Epidemiological Alert:

Dissemination of Carbapenemases in *Klebsiella Pneumoniae* in Latin-America

(2 July 2010)

In light of the increase in carbapenemases in enterobacteria detected in several countries of the Region, the Pan American Health Organization (PAHO) emphasizes the importance of the detection of this mechanism of resistance, which increases considerably morbidity and mortality of the infections by *Klebsiella pneumoniae*.

Recently, the INEI-ANLIS "Dr. Carlos G. Malbrán" Laboratory in Buenos Aires, Argentina, published a national alert on the dissemination of carbapenemases in Argentina. This laboratory is responsible for the external quality assurance program of the Latin American Network for Monitoring Antimicrobial Resistance, coordinated by PAHO. In this alert, the laboratory reported an increase of 800% in isolations of enterobacterium with carbapenemases in the first four-month period of 2010, in comparison to the same period in the previous year.

It is estimated that *Klebsiella pneumoniae* is the etiologic agent responsible for 20-30% of nosocomial pneumonias in the Region, and is among the top three pathogens isolated in hospital bacteremias by Gram-negative[i]. Klebsiella has natural resistance to ampicillin, by the presence of a chromosome gene that codes a specific β lactamase. The strains of nosocomial *K. pneumoniae* are resistant to other antibiotics by acquisition of multiresistant plasmids (β lactamases of extended spectrum); these strains cause greater therapeutic failure and mortality. In this situation, the carbapemenes are the most appropriate therapeutic option.

One of the principal problems of the microbiology laboratory is the detection of the carbapenemases, due to the fact that the standard methods can report strains of carbapenemase-producing *K. pneumoniae* as "sensitive to carbapenem". The clinical implications are noteworthy, because clinical and microbiological failures are observed frequently in patients infected by these carbapenemase-producing strains[2]. The case-fatality from carbapenemase-producing *K. pneumoniae* ranges between 47 and 68%, according to various studies[3,4,5].

What are Carbapenemases?[1]

Carbapenemases are bacterial enzymes that inactivate the carbapenemes, causing a resistance to this entire group of antimicrobial drugs.

The consequences for the empirical treatment of the infections caused by these bacteria are noteworthy, practically eliminating this therapeutic effectivity for the infections caused by the pathogens produced by carbapenemases.

The dissemination of KPC (*Klebsiella pneumoniae* carbapenemases) or MTL (metallo-beta-lactamases) occurs by plasmids; therefore the control is based on the isolation of patients with presence of these bacteria and mechanism.

Situation of Klebsiella spp in the Region

The **Latin American Network for Monitoring Antimicrobial Resistance** (RELAVRA) includes hospital surveillance of the Klebsiella microorganism, and requests sensitivity test data for a number of antibiotics from the countries [6].

With regard to the trend of the different types of resistance, data from the annual reports from the Network[vi], 2000-2007, reveal about 40% of resistance to cefotaxime (Figure 1), while the resistance to imipenem stays at very low levels. For further detail, Figure 2 displays average resistance to imipenem, less than 1% during the reported period.

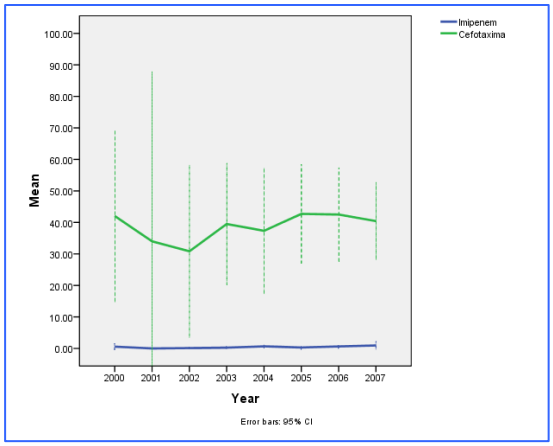

Figure 1. Trend of *Klebsiella spp* resistance to cefotaxime and imipenen, 2000-2007.

Source: Latin American Network for Monitoring Antimicrobial Resistance.

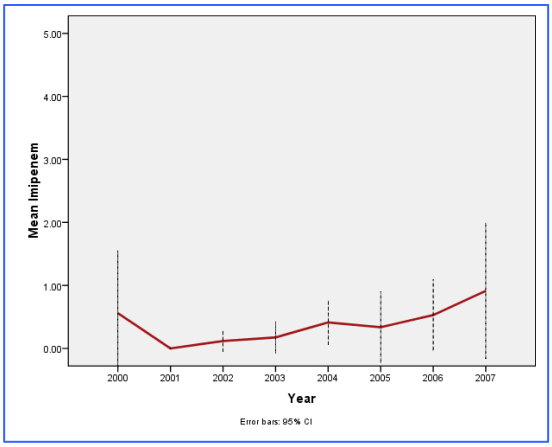

Figure 2. Trend of *Klebsiella spp* resistance to imipenen, 2000-2007.

Source: Latin American Network for Monitoring Antimicrobial Resistance.

Challenges for surveillance: Laboratory detection.

The first line of containment of these multiresistant pathogens are the laboratorios, through adequate detection of this mechanism, research of the prevalence, and informing the authorities, those responsible for the control of hospital infections as well those at the national level, in order to alert other hospital centers.

The laboratory detection of carbapenemases has been a challenge given that currently the test recommended by the standards used in RELAVRA following the *Clinical Laboratory Standard Institute* (CLSI) is the modified Hodge test, which requires experience in the technique to detect them adequately. Pasterán et al.[7] have described a sensitive and high specific method for the detection of the KPC-type carbapenemases. This technique consists in the utilization of the acid phenyl-boronic disk which acts on the A-type serin-carbapenemases.

There are molecular methods available for the complete characterization of the carbapenemases, but what is currently most important is to urge all the national reference laboratories to prioritize case-finding of this mechanism in each country

through their sentinel surveillance networks in order to characterize the situation in each country and establish the guidelines for control and prevention.

Recommendations

a) Surveillance measures and epidemiological research:

1. Increase the participation of laboratories in the surveillance systems for the early detection of outbreaks, so as to provide early guidance for the control measures. In case of suspicion of carbapenemases, send the strain to the national reference laboratory for confirmation.
2. At the national level, the reference laboratories have to establish a protocol for detection of carbapenemases and referencing of strains in case of suspicion.
   - NOTE: It is recommended that the sentinel laboratories, primarily when facing gram-negative hospital pathogens, should follow an algorithm for the detection of these mechanisms of resistance, and send the first strain detected by an institution for confirmation by the national reference laboratory.
3. The first strain that is suspected or confirmed as a producer of carbapenemases identified at the national level should be sent for confirmation to the INEI-ANLIS Dr. Carlos G. Malbrán Laboratory in Buenos Aires, Argentina.
4. At all levels, to disseminate the information and recommendations in order to alert health workers and decision-makers.

b) Antimicrobial treatment:

The limited clinical experience indicates that combinations of antibiotics provide better results than the monotherapy, but the lack of scientific evidence prevents the recommendation of more specific guidelines for treatment.

c) Control Measures for Infections:

Type of precaution	▪ Contact precautions.
Duration of the precautions:	▪ Until the cure of the disease.
Recommendations:	• Hand-washing with water and soap or glycerinated alcohol. • Use of gloves and gowns for close contact with the patients and for contact with secretions. • Isolation in an individual room or cohort. • Separation between beds of over 1 meter. • Cleaning of the environment with chlorine (bleach) dilution (1:10).

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