Trends of 9,416 multidrug-resistant Gram-negative bacteria

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Summary

Objective: a resistance of hospital-acquired bacteria to multiple antibiotics is a major concern worldwide. The objective of this study was to investigate multidrug-resistant (MDR) bacteria, clinical specimens, origin of specimen and trends, and correlate these with bacterial sensitivity and consumption of antimicrobials.

Methods: 9,416 bacteria of nosocomial origin were evaluated in a tertiary hospital, from 1999 to 2008. MDR was defined for Gram-negative bacteria (GNB) as resistance to two or more classes/groups of antibiotics.

Results: GNB MDR increased by 3.7 times over the study period (p<0.001). *Acinetobacter baumannii* was the most prevalent (36.2%). Over the study period, there were significant 4.8-fold and 14.6-fold increases for *A. baumannii* and *K. pneumoniae* (p<0.001), respectively. Sixty-seven percent of isolates of MDR GNB were isolated in intensive care units. The resistance of *A. baumannii* to carbapenems increased from 7.4 to 57.5% during the study period and concomitant with an increased consumption.

Conclusion: that decade showed prevalence of GNB and a gradual increase in MDR GNB. There was an increase in carbapenem resistance of 50.1% during the study.

Keywords: Gram-negative bacteria, drug resistance, microbial, hospitals, university.

Introduction

Currently, infections by multidrug-resistant (MDR) bacteria are considered a public health problem by the World Health Organization (WHO).[1] Control of the emergence of multidrug-resistant pathogens is a challenge for healthcare institutions and professionals.[2] Among these microorganisms, Gram-negative *bacilli* (GNB), such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, and *Enterobacteriaceae*, such as *Klebsiella pneumoniae,* which produce extended spectrum beta-lactamase[3] are important, because there are very few treatment options.[1] Several studies have demonstrated the impact of nosocomial infections on morbidity and mortality of patients, as well as on length of hospital stay and costs.[4,5]

In recent decades, rapid increases in MDR strains have been documented in several countries in Europe[6] and in the United States of America.[7] Mera et al. studied 55,330 strains of *A. baumannii* showing an increase in resistance to carbapenems from 22%, in 2002, to 52%, in 2008.[8] Recently, another U.S. study using data from the Centers for Disease Control and Prevention evaluated the epidemiology of MDR Gram-negative *bacilli* from 2000 to 2008. The authors showed that during the period there were increases in the frequencies of *A. baumannii* (from 64 to 74%), *K. pneumoniae* and *E. coli* (from 7 to 13%), and *P. aeruginosa* (from 17 to 22%) in intensive care units (ICUs).[9]

Data from the Sentry antimicrobial surveillance program documented increases in MDR in Latin America,[10] as have other microbiological studies.[11-14]

Few studies have evaluated hospitals in respect to the epidemiology and trends of overall resistance of MDR GNB.[15] Steady increases of different types of phenomena of multidrug resistance are observed in day-to-day practice in our hospital due to the growing complexity of procedures. According to the literature, there are geographical differences, different rates of sensitivity and specific mechanisms of resistance characteristic to each region and each institution; therefore, it is essential to know the local epidemiology.

Our objectives were to describe and to correlate the distribution of MDR GNB bacteria with their source; to evaluate the trends of species and the bacterial sensitivity of the most frequent isolates; to determine the most common species, specimens and sources, and to correlate these with bacterial sensitivity and consumption of antimicrobials in a tertiary hospital.

METHODS

This was a descriptive, retrospective study, covering the period from January 1st, 1999 to December 31, 2008. It was carried out in a tertiary teaching hospital linked to a medical school, where 80% of patients are from the National Health Service (NHS) and 20% are private. The hospital offers 40 medical specialties, with 3,500 admissions per month. It has 714 beds, 574 of which are NHS (Wards: 188 clinical, 227 surgical, 72 obstetric, 75 pediatric and 14 day hospital beds). There are 138 beds in ICUs: 43 in pediatric and/or neonatal, 43 in adult medical and surgical I, 18 in adult medical and surgical II, 20 adult medical and surgical cardiology, and 14 in an intermediate unit. High complexity procedures are made, including organ transplantation (bone marrow, liver, kidney and heart) and infant heart surgery. The service of the central laboratory performs all microbiology tests at the hospital (9,500 exams/month).

The microorganisms isolated between 1999 and 2008 were identified and the frequency of each was calculated using the electronic database of the Microbiology Laboratory. Only clinical samples isolated from the hospital wards and ICUs were included in this study; samples from outpatients and emergency departments were excluded. To avoid the duplication of results, only the first sample from each source in the month was considered with the others being excluded, except for samples from catheters. MDR bacteria were identified. After calculating the frequencies, we chose to study the 12 most common MDR GNB. Of these, only five MDR GNB species were chosen as relevant to the study and further analysis.

All GNB that were resistant to two or more distinct classes/groups of antibiotics were defined as MDR. The classes of beta-lactams were assessed as separate groups. The bacteria should exhibit resistance to all antibiotics within a class or group. All the antibiotics of the class/group that were tested are routinely tested in the laboratory and utilized in the clinical practice, according to the criteria of the National Committee for Clinical and Laboratory Standards/Clinical and Laboratory Standards Institute (NCCLS/CLSI); the results of the antibiogram should show intermediate sensitivity or resistance.

The laboratory routinely uses the Kirby-Bauer disk diffusion method (CLSI), and the E-test was used for Polymyxin B.

The following classes/groups were considered: aminoglycosides (AG – amikacin and gentamicin), quinolones (ciprofloxacin), beta-lactam (BL – cephalosporins), beta-lactamase inhibitors (IBL), carbapenems (CB) and polymyxin B. Except for urinary tract specimens, for which all classes/groups of antibiotics were evaluated, the antibiogram used specific antibiotics for the following agents:

- *Acinetobacter baumannii*: BL – cephalosporins (ceftazidime, cefepime and ceftriaxone), IBL (ampicillin/sulbactam), CB (imipenem and meropenem), quinolones, polymyxin B;
- *Pseudomonas aeruginosa*: BL – cephalosporins (ceftazidime and cefepime), IBL (piperacillin/tazobactam), CB (imipenem and meropenem), quinolones and polymyxin B;
- other GNB: AG, BL – cephalosporins (ceftazidime, cefepime and ceftriaxone), IBL (piperacillin/tazobactam), CB (imipenem), quinolones and polymyxin B.

The following variables were evaluated: microbial species, clinical specimens, the origin of the isolates (ICU and non-ICU) and antimicrobial susceptibility. The consumption of antimicrobials was calculated using data from the pharmacy database and the defined daily dose (DDD) was used[16] and divided by the total patient days for each unit by 1000.

Data were entered on a spreadsheet of the Excel Windows Office application, version 2007 (Microsoft), and percentages were calculated. Data were analyzed using the chi-square test. Significance was defined for p-values ≤0.05. The project was approved by the Research Ethics Committee of the institution.

RESULTS

During the study period, 53,316 nosocomial bacteria were isolated. Of these, 35,250 (66.1%) were GNB and 18,066 (33.9%) were Gram-positive *cocci*. The 12 most common GNB in order of frequency were *Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae, Acinetobacter baumannii, Citrobacter freundii, Proteus mirabilis, Enterobacter aerogenes, Enterobacter cloacae, Morganella morganii, Citrobacter diversus, Serratia marcescens*, and *Providencia stuartii*, totaling 29,824 (84.6%) of the isolates selected to evaluate MDR; the remainder had no microbiological or epidemiological interest. A total of 10,732 (36%) were characterized as MDR GNB; the top five agents represented 9,416

(87.7%) of these and were, thus, chosen for analysis. The distribution of these was as follows (Table 1): *Acinetobacter baumannii*: 3,410 (36.2%); *Pseudomonas aeruginosa*: 2,700 (28.7%); *Klebsiella pneumoniae*: 2,173 (23.1%); *Escherichia coli*: 577 (6.1%) and *Citrobacter freundii*: 556 (5.9%).

TABLE 1 Distribution of MDR Gram-negative bacteria comparing the year of start and end of the study.

Agents	n	(%)	1999	2008	Increase	p-value
A. baumannii	3,410	36.2	111	537	4.8	< 0.001
P. aeruginosa	2,700	28.7	142	211	1.5	N/S
K. pneumoniae	2,173	23.1	27	394	14.6	<0.001
E. coli	577	6.1	32	39	1.2	N/S
C. freundii	556	5.9	20	40	2.0	N/S
Total MDR BGN	9,416	100	332	1221	3.7	< 0.001

When all the specimens of the study were evaluated, the frequencies were as follows: urinary tract 30%, respiratory tract 25.4%, blood and catheters 23.8%, non-respiratory tract secretions 17.4% and others 3.4%. The specimens were analyzed according to the MDR found: MDR *A. baumannii* were most commonly isolated in respiratory tract and blood/catheter specimens (50.7 and 47.8%, respectively) and *K. pneumoniae*, *E. coli* and *C. freundii* were most commonly isolated in urinary tract specimens. A homogeneous distribution was observed in relation to *P. aeruginosa*.

In 1999, at the beginning of the study, there were 332 (3.5%) MDR GNB, while by the end of the study, in 2008, this number had increased to 1,221 (13%) isolates (p<0.001, Table 1). The evolution of the different agents over the study period was as follows (Table 1): *A. baumannii* 111/537

(p<0.001), *K. pneumoniae* 27/394 (p< 0.001), *P. aeruginosa* 142/211 (p>0.005), *E. coli* 32/39 (p>0.005) and *C. freundii* 20/40 (p>0.005). Significant increases were observed for *A. baumannii* and *K. pneumoniae*; however, the MDR of *P. aeruginosa* increased until 2006 and, then, decreased over the last two years. The number of isolates per year for *E. coli* and *C. freundii* remained stable during the period. A progressive but significant increase (p=0.002) of *A. baumannii* was observed over the period in respiratory tract and blood and catheter specimens; for the other types of specimens the rate for this bacteria remained constant over the period.

An evaluation of the origin of MDR GNB (Table 2) shows that 6,314 (67.0%) isolates originated in ICUs compared to 3,102 (33%) outside of the ICU (p<0.001). Three units (ICU I 48.5%, ICU II 19.3% and the intermediate unit 15.3%) accounted for 83.1% of the isolates from ICUs. When the evolution of agents found in the ICU were assessed, there were progressive increases in *A. baumannii* and *P. aeruginosa* (p<0.001 for both), while the increase of *C. freundii* outside the ICU was significant (p=0.002).

On analyzing the percentage of *A. baumannii* isolates resistant to carbapenems throughout the hospital, there was a progressive increase in resistance from 7.4% at the beginning to 57.5% by the end of the study; in ICU I the resistance of *A. baumannii* increased from 9.3 to 62.5% and, in ICU II, the increase was from 0 to 55.7%. There was an increase in resistance from 1999 to 2008 in ICUs I (9.3 to 62.5%) and II (0 to 55.7%). Concomitantly, there was a progressive increase in the consumption of carbapenems; the initial consumption of 88 DDD in ICU I increased to 248 DDD by the end of the study period and for ICU II, the consumption increased from 23.4 DDD

TABLE 2 Distribution of MDR Gram-negative bacteria in relation to the year and the origin of isolation.

Year	*A. baumannii*		*P. aeruginosa*		*K. pneumoniae*		*E. coli*		*C. freundii*		
	n	ICU	n	ICU	n	ICU	n	ICU	n	Non-ICU	Total
1999	111	78	142	85	27	15	32	11	20	10	332
2000	228	157	269	178	59	32	65	23	31	26	652
2001	242	168	238	160	90	57	68	27	25	15	663
2002	261	180	246	157	135	78	81	40	45	27	768
2003	222	161	242	155	198	115	66	28	70	55	798
2004	338	254	283	177	365	215	65	32	123	71	1,174
2005	538	451	382	290	304	190	63	36	77	44	1,364
2006	507	408	385	268	248	166	48	24	63	28	1,251
2007	426	354	302	228	353	230	50	16	62	37	1,193
2008	537	441	211	140	394	256	39	16	40	26	1,221
p-value	< 0.001		< 0.001		NS		NS		0.002		

in 2001 (the first measurement for this unit) to 221 DDD, by 2008.

On analyzing *A. baumannii* in terms of resistance to aminoglycosides, there was a 4.3-fold increase in resistance from 3.5%, in 1999, to 14.8%, in 2008. An analysis of the resistance to aminoglycosides of all five agents showed a 3-fold increase in resistance from 3.4 to 10.4%.

In relation to the resistance of *P. aeruginosa* to carbapenems in ICU I and II, there was a gradual increase (from 23.4 to 64.6%) during the study. On analyzing the resistance of *K. pneumoniae* to cephalosporins in ICU I and II, there was a gradual increase from 36.4 to 96.9%. Additionally, there was a progressive increase in the consumption of carbapenems and cephalosporins in 2001 (73.0 and 417.5 DDD, respectively) until the end of the study (221.8 and 494.9 DDD, respectively) in ICU I and II.

An analysis of the percentage of classes/groups to which *P. aeruginosa* was resistant showed that there was an increase in resistance of 14 to 57.1%, for 5 classes/groups, between 1999 and 2002, and a decrease in resistance of 34 to 18.4% for 2 classes/groups in the same period. From 2003 to 2008, there was an inverse effect with a decrease in resistance from 21.9 to 0% for 5 classes/groups and an increase in resistance for 2 and 3 classes/groups from 24 to 36.4% and from 29.1% to 41.4%, respectively.

DISCUSSION

This study evaluated bacterial isolates and correlated them with the clinical specimens, origin, antimicrobial profile and use of antibiotics. Selection criteria according to MDR groups of antimicrobials used in the clinical practice were employed. The class of beta-lactams was evaluated as separate groups. Resistance to two or more classes/groups was used to define MDR. This criterion is arbitrarily used in the literature and change over time.[17,18] We used these definitions because we studied a long period and only in the last years there were an increase of resistance. It is very difficult to create specific criteria for each bacterial species, so we chose to use this criterion for all GNB.

Of the 12 selected species (29,824), 36.0% were MDR GNB; and of these the five most common agents represented 9,416 (87.7%) of the total and were chosen for epidemiological evaluation. The three most common MDR GNB (*A. baumannii*, *P. aeruginosa* and *K. pneumoniae*) accounted for 88% of the total (Table 1). Recent data from the CDC/NNISS on evaluating the epidemiology of MDR GNB in the United States found that these species are the most prevalent.[9] However, this study only evaluated clinical and surgical ICU patients and isolates from three types of in-fection-related devices (blood stream/central venous catheters, urinary tract/bladder catheter and respiratory/mechanical ventilation equipment). In the current study, 67% of the isolates were from ICUs (p<0.001), while 79.1% were from similar specimen types, as the CDC/NNISS report; so the results of these two studies are similar.

There were no great differences in the frequencies of the different types of clinical specimens in this study. Specimens from the urinary tract were the most common (30%), followed by respiratory tract (25.3%) and blood/catheter specimens (23.8%). In a similar study evaluating the epidemiology of MDR GNB in a tertiary hospital in Germany, the most common specimens were from the lower respiratory tract (21.3%), urinary tract (18.1%) and blood/catheters (6.8%).[15] The following distributions were found when comparing all specimens isolated in wards and in ICUs, respectively: respiratory tract 4.5 and 35.6%; urinary tract 44.8 and 22.7% and blood and catheters 18.7 and 26.3%.

There was a significant difference in respect to respiratory tract specimens from these two sources, probably due to the more frequent collection of tracheal aspirate specimens in the ICU. Additionally, there were almost twice as many MDR urinary tract specimens from the wards than from the ICUs. The difference was smaller in respect to blood and catheter specimens. An analysis of the three most common types of specimens according to species, *A. baumannii* (50.7%) and *P. aeruginosa* (31.6%) were more common in respiratory tract specimens and the other species were more common in the urinary tract.

Regarding the trends of all the MDR GNB, there was a gradual increase each year; during the decade the total increase was from 332 to 1,221, an increase of 3.7-fold (Table 1 and 2). *A. baumannii* and *K. pneumoniae* had statistically significant increases of 4.8 and 14.6 times, respectively, during the study (Table 1). Several studies have documented increases in MDR *A. baumannii*[8,19] and *K. pneumoniae*[9] over the last decade. *P. aeruginosa* showed a non-significant increase of 1.5 times. Kallen[9] reported a decrease in MDR *P. aeruginosa* bloodstream and urinary tract infections from 2000 to 2008; however, the overall frequency of this GNB remained stable, probably due to an increased frequency in respiratory specimens. It is difficult to compare our results with most of other published studies, since generally one species is evaluated with regard to a specific antimicrobial or only specimens from the ICU are analyzed from national data, such as from the NNISS.

A significant majority of MDR GNB (83.1%) in this study were isolated in three adult clinical and surgical ICUs (ICU I: 48.5%; ICU II: 19.3% and the intermediate unit:

15.3%). Table 2 shows the progressive and significant increases of *A. baumannii* and *P. aeruginosa* in the ICUs, which was associated to a significant increase in MDR GNB in respiratory tract and blood/catheter specimens, mainly from 2005/2004 on. This suggests that the increased frequency of respiratory tract specimens impacted on the occurrence of bacteremia. When *P. aeruginosa* was evaluated over time, there were increases in respiratory and urinary tract specimens until 2005 and 2004, respectively. Thus, there was a significant correlation between respiratory tract and blood/catheter specimens (p=0.002). There were significantly more urinary tract *C. freundii* specimens outside ICUs rather than in ICUs (Table 2).

On evaluating the resistance of *A. baumannii* to carbapenems, there was a higher increase from 2004 on (16.6%) in the hospital as a whole and in ICUs I (22.4%) and II (19.6%). There were great fluctuations in the consumption of carbapenems in ICU I until 2005 (from 88 to 108.2); from 2006 on, there was a concomitant increase in resistance of GNB and consumption of carbapenems. In ICU II, resistance increased later as this unit was created in 1999; however, from 2004 on there was a concomitant increase in MDR GNB and in the consumption of carbapenems. It is interesting to note that non-original carbapenems were introduced, as institutional policy of purchase of antibiotics changed in 2004, which may partly justify the increase in consumption.

A study evaluating the resistance of *A. baumannii* to carbapenems from 2002 to 2008 in the United States of America found an increase from 24%, in 2004, to 52%, in 2008. Despite differences in terms of population, there were similarities in the evolution of resistance.[8]

In regards to aminoglycosides, although there was a higher than 3-fold increase in resistance in recent years, levels of resistance are considered low compared to other antibiotics; this class of antibiotics may be a therapeutic alternative for MDR. On evaluating the resistance of *P. aeruginosa* to carbapenems, although there was a drop in the number of MDR in 2007 and 2008, a fluctuation in resistance of more than 50% was observed in recent years, as was the increase in the consumption of this antibiotic. Similar to the current study, Kallen et al. reported that there was no increase in MDR *P. aeruginosa* during the period of 2000 to 2008.[9]

There was a progressive increase from 36.4 to 96.9% of MDR *K. pneumoniae* in respect to cephalosporins during the decade. Moreover, a small fluctuation in the use of cephalosporins was observed with a total increase of 18.52% over the study period. When the consumptions of carbapenems/cephalosporins in 2004 for both ICU I and ICU II (70.3 and 578.1, respectively) were compared with the consumption of the CDC/NNISS, the 90th percentile was 62.9/200.6. We observed that the consumption of these antibiotics was lower in the American study. From 2006 on, consumption data were no longer published in the reports from the CDC/NHSN.[20]

In relation to resistance of *P. aeruginosa* to antibiotics, an inverse correlation was found between the increase and decrease in resistance for five and two classes/groups up to 2002 and, then, after 2003. These data are in accordance with the overall decrease detected over the last two years. This shows that, in addition to decreases in the frequency of MDR, there was an increase in sensitivity. We observed a very low resistance to 6 classes/groups (pan-resistant bacteria).

Limitations of the study include that the definition of MDR as resistance to two or more classes/groups of antibiotics is not universally used in the literature. A new study using other definitions for pan-resistant bacteria would probably be necessary to assess the last years. The specimens in this study do not exclusively represent isolates from nosocomial infections.

CONCLUSION

In this study, we conclude that during the decade in question there was a prevalence of GNB and a gradual increase in the MDR of GNB. *A. baumannii* was the most prevalent GNB and the MDR of *K. pneumoniae* increased the most during the study period. A decrease in MDR *P. aeruginosa* was detected over the last two years. Respiratory tract specimens were the most common, particularly in respect to *A. baumannii*. ICUs were the primary source of MDR GNB. We observed a significant loss of sensitivity of *A. baumannii*, mainly from 2004, concomitant with the increase in consumption of carbapenems. The resistance of GNB to cephalosporins increased dramatically during the decade. Measures to prevent and control the spread of organisms and rational use of antibiotics should be a priority to optimize hospital costs. Future studies at our institution are needed to evaluate the molecular microbiology of MDR GNB species and correlate them with clinical syndromes and mortality.

RESUMO

Evolução de 9.416 bactérias Gram-negativas multirresistentes.

Objetivo: a resistência bacteriana hospitalar a múltiplos antibióticos é uma grande preocupação mundial. O ob-

jetivo deste estudo foi conhecer os agentes multidroga-resistentes (MDR), materiais clínicos, origem e evolução, e correlaciona-los à sensibilidade bacteriana e ao consumo de antimicrobianos.

Método: foram avaliadas 9.416 bactérias de origem nosocomial, em um hospital terciário, durante o período de 1999 a 2008. Foram definidas como MDR as bactérias Gram-negativas (BGN) que apresentaram resistência a duas ou mais classes/grupos de antibióticos.

Resultados: as BGN MDR tiveram um aumento global de 3,7 vezes no final do período (p<0,001). O *Acinetobacter baumannii* foi o mais prevalente (36,2%). Durante o período do estudo, houve um aumento significativo de 4,8 e 14,6 para *A. baumannii* e *K. pneumoniae* (p<0,001), respectivamente. Sessenta e sete por cento das BGN MDR foram isoladas em unidade de terapia intensiva. A resistência do *A. baumannii* aos carbapenêmicos aumentou de 7,4 para 57,5% durante o período, concomitante ao aumento do consumo.

Conclusão: durante essa década, houve uma prevalência de BGN e um aumento gradual das BGN MDR. Houve um aumento da resistência aos carbapenêmicos de 50,1% durante o estudo.

Palavras-chave: bactérias Gram-negativas, resistência microbiana a medicamentos, hospitais universitários.

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