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Isepamicin and other antibiotics comparative activity against gram-negative bacilli

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Abstract
The *in vitro activity* of isepamicin was compared to that of amikacin, gentamicin, cefepime, ciprofloxacin and meropenem against Gram-negative bacilli isolated from patients hospitalized in the intensive care unit (ICU). The minimal inhibitory concentrations (MIC) for 1087 non-duplicate, consecu- tive aerobic Gram-negative isolates, including *797 Enterobacteriaceae* and 289 non-fermenters, were deter- mined by E-test for each antibiotic. Overall, isepamicin was active against 91% of all isolates and was found more active than ciprofloxacin (84% susceptibility), gentamicin (88% susceptibility), cefepime and amikacin (89% susceptibility each), but less active than meropenem (94% susceptibility). *Enterobacter aerogenes* isolates exhibited the highest resistance rate to ciprofloxacin (72%) while *P. aeruginosa* appeared the most resistant (frequently multi-resistant) pathogen. Compared to amikacin, MIC values for isepamicin were usually two to fourfold lower for most inducible *Enterobacteriacieae* species and for *Klebsiella* spp., while they were identical for *P. aeruginosa* and other non-fermenters. Complete cross-susceptibility or cross- resistance between amikacin and isepamicin was observed in more than 95% of all tested isolates. On the other hand, 12% of all *E. aerogenes* isolates appeared resistant to amikacin and susceptible to isepamicin, while 6% of the *P. aeruginosa* were found to be resistant (or intermediate) to isepamicin and intermediate (or susceptible) to amikacin. No significant differences in pathogen distribution nor in resistance rates were observed between hospitals except for *P. aeruginosa.* Taking into account the species distribution and the prevalence of resistance to the different antibiotics tested, isepamicin appears as a suitable agent for empiric therapeutic use in severe ICU-acquired Gram-negative infections in India.

Keywords: Resistance, Gam-negative bacteria, nosocomial infections

Introduction
Aminoglycosides are broad-spectrum antimicrobials which have been widely used as first-line treatment for many severe and life-threatening systemic and local infections, particularly those caused by Gram-negative bacteria. Development of resistance is an acknowledged problem with all antibiotics. It has been increasingly reported in specific geographical areas, particularly in the hospital where aminoglycoside use is common. Bacterial resistance to aminoglycosides is most commonly caused by plasmid-mediated aminoglycoside-inactivating enzymes and less frequently by membrane impermeability and/or active efflux or by mutation of a ribosome target [1]. Amikacin was originally developed to counteract bacterial resistance to the other aminoglycosides then in clinical use (e.g. gentamicin, tobramycin or netilmicin). However, amikacin-resistant pathogens producing a specific enzyme - 6'-N-aminoglycoside acetyltransfrase [AAC(6')-I] - have gradually emerged and currently account for more than 30% resistance of all aminoglycoside-resistant Gram-negative isolates in the US and in most Western European countries including India [2-5]. Isepamicin, an aminoglycoside recently released in Belgium, is a 1-N-S-a-hydroxy-b-aminopropionyl derivative of gentamicin B. It has been developed as a response to the need for a molecule exhibiting greater stability to resistance enzymes. Isepamicin is a potent bactericidal antibiotic with broad activity spectrum and a pharmacokinetic profile similar to that of amikacin. *In vitro* sensitivity tests have shown fewer isolates to be resistant to isepamicin than to other aminoglycosides, including amikacin. Of particular importance is the stability of isepamicin to the increasingly common 6'-N- aminoglycoside acetyltransferase AAC (6')-I which in- activates amikacin and all other aminoglycosides except gentamicin.

The present study aimed at evaluating the *in vitro* activity of isepamicin against Gram-negative bacilli iso- lated from ICU patients in January - 2023 to December - 2023, and at

comparing it with five major antibiotics, commonly used empirically for the treatment of severe nosocomial infections.

Materials and Method

A prospective study was conducted over a period of one year (January - 2023 to December - 2023) at the Clinical Microbiology Laboratory at Chhattisgarh Institute of Medical Sciences, Bilaspur, Chhattisgarh, India. We performed a descriptive surveillance study aimed at assessing the prevalence of Gram-negative aerobic bacteria and their antimicrobial susceptibility profile to isepamicin and five other agents frequently used for the treatment of severe nosocomial infection in intensive care patients. Participating investigators were requested to prospectively collect 100 consecutive Gram-negative isolates from intensive care unit patients and determine their susceptibility to six selected antibiotics. The collection took place from January - 2023 to December - 2023. Identification of the organisms to the species level was carried out at each center using conventional methods [6, 7]. The sites of origin and date of sampling of the isolates were recorded. No attempt was made to assess the infection status (infection vs. colonization), the exact pathogenic role of the isolates in the underlying condition, nor their influence on the final outcome.

All first isolates of the same species were included. Duplicate isolates from the same patient were not included in the analysis. Isolates from paediatric intensive care or coronary care units were also excluded. Bacterial strains belonging to *Moraxella* or *Neisseria* species were discarded. Isolates from all clinical sites were allowed provided the patients had been hospitalized in the ICU for at least 48 h. Specimens obtained as screening samples from the inanimate external patient environment were not included in the study.

The minimal inhibitory concentrations (MICs) were determined in each centre by E-Test (AB BIODISK, Sweden) over a range of concentrations from 0.016 to 256 mg/l for cefepime, amikacin, gentamicin, isepamicin and from 0.008 to 32 mg/l for ciprofloxacin and meropenem. E-test MICs were performed on 140 mm diameter Petri dishes with 60 ml PDM ASM II agar (AB BIODISK, Sweden). Inocula were prepared by picking 4 to 5 individual colonies from an over- night fresh growth on blood agar plate and adjusting the suspension to a density corresponding to 0.5 McFarland, in Mueller-Hinton broth. Plates were inoculated by flooding with the adjusted inoculum suspensions, and then left to dry before adding the E-test strips. After overnight incubation at 37ºC, the MIC value was read by recording the point of intersection between the zone edge and the E-test strip. Breakpoints for susceptibility were defined according to the NCCLS criteria for amikacin: 16 µg/ml, cefepime: 8 µg/ ml; ciprofloxacin: 2 µg/ml; gentamicin: 4 µg/ml and meropenem: 4 µg/ml (8). For isepamicin, we used a susceptibility breakpoint of 16 µg/ml as recommended by the "Comité de l'antibiogramme de la Société Française de Microbiologie (CA-SFM) (9). Quality control testing was performed in each laboratory with *Pseudomonas aeruginosa* ATCC 27853 and *Escherichia coli* ATCC 25922 as control strains. The results obtained from all participating centers were entered in a data base allowing pooling in order to yield a global overview, as well as individual center statistics when needed.

Results

A total of 1087 Gram-negative isolates were obtained from clinical specimens of adult patients hospitalized in intensive care units. The vast majority of the isolates originated from the respiratory tract (62%). Other sources included urine (18%), wound and pus (11%), or blood (6%). The most prevalent organisms were *P. aeruginosa* and *E. coli* (23% each), followed by *Enterobacter* spp. (16%) and Klebsiella spp (12%). As far as groups of bacterial species are concerned, the non-inducible *Enterobacteriaceae* (*E. coli, Klebsiella* spp. and *Proteus* spp.) were more prevalent than the inducible ones (*Enterobacter* spp., *Serratia* spp., *Citrobacter* spp., *M. morganii* and *Providencia* spp.) 45% vs. 27%, respectively. Non-fermenters (including *Pseudomonas* spp., *Acinetobacter* spp. and *Stenotrophomonas maltophilia*) contributed altogh ether 26% of the organisms. No difference, neither in the origin nor in the distribution of prevalence of the organisms, was found between the different centres. Table 1,3,4,5 shows the percentage of resistance of the various species to all six tested antibiotics. The highest level of resistance against a single agent was observed in *E. aerogenes* (72% to ciprofloxacin), whereas *P. aeruginosa* exhibited the highest resistance on aver- age to all tested drugs. The overall resistance rates to the various antibiotics were in descending order: ciprofloxacin (15.8%), gentamicin (11.7%), cefepime (10.7%), amikacin (10.5%), isepamicin (8.9%) and meropenem (6.0%). Overall, no significant variation in resistance rates was observed between hospitals except for *P. aeruginosa.* Among non-inducible *Enterobacteriaceae*, the resistance rate was low for all antibiotics except ciprofloxacin (7%). The highest rate of ciprofloxacin non-susceptible strains in this group of organisms was reported among *E. coli* (9%).

A high percentage (24%) of the inducible *Enterobacteriaceae* was found to be resistant to ciprofloxacin. This high resistance rate to ciprofloxacin mainly reflects the lack of susceptibility of *E. aerogenes* isolates to this agent (72% non-susceptible strains). Meropenem and cefepime on the other hand displayed excellent activity against this group of organisms (3% and 2% non-susceptible strains, respectively). Among the aminoglycosides, isepamicin (2% resistance) and gentamicin (3% resistance) showed the best activity while amikacin was found to be slightly less active (7% non-susceptible strains). Of note was the lower activity of amikacin (12% non-susceptible strains) in comparison to gentamicin and isepamicin (6% and 2% resistance rates) against *E. aerogenes* isolates.

P. aeruginosa was by far the most frequent species among the non-fermenters. It represented the most fre- quent organism together with *E. coli*, accounting on its own for almost one quarter of the total number of strains. Overall, *P. aeruginosa* isolates displayed high rates of resistance to all tested drugs (24 to 35%) with the exception of meropenem (14% non-susceptible strains). Among the aminoglycosides, amikacin had the highest activity on this species. The highest mean rate of resist- ance in *P. aeruginosa* was observed with cefepime (35%), but it varied appreciably between centres (from 6% up to 57%).

The cumulative MIC distribution of the six antibiotics against the three major groups of organisms (non- inducible *Enterobacteriaceae*, inducible *Enterobacteriaceae* and *Pseudomonas aeruginosa*). Among non-inducible

Enterobacteriaceae, ciprofloxacin had the highest intrinsic activity (MIC50 of 0.016 µg/ml) followed by meropenem (MIC50 of 0.03 µg/ml) and cefepime (MIC_{50} of 0.06 µg/ml). Gentamicin had a MIC 50 of 0.5 µg/ml while isepamicin and amikacin were slightly less active (MIC_{50} of 2 µg/ ml and 4 µg/ml, respectively). Against the inducible *Enterobacteriaceae*, the three aminoglycosides showed a roughly parallel curve, gentamicin being about one dilution (twofold) more active than isepamicin and two dilutions (four fold) more active than amikacin. Ciprofloxacin exhibited a much flatter curve, not reaching the 90% activity threshold within the tested concentrations. Meropenem displayed the highest intrinsic activity (MIC50 of 0.06 µg/ml and MIC90 of 0.12 µg/ml). For *P. aeruginosa* the pattern of activity is roughly similar to the other groups of organisms but with a shift of all curves to the right, reflecting higher MIC values for all antibiotics. The distribution curves for amikacin and isepamicin are parallel and almost identical while gentamicin proved substantially less active. On the whole, amikacin and isepamicin had very similar activity. Identical categorization results (percent- age of susceptibility or resistance at their respective breakpoint MIC value) were observed between amikacin and isepamicin for more than 95% of all Gram-negative isolates Table 2.

Discordant results were observed be- tween both antibiotics in only 4.2% of all isolates. In most instances these differences resulted in minor cat- egorization differences (susceptible vs intermediate; or intermediate vs resistant). Major discordances in categorization (susceptible to isepamicin and resistant to amikacin) occurred in only 3% of all tested isolates and were exclusively reported among *E. aerogenes* isolates Table 2. By contrast, most minor discordances (amikacin-susceptible or -intermediate vs. isepamicin- interrmediate or -resistant) did occur in *P. aeruginosa* strains.

Discussion

Overall, the large predominance of isolates originating from respiratory specimens does essentially reflect the propensity of intensive care physicians to obtain samples from the respiratory tract in order to guide the anti- biotic therapy in case of lower respiratory tract infection [10]. A similar finding was already observed in an- other recent survey also carried out in a population of patients hospitalized in ICUs [11]. The predominance of *E. coli* and *P. aeruginosa* among the Gram-negative isolates recovered from clinical specimens is also in line with the observations made in other surveys dealing with ICU patients [11-15]. Isolates belonging to the genus *Enterobacter* ranked as the third most frequent group of organisms. The high prevalence of *E.aerogenes* isolates found in this study has already been noticed in several recent single center reports as well as in other metacentric surveys carried out in India .Overall, all six antimicrobial agents tested remained very active against most Gram-negative bacterial spe- cies, with resistance rates averaging around 10% for all agents, except for ciprofloxacin (15.8% resistance rates) and meropenem (6.0% resistance rates), as shown in Table 1, 3, 5.

As a group, the coliforms and the other non-inducible *Enterobacteriaceae* (*Klebsiella* spp. and *Proteus* spp.) were the most prevalent organisms (45%). These organisms proved highly susceptible to all antibacterial drugs tested except to ciprofloxacin for which a non- susceptibility rate of 7% was reported. Noteworthy, all three aminoglycosides proved highly active against the different species in this group of organisms. On the other hand, species belonging to the inducible *Enterobacte- riaceae* (*Citrobacter* spp., *Enterobacter* spp., *Serratia* spp., *Morganella* spp., *Providencia* spp.) appeared on the whole more resistant than the non-inducible species Table 1,3,4,5. *E. aerogenes* in particular displayed a high rate of resistance to ciprofloxacin (72%) and it was also more resistant than the other *Enterobacteriaceae* species to the five remaining agents. Overall, isepamicin appeared as the most active drug against *E. aerogenes* (2% non-susceptible). Of particular interest was its superior activity in comparison to the other aminoglycosides: gentamicin (6% non-susceptible) and amikacin (12% non-susceptible). Compared to amikacin, the MICs of isepamicin (and also those of gentamicin) were two- to four-fold lower against *E. aerogenes* isolates. The higher rate of resistance to amikacin in particular can most probably be attributed to the presence of a plasmid born AAC (6')-I aminoglycoside inactivating enzyme which is commonly found in *E. aerogenes* (5), although this was not specifically tested in the present study.

Among the non-fermenters, *P. aeruginosa* was not only the most frequent organism but it also appeared as the species being the most frequently resistant to different antibiotics. Meropenem retained the best activity (14% non-susceptible) while gentamicin (34% non-susceptible) and cefepime (35% non-susceptible) were the least active compounds. Worth mentioning were the large differences in the rates of resistance that were observed between hospitals for *P. aeruginosa*. For instance, the rate of resistance varied between centers from 6% to 57% for cefepime and from 0 to 52% for ciprofloxacin. Among the aminoglycosides, amikacin and isepamicin proved equally active (MIC_{90} of 64 µg /ml for both agents) but minor differences in susceptibility categorization to both agents (susceptible vs. intermediate, or intermediate vs. resistant) were observed for about 6% of the *P. aeruginosa* isolates Table 2. These differences do essentially reflect the higher rate of intermediate susceptibility for isepamicin (15% vs. 9% for amikacin) while the rate of resistance appears similar for both agents (15% resistance each).

Membrane permeability mutations can also account for resistance to this class of compounds. This mechanism occurs essentially in non-fermenters (e.g. *P. aeruginosa*). In contrast to enzyme modifications, permeability mutations penetration affects all aminoglycosides almost equally and is associated with a moderate level of resistance (MIC of 8-64 µg/ml).

Among Gram-negative bacteria, amikacin and isepamicin have superior stability to enzymatic inacti- vation as compared to gentamicin, tobramycin and netilmicin (1-4, 20). Indeed, the latter antibiotics are partially or completely inactivated by ANT (2"), AAC (3) - II, AAC(2') and AAC (6')-II enzymes while these have no effect on amikacin and isepamicin. Despite their superior stability to enzyme inactivation, amikacin and isepamicin can both be degraded by APH (3')-VI and ANT (4')-II enzymes which occur only very exceptionnally in *Acinetobacter* spp. and in *P. aeruginosa*. On the other hand, isepamicin presents a distinct advantage over amikacin (in terms of stability) against organisms producing AAC (6')-I (e.g. several *Enterobacteriaceae*, including *Klebsiella* spp. and several inducible species such as *Citrobacter* spp., *Enterobacter*

spp., and *S. marcescens*). Actually, AAC(6')-I alone or associated with other inactivating enzymes (AAC(3)-II or ANT (2')) accounts as the most predominant resistance mechanism in Gram- negatives in several countries including Belgium (2-5). Impermeability resistance mechanisms alone or in association with enzyme inactivation (e.g. AAC (6')-I, AAC (6')-II, ANT (2')) are mainly found among non- fermenters. Like for other classes of antibiotics, geo- graphic variations in the prevalence of resistance to aminoglycosides may be encountered. These differences may depend on the nature of the genetic determinants encoding for resistance. The exchanges of plasmids and of transposable elements (i.e. transposons) can explain the dissemination of resistance genes trough several bacterial species and genera. The pressure exerted by the usage of antibiotics (selection) and the lack of hygiene (dissemination by horizontal transmission) are also likely to influence greatly the epidemiology of antimicrobial resistance. On the whole however, the resistance rates of Gram- negative organisms to the aminoglycosides have remained rather low despite their extensive usage in hospitals for more than two decades. Indeed, all three aminoglycosides tested compared favorably to ciprofloxacin and cefepime (a fourth generation cephalosporin) and were found to be almost as active as meropenem, a new carbapenem which resists to hydrolysis by most of the chromosomal and plasmatic ß-lactamases. Isepamicin proved on the whole the most active of the three aminoglycosides against *Enterobacteriaceae* and it was found as active as amikacin against *P. aeruginosa* and other non-fermenters. Similar findings were reported in another recent Belgian survey (5) in which the activity of five aminoglycosides was in- estimated against more than 1100 Gram-negative clinical blood isolates collected in 13 university and university-affiliated hospitals.

Table 1: Overall percentage of susceptible organisms

NCCLS Breakpoint (µg/ml)	**Cefepime** 8	**Meropenem** 4	**Ciprofloxacin** 1	**Gentamicin** 4	**Amikacin** 16	**Isepamicin** 16*
Non-inducible *Enterobacteriaceae* (490)	99	100	93	96	96	99
E. coli (255)	98	100	91	97	98	100
Klebsiella spp. (134)	99	100	98	94	94	98
P. mirabilis (75)	100	100	96	95	100	100
Inducible *Enterobacteriaceae* (298)	97	98	76	97	93	98
E. aerogenes (82)	95	96	28	94	88	98
E. cloacae (69)	100	100	97	98	97	99
Serratia spp. (54)	94	96	85	98	89	93
M.morganii (51)	100	100	100	98	98	98
Citrobacter spp. (27)	100	100	96	96	93	100
Non fermenters (299)	65	79	73	67	74	71
P. aeruginosa (223)	65	86	76	66	76	70
S. maltophilia (31)	42	13	35	52	42	52
Acinetobacter spp. (25)	96	100	96	100	96	100
All species (1087)	89.3	94.0	84.2	88.3	89.5	91.1

Table 2: Comparative activity of isepamicin and amikacin against selected organisms

% OF Both Amikacin and Isepamicin		**R to both Amk and Ise**	**S to Ise* R to Amk**	**R/I to Ise S to Amk****
All isolates (1086)	88%	8%	3%	1%
E. aerogenes (82)	87%	1%	12%	0%
P. aeruginosa (222)	69%	24%	<1%	6***%

Ise* = Isepamicin;
Amk** = Amikacin
S: Susceptible.
I: Intermediate.
R; Resistant.

Table 3: Percentage of Non-inducible enterobacteriaceae

NCCLS Breakpoint (µg/ml)	**Cefepime 8**	**Meropenem 4**	**Ciprofloxacin** 1	**Gentamicin** 4	**Amikacin** 16	**Isepamicin** 16*
Non-inducible *Enterobacteriaceae* (490)	99	100	93	96	96	99
E. coli (255)	98	100	91	97	98	100
Klebsiella spp. (134)	99	100	98	94	94	98
P. mirabilis (75)	100	100	96	95	100	100

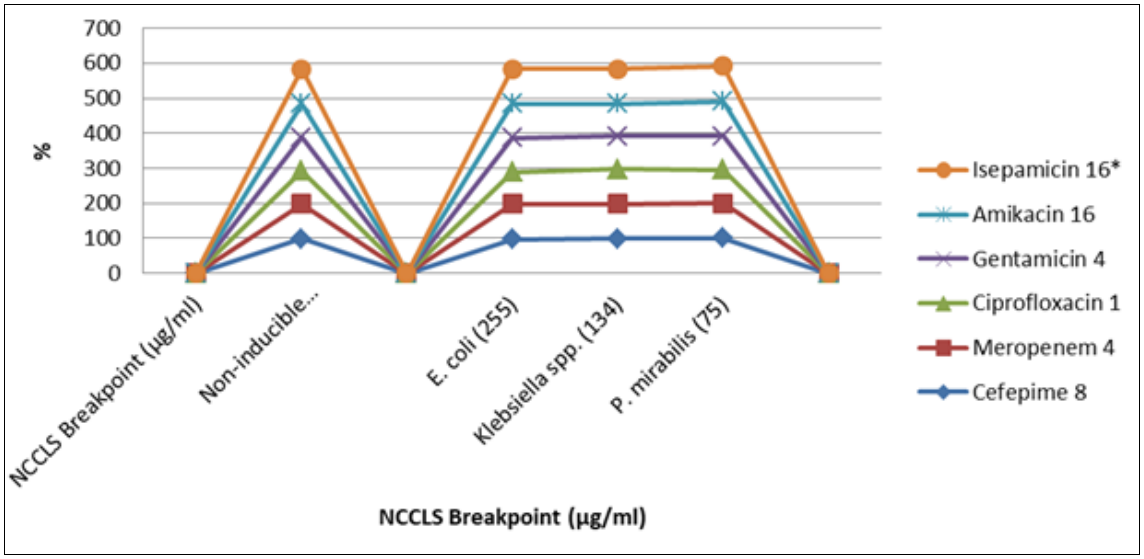

Fig 1: Non-Inducible Enterobacteriaceae

Table 4: Percentage of Enterobacteriaceae

NCCLS Breakpoint (µg/ml)	Cefepime 8	Meropenem 4	Ciprofloxacin 1	Gentamicin 4	Amikacin 16	Isepamicin 16*
Enterobacteriaceae (298)	97	98	76	97	93	98
E. aerogenes (82)	95	96	28	94	88	98
E. cloacae (69)	100	100	97	98	97	99
Serratia spp. (54)	94	96	85	98	89	93
M.morganii (51)	100	100	100	98	98	98
Citrobacter spp. (27)	100	100	96	96	93	100

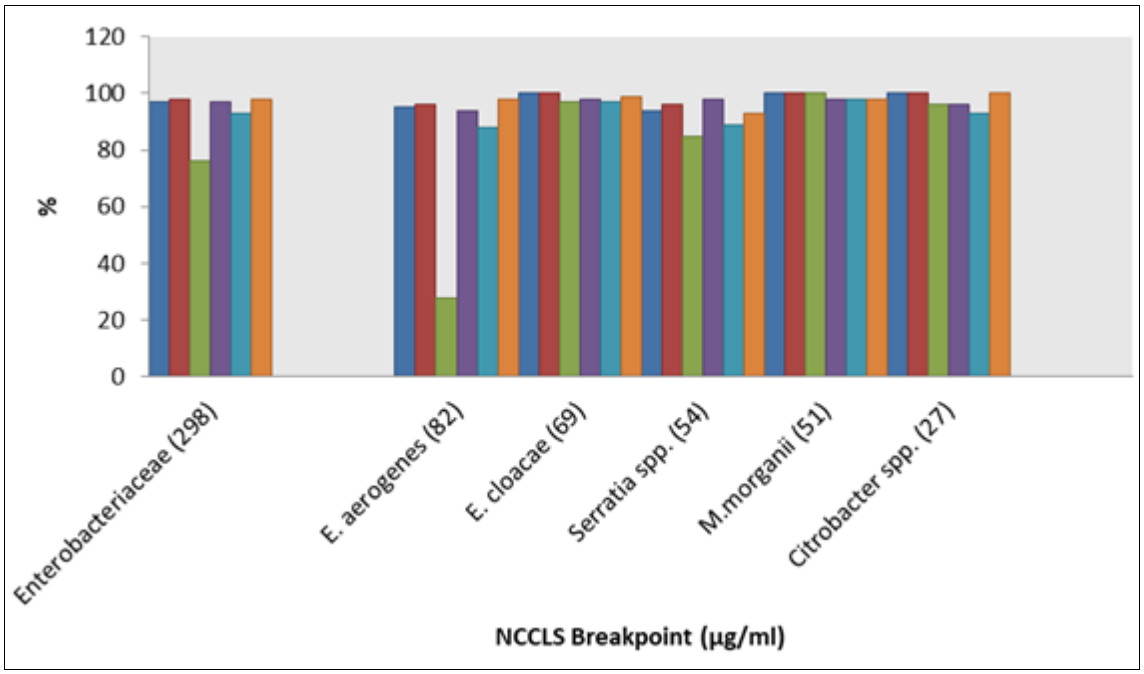

Fig 2: Enterobacteriaceae

Table 5: Percentage of Non Fermenters

NCCLS Breakpoint (µg/ml)	Cefepime 8	Meropenem 4	Ciprofloxacin 1	Gentamicin 4	Amikacin 16	Isepamicin 16*
Non fermenters (299)	65	79	73	67	74	71
P. aeruginosa (223)	65	86	76	66	76	70
S. maltophilia (31)	42	13	35	52	42	52
Acinetobacter spp. (25)	96	100	96	100	96	100

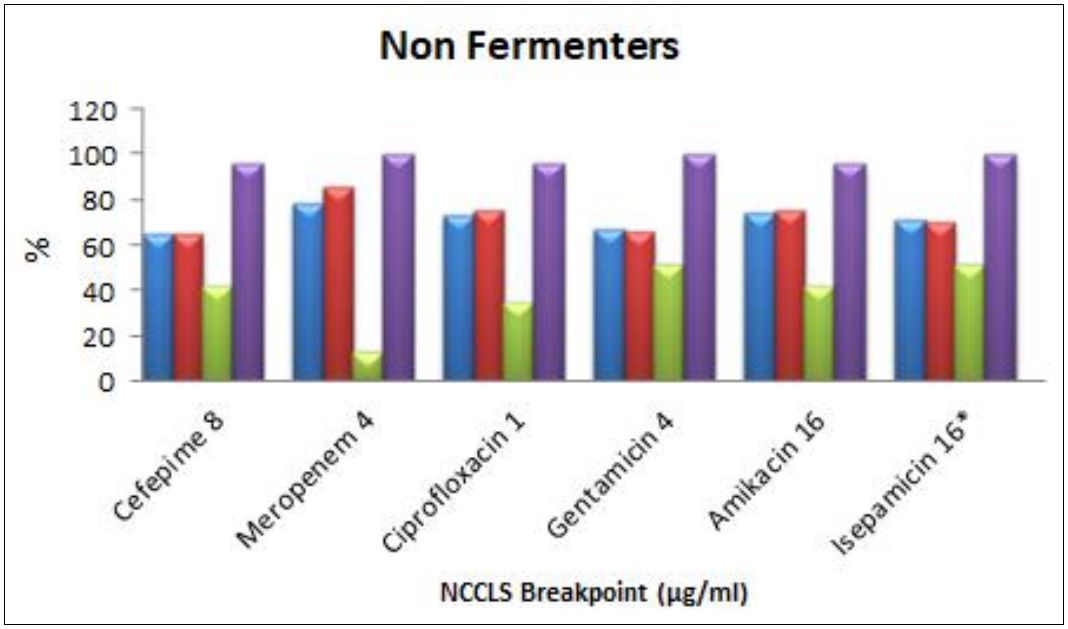

Fig 3: Non Fermenters

Conclusion

Our study confirms the preserved activity of the different antibiotics tested against most Gram-negative organisms (except *P. aeruginosa*) isolated from patients hospitalized in ICUs. In particular, the activity of the three aminoglycosides appeared well-preserved with isepamicin being usually the most active of the three aminoglycosides against *Enterobacteriaceae* while both isepamicin and amikacin proved equally active against *P. aeruginosa.* Compared to amikacin, MIC values for isepamicin were usually two- to fourfold lower for most inducible *Enterobacteriaceae* species as well as for *Klebsiella* spp., while they were identical for *P. aeruginosa* and other non-fermenters. Complete cross-susceptibility or cross-resistance between amikacin and isepamicin was observed in more than 95% of all tested isolates. On the other hand, 12% of all *E. aerogenes* isolates appeared resistant to amikacin and susceptible to isepamicin, while 6% of the *P. aeruginosa* were found to be resistant (or intermediate) to isepamicin and inter- mediate (or susceptible) to amikacin. No significant differences in pathogen distribution nor in resistance rates were observed between hospitals except for *P. aeruginosa*. Les concentrations minimalist inhibit ices notate determines par la method du E-test pour claque antibiotique vis-à-vis de 1087 isolates non dupliqués debacles à Gram-negative..

Conflict of Interest

Not available

Financial Support

Not available

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