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Research Article

Clinical Evolution of Carbapenemase Producing Gram-negative Bacteria Infections Treated by Monotherapy Versus Dual Therapy

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Abstract

Introduction: During the last few years, the emergence of carbapenemase producing gram-negative bacteria infections has been reported worldwide. These infections are very difficult to treat since there is no consensus on the antibiotic treatment modalities.

Methods: This study is an observational, retrospective study reviewing the clinical course and prognosis of patients treated for carbapenemase secreting Enterobacteriaceae infection, according to different antibiotic treatment protocols. The population consists of all patients infected by enterobacteriaceae with a decreased sensitivity to carbapenems, between September 2014 and January 2016. The primary objective of this study is to compare the recurrence and mortality rates between the group of patients treated with a monotherapy and the one receiving a combination antibiotic therapy.

Results: Amongst the 29 patients that received a monotherapy, 15 patients (51.7%) had a recurrent infection compared to 9 patients (33.3%) out of 27 that received a combination therapy without a statistically significant difference between these 2 groups. The interval of trust is [0,16- 1,38] (p-value at 0.467 > 0.05).

10 patients (34.5%) out of the 29 patients who received a single antibiotic died compared to 14 (51.9%) of the 27 patients who received a combined antibiotherapy. There was no statistical significant difference between these 2 groups: [0,7-6] is the interval of trust for this analysis with a p-value at 2.046 > 0.05.

Conclusions: The number of antibiotics used, whether one or more, does not influence the recurrence rate of carbapenemase-secreting enterobacteriaceae. And the type of therapy used, has no effect on the mortality rate, following a carbapenemase-secreting enterobacteriaceae.

Keywords: Penicillin G; Carbapenemase; Enzymes

Introduction

One of the most important discoveries in the world of medicine was made by coincidence: in 1928, the fungus Penicillium inhibited the growth of the pneumococcus, with a substance that it secreted in the medium, an inhibitory substance, which Sir Flemming named later on ‘‘Penicillin G”.

Unfortunately, short after the introduction of antibiotics, resistant strains started to emerge, to a point that the idea of “antibiotic resistant bacteria” has become one of the major problems of the contemporary medicine [1], and a serious public health concern especially in Lebanon [2].

The carbapenem resistance emerged caused mainly by an uncontrolled use of carbapenems, the lack of epidemiological data of multi-drug resistant Gram-negative bacilli especially in the Middle East [3], and the over prescription of broad spectrum antibiotics during pandemics as the Covid-19 crisis [4].

Preventive measures are still necessary to counteract this rapid evolution of resistant strains, which can only be ascertained through a good comprehension of the mechanisms of acquisition of resistance; which can be non-enzymatic like the loss of expression of porin-encoding genes, or by the hydrolysis of the carbapenems by carbapenemase enzymes [5].

Over the past few years, the emergence of carbapenemase-producing bacteria has been reported worldwide.

Various enzymes were discovered to be responsible of the degradation of carbapenems, most notably KPC (c), VIM(d), IMP, NDM, and OXA-48 [6].

The major remaining issue is the rapidity of dissemination of this resistance between humans mainly due to the socio-economic crisis and wars forcing people from third world countries to move into more stable lands, and due to the delay in the diagnosis of the resistant pathogens, which affected the early establishment of an appropriate therapy [5].

Though, this dissemination does not only occur in people, but also in animals and in the environment [3]. In addition, it could be spread from animals to humans via the food chain [7].

Gram-negative carbapenemase-producing bacilli infections are still very difficult to treat due to the lack of consensus on the antibiotic treatment modalities.

The objective of this study is to review the clinical evolution through different antibiotic protocol modalities, and the patient's prognosis.

Materials and Methods

Type of study

This study is an observational, monocentric retrospective study, which consists of reviewing the follow up and prognosis of patients treated for a carbapenemase-secreting enterobacteriaceae infection, according to different antibiotic treatment protocols.

Targeted population

The population consists of all patients infected by Enterobacteriaceae with a decreased sensitivity to carbapenems between September 2014 and January 2016.

Methods

A total of 81 patients were recruited at a tertiary care medical center hospitalized for a carbapenemase-secreting enterobacteriaceae infection, between September 2014 and January 2016.

The isolated microorganisms are: Escherichia *coli* (28 strains, 35%), Klebsiella *pneumonia* (8 strains, 10%)., Klebsiella *oxytoca,* Enterobacter *aerogenes*, Enterobacter *cloacae*, and Morganella *morganii*.

The institutional review board (IRB) has approved our study.

The information related to each patient, useful for the study, was found in the archives of the tertiary care hospital, and were transcribed to an Excel file.

This information included the patient's first and last name, PIN number, age, gender, date of birth, name of the treating infectious diseases specialist, place of residence, telephone number, date of hospitalization, the microorganism responsible for the infection, the source of the infection, the antibiotic sensitivity test including the following antibiotics: Colistin, Meropenem, Amikacin, Gentamicin, Tobramycin, and Tigecycline, and the type of therapy received by the patient (monotherapy or combined therapy) in addition to subsequent admissions due to a recurrence of the carbapenemase-secreting enterobacteriaceae infection.

Concerning the last topic, we called each patient, or his relatives, to assess whether the recurrence was treated in another medical institution. In case of death, the family was asked if this event was due to an infection.

It should be noted that the confidentiality and anonymity of the information related to each patient have been respected. This was ensured by assigning a number to each medical file. This number is known only by the investigators.

Statistical analysis

Following the data collection, a statistical study was conducted to compare the rate of recurrence and mortality related to both groups: monotherapy versus combineation therapy.

In order to carry out this statistical analysis, we used the ''Fisher-Irwin-Yates Test'', a test of proportions, on two independent samples.

Two null hypotheses (H0) were put forward:

- H01: The recurrence rate depends on the therapeutic protocol used.
- H02: The mortality rate depends on the therapeutic protocol used.

The p value is used to refute or support the null hypothesis. The smaller the p value is, the stronger is the statistical evidence that the ''null hypothesis'' must be disproved. Conventionally, the confidence interval is 95%, and the p value must be less than 0.05 in order to have a significant result and to reject the null hypothesis.

Results

81 patients with carbapenem-resistant microorganisms were enrolled between September 2014 and January 2016. Of these 81 patients, 25 patients were withdrawn from the study: the records of 15 patients were not found in the archives, 5 patients had lack of data regarding the sensitivity testing, and 5 patients did not answer the phone call.

The average age of these 56 eligible patients was 45.6 years (5 to 94 years old).

Of the 56 patients, 29 patients (51.7%) received a monotherapy, and 27 patients (48.2%) a combined therapy.

Monotherapy Combination therapy			Treatment		Total
Recurrence	No	Number	14	18	32
		%within Recurrence	43.8%	56.3%	100.0%
		%within Treatment	48.3%	66.7%	57.1%
	Yes	Number	15	9	24
		%within Recurrence	62.5%	37.5%	100.0%
		%within Treatment	51.7%	33.3%	42.9%

Table 1: Table showing the percentage of recurrence rate in the groups representing patients who were treated with a single type and with several types of antibiotics following carbapenemase secreting enterobacteriacae infection.

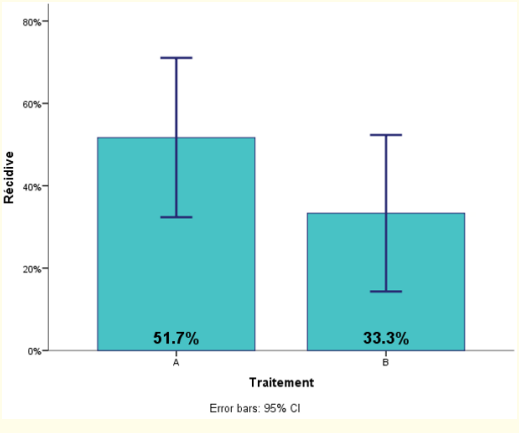

Figure 1: Graph representing the recidivism rate in group A (monotherapy) and group B (combination therapy) as well as the error bars of each group.

The table in table 1 shows the post-treatment recidivism rate in the two study groups.

- Of the 29 patients that received a single antibiotic as a treatment for their infection, 15 patients (51.7%) developed another carbapenemase secreting enterobacterial infection in the next 6 months.
- On the other hand, only 9 patients (33.3%) of the 27 patients who received a combination antibiotic therapy were re-infected with another enterobacteriaceae secreting carbapenemase in the next 6 months.

The graph in Figure 1, shows the recurrence rate related to each group. (51.7% for the monotherapy, group A and 33.3% for the combination therapy, group B) as well as the error bars of each group.

[0,16-1,38] is interval of trust for this analysis with a p-value at 0.467 > 0.05.

The statistical analyses do not show any significant difference between the 2 groups. Hence, the hypothesis H01 was refuted: our study did not show a difference in terms of recurrence after treatment with one or multiple types of antibiotics following an infection with a carbapenemase-secreting enterobacteriaceae.

Monotherapy Combination therapy			Treatment		Total
Death	No	Number	19	13	32
		% within death	59.4%	40.6%	100.0%
		% within Treatment	65.5%	48.1%	57.1%
	Yes	Number	10	14	24
		% within death	41.7%	58.3%	100.0%
		% within Treatment	34.5%	51.9%	42.9%

Table 2: Table representing the percentage of mortality and non-mortality in the groups representing the patients who were treated with a single type and multiple types of antibiotics following an infection with carbapenemase-secreting enterobacteriacea

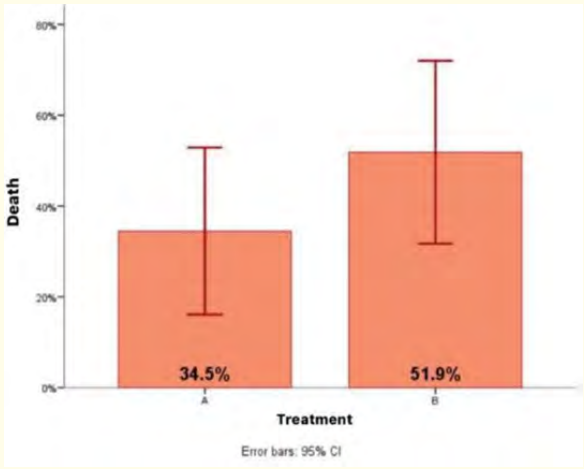

Figure 2: Graph representing the mortality rate in group A (monotherapy) and group B (combination therapy) as well as the error bars of each group.

The table in table 2 shows the post-treatment mortality rate in the 2 study groups.

- Of the 29 patients that received a single antibiotherapy as a treatment for their infection, 10 patients (34.5%) died.
- On the other hand, only 14 patients (51.9%) of the 27 patients who received 2 or 3 antibiotics as a treatment for their infection, died.

The graph in figure 2, shows the recurrence rate in relation to each group, (34.5% for the monotherapy, group A and 51.9% for the combination therapy, group B) as well as the error bars of each group.

[0,7-6] is the interval of trust for this analysis, with a p-value at 2.046 > 0.05.

Therefore, there is no significant difference between these 2 groups and the H02 hypothesis was refuted.

The study therefore, shows no difference in mortality after treatment with a single or multiple types of antibiotics, following an infection with a carbapenemase-secreting enterobacteriaceae.

Discussion

This study is an observational monocentric retrospective study, which followed patients for 5 years after their admission to the Hôtel-Dieu de France hospital, for a carbapenemase-secreting enterobacteriaceae infection.

This study showed a recurrence rate of 51.7% in the group of patients that got a monotherapy and 33.3% in the islet with a combination antibiotherapy. But these rates did not show a significant difference.

Therefore, according to our study, the number of antibiotics used, whether one or more, has no effect on the recurrence rate of carbapenemase-secreting enterobacteriaceae infections.

This same result is obtained in a study by Paul., *et al*. where they found a non-significant difference between colistin used as a monotherapy and colistin used in a combined therapy with a carbapenem during the treatment of gram-negative infections, resistant to carbapenems, in terms of recidivism [8]. Similarly, a study conducted by De la Calle., *et al*. in Barcelona, did not show any significant difference in terms of recidivism when using ceftazidim-avibactam as a monotherapy or in combination with another antibiotic [9]. Besides, another study conducted by Adam., *et al*. didn't show better clinical outcomes while treating a carbapenem-resistant Gram-negative with colistin and meropenem [10].

On the other hand, a retrospective study conducted in Turkey on patients with a urinary carbapenemase-secreting enterobacteriaceae, shows a lower recurrence rate while using several families of antibiotics [11]. In addition, the study by Schmid., *et al*. in Zurich, noted the effectiveness of the combined therapies on reducing the number of recurrences [12]. Furthermore, a retrospective study conducted by Thaner., *et al*. in Saudi Arabia, showed that the combination of Ceftazidim and Avibactam is associated with a higher rate of clinical cure from Carbapenem-Resistant infections, compared to the use of colistin alone [13].

These different results can be explained in different ways. The first explanation is, that each study adopted a different therapy from the other, in the absence of the guidelines capable of unifying the treatment for Enterobacteriaceae infections that secreted carbapenemase.

Second, some studies have worked on a single specific germ, whereas in our case, we used different types of germs as long as they belong to the family of the carbapenemase-secreting enterobacteriaceae.

Our study showed a mortality rate of 34.5% while using a single type of antibiotics, and 51.9% in case of combined therapy. Similarly, there was no significant difference between both groups, where the type of therapy used had no effect on the mortality rate during the post-infection phase with carbapenemase-secreting enterobacteriaceae.

The study held by Schmid., *et al*. [12], has led to the same result where the mortality rate did not differ between the monotherapy and the combination therapy. Similarly, the mortality rate did not differ in the study of De la Calle., *et al*. [9], after the use of ceftazidim-avibactam as monotherapy and in combination with another antibiotic.

On the other hand, the mortality rate decreased in the case of combined therapies, in the Turkish study on urinary tract infections, with carbapenemase-secreting germs [11]. While in another study, it was noted that the mortality rate has decreased when using multiple antibiotic therapies, among the patients with septic shock or chronic diseases [14].

This significant difference between the different studies, concerning the death of the patients, may just be related to the fact that in some, the group of patients has a mean age higher than others, exposing the patients to a greater mortality risk due to the comorbidities they present.

This study has several limitations. First, the sample size is relatively small. The mortality and recidivism rates were the same for different therapeutic approaches, unlike other studies. Second, the study was conducted on a sample collected from a single hospital in Beirut. This sample is not representative of the Lebanese population. Thirdly, patients of different ages were considered as a single entity without taking into consideration the comorbidities that may be related to their age and gender.

Conclusion

Carbapenemase-secreting Enterobacteriaceae, emerged in the 1990s, and currently have become quite widespread throughout the world. These germs, especially the OXA-48, have a very particular and fast transmission mechanism. In fact, they are associated with a high mortality rate. Hence the urge for a good diagnosis and a quick eradication.

This study is a retrospective study, studying the recurrence and the mortality rates in patients infected with a carbapenemase-secreting enterobacteriaceae according to the therapeutic choice: mono-antibiotherapy or a combination of antibiotics.

Our study showed that the recurrence and the mortality rate did not significantly differ between the two groups of patients,

subjected to different therapeutic protocols, characterized by a different number of antibiotics (one or more).

Thus, in the case of a bacterial infection with a carbapenemase-secreting enterobacteriaceae, the number of antibiotics used, has no effect on the subsequent prognosis of patients; the rate of recidivism and mortality are not affected.

It is very important to remember that the only way to counteract this global scourge is prevention: antimicrobial stewardship programs and the application of strict isolation and hygiene methods.

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