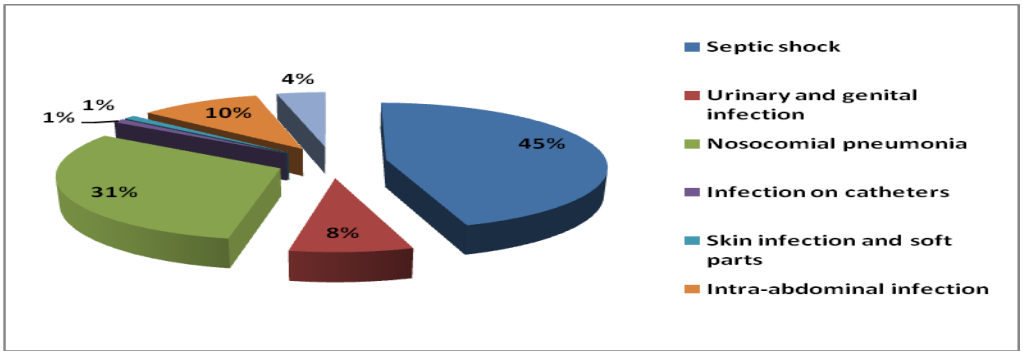

Figure 2: the different indications motivating the prescription of carbapenems at the level of resuscitation services at the University Hospital of Marrakech (n = 100)

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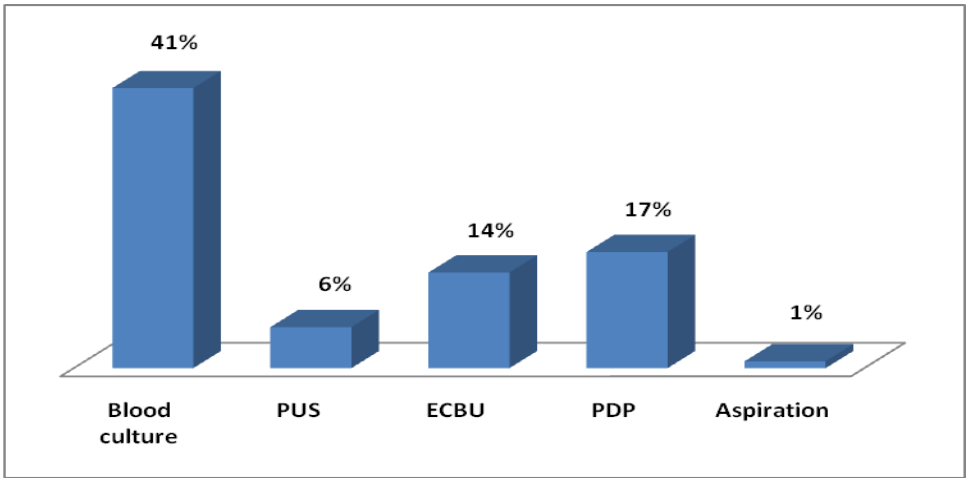

Figure 3: Distribution of positive samples for carbapenem prescription (n = 79)

Table I : Distribution of bacterial species isolated from documented infections requiring CBP (n = 74)

Germs identified	*Number*	*Percentage*
Klebsiella pneumoniae	***32***	***43%***
Acinetobacter baumanni	***17***	***23%***
E .coli	***7***	***9%***
Serratia marcesens	***6***	***8%***
Pseudomonas aeruginosa	***5***	***7%***
Enterobacter cloacae	***3***	***4%***
Enterobacter aerogenes	***2***	***3%***
Achromobacter spp	***2***	***3%***

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Table II: Distribution of bacterial species isolated from documented infections requiring CBP (n = 74)

carbapenems prescribed	medical resuscitation (n=18)	chirurgical resuscitation (n=16)	pediatric resuscitation (n=30)	neonatal resuscitation (n=36)
CBP Monotherapy (n = 26)	16.6%(3)	25%(4)	33.3%(10)	20,5%(9)
CBP in Association (n=74)				
Carbapenem + Aminosid	50%(9)	43.7%(7)	20%(6)	70%(25)
Carbapenem + Vancomycin	11,1%(2)	18,7%(3)	36.6%(11)	5,5%(2)
Carbapenem + Tigecyclin	0,5%(1)	6.3%(1)	3.3%(1)	0%
Carbapenem + Colistin	0%(3)	6.3%(1)	6.6%(2)	0%

Table III: General cartography of the use of carbapenems in different intensive care unit in the Marrakech University Hospital Center

Department	% Of prescription the CBP	% Of nosocomial infection prescription	% Of probabilistic Prescription	Bacteria of documented infections	% Of prescription of imipenem	average dosage	Average Duration	Reassessment at 48h-72h
Neonatal resuscitation	36%	86%	50%	*K.pneumonia* (n=20)	100%	20mg/kg/8h	9 jrs	92%
Pediatric resuscitation	30%	57%	76%	*A.baumannii* (n=5)	70%	18mg/kg/8h	9 jrs	90%
Adult resuscitation	34%	85%	79%	*A.baumannii* (n=10)	76%	1-2 g/jr	8 jrs	88%