Evaluation with E-test of the meropenem/vaborbactam association in carbapenem-resistant and sensitive negative control strains isolates of samples processed at the Laboratory of the Rivoli Hospital

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Summary

Background and aims. Meropenem (Mer) and vaborbactam (Vab) is a combination of a carbapenem and a new β-lactamase inhibitor used in adults to treat different types of infections caused by Gram-negative bacteria. This combination is chosen as an alternative in infections caused by Gram-negative bacteria when carbapenem-only therapies are unsatisfactory.

Materials and methods. Based on this, we report our assessment of such meropenem/vaborbactam association through the E-test and the Microscan routine automated system. This evaluation was performed on 22 samples, carbapenem-resistant strains of Gram-negative bacteria isolated from different types of biological material. Five *E. coli* and 1 *P. mirabilis* were respectively susceptible to both carbapenems and Mer/Vab, 6 *P. aeruginosa* and 2 *A. baumannii* were respectively resistant to both carbapenems and Mer/Vab and out of 8 *K. pneumoniae* which were resistant to carbapenems only one was resistant to the Mer/Var combination.

Results and conclusions. From the data obtained, it can be seen that resistance to carbapenems is 72%, and drops to 36% with the combined use of Mer/Vab. However, this combination cannot be used in the treatment of patients with diseases caused by *P. aeruginosa* and *Acinetobacter spp*., resistant to meropenem.

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Introduction

Meropenem (Mer) and vaborbactam (Vab) (Vaborem, Menarini, Florence, Italy) is a combination of a carbapenem and a new β-lactamase inhibitor used in adults to treat: bacteraemia, complications in urinary tract infections, including infections of the kidney tissue, complications in infections of the tissues and organs of the abdomen (intra-abdominal infections), hospital-acquired pneumonia including ventilator-associated pneumonia supported by Enterobacteriaceae (3).

The Mer and Vab combination is chosen as an alternative in infections caused by Gram-negative bacteria when carbapenem-only therapies are unsatisfactory (2).

Mer-Vab works in different ways.

Mer belongs to the carbapenem class of antibiotics, which are part of the larger group of antibiotics known as β-lactams, and it was authorized in the EU in the 1990s. It works by interfering with the activity of certain proteins in which bacteria need cell wall synthesis. This action weakens the bacterial cell walls causing them to collapse and ultimately causing the death of the bacteria themselves.

Vab, on the other hand, is a β-lactamase inhibitor derived from boronic acid: it prevents bacterial enzymes, called β-lactamases, from breaking the structure of β-lactam antibiotics, such as meropenem, and from ceasing their effect. This inhibitor has no antibacterial activity when administered alone; by blocking the action of these enzymes, however, Vab allows Mer to act against these otherwise resistant bacteria (1).

The drug is administered in the facility, by intravenous infusion, for 3 hours, every 8 hours, and the duration of treatment depends on the type of infection (3) and its severity.

Materials and Methods

Twenty-two samples of different nature (respiratory, blood cultures, urine) were tested with different germs, coming from hospitalized patients with various types of infections, previously analyzed by the Microscan automated system (which is based on the evaluation of sensitivity and resistance to different antibiotic molecules through the reading of the Minimum Inhibitory Concentration (MIC)).

Therefore, the analyzed samples from which we obtained the results as MIC made it possible to evaluate their sensitivity and /or resistance.

The data obtained with the routine reference method, used in the microbiological analysis laboratory of the Ospedale degli Infermi di Rivoli (ASL TO3), were compared with the E-test method "MIC Test Strip MEROPENEM*/VABORBACTAM (8 µg/mL)(FDA cleared) 0.016-256".

Results and Discussion

The data from the Microscan automated system and the MIC values deriving from the E-test performed with MIC "Test Strip MEROPENEM*/VABORBACTAM (8 µg/mL)(FDA cleared) 0.016-256" were collected and compared.

Of the 22 isolates, we identified: 5 *Escherichia coli* and 1 *Proteus mirabilis,* respectively susceptible to both carbapenems and Mer/Vab; 6 *Pseudomonas aeruginosa* and 2 *Acinetobacter baumannii*, respectively resistant to both carbapenems and Mer/Vab; 8 *Klebsiella pneumoniae* were resistant to both carbapenems, 7 were susceptible to Mer/Vab, and only 1 was also resistant to the Mer/Vab combination (Table 1).

The data we obtained is comparable to the data reported in the literature: it is noted, in fact, that the resistance to carbapenems is 72%, and drops to 36% when combined with the use of Mer/Vab (4,5) (Figure 1).

The small number of tested samples is due to the fact that the E-tests have been provided free of charge by the manufacturer as a proof test, therefore the results obtained *in vitro* cannot be supported by clinical data.

It should be kept in mind that, although the number of tests is

Table 1. Comparison of data obtained from the analysis of the isolates with the Microscan automated system and with the E-test "MIC test strip". The data in the Table show an increased antibiotic sensitivity, twice as compared to classic therapy; even if the analyzed samples are few, there is a good chance of efficacy.

	Carbapenems	Meropenem-vaborbactam
EC	5 (S)	5 (S)
PSA	6 (R - XDR)	6 (R)
KP	7 (R - XDR) 1 (R - MDR)	6 (S) 1 (I) 1 (R)
AC	2 (R - XDR)	2 (R)
PM	1 (S)	1 (S)

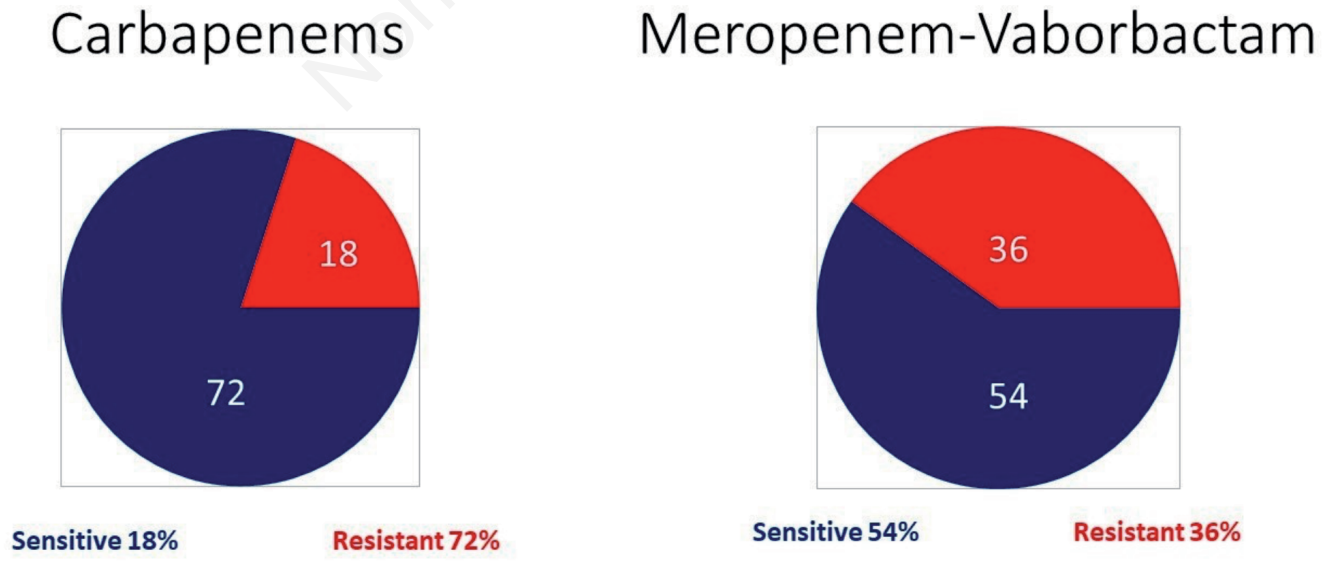

Figure 1. Comparison of the percentage of Sensitive and Resistant isolates of the data obtained with the Microscan automated system and with E-test "MIC test strip".

quantitatively low, some bacterial species are highly resistant to both carbapenems and the Mer/Vab combination, such as *P. aeruginosa* and *A. baumannii*.

All this should be supported by clinical data, which we do not yet possess, as for the *in vitro* behavior, especially for cases of resistance to Mer/Vab molecules, there may have not been the same result *in vivo*; this has already been found with the use of other molecules which, considered resistant *in vitro*, have given good results *in vivo* (6), as reported in the literature. The reported data are not accompanied by clinical data on drug administration due to the reduction of medical personnel in the wards during the period of the pandemic.

It should be remembered, as reported in some papers (8), that Vab (a β-lactamase inhibitor derived from boronic acid) was developed to restore the activity of meropenem against carbapenemase-producing bacteria, in particular against producing strains by *K. spp* resistant to carbapenems. Vab inhibits class A (KPC, IMI, SME, NMC-A and FRI-1) and class C (AmpC, CMY) serine beta-lactamases. With *P. aeruginosa* and *Acinetobacter spp*. the activity of Mer/Vab was overall similar to that of Mer alone. This is apparently due to the fact that, in *P. aeruginosa* and *Acinetobacter spp*., resistance to Mer is largely mediated by mechanisms that are not antagonized by Vab (*e.g.* membrane not-permeability, efflux pumps and production of class B or D β-lactams).

Therefore, with all the limitations of our work, our data suggest that the Mer/Vab combination cannot be used in the treatment of patients with diseases caused by *P. aeruginosa* (7) and *Acinetobacter spp*., resistant to Mer.

Further studies are required to confirm or not this association between molecules in order to favor the best therapeutic approach and without triggering further resistance.

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