Resistance patterns among selective Gram-negative bacilli from an intensive care unit in Trinidad, West Indies

Fitzroy A. Orrett, *MD.*

ABSTRACT

Objectives: To determine the prevalence of antimicrobial resistance among gram-negative aerobic bacteria isolated from infected patients on the intensive care unit (ICU) and the outcome of infected patients.

Methods: Over a 5-year period (January 1998 to December 2002), all gram-negative aerobic bacteria (GNB) consecutively isolated from infected ICU patients at General Hospital, San Fernando, Trinidad and Tobago, West Indies. were tested for susceptibility to 10 commonly prescribed antimicrobial agents. Bacterial strains were identified according to standard microbiological procedures. The antimicrobial agents used and the amounts consumed by patients on the ICU were obtained from the hospital pharmacy records. Hospital discharges and deaths due to infectious complications were obtained from the medical records office and the ICU.

Results: During the study period, there were 1160 admissions to the ICU. From this, 530 (45.7%) were suspected episodes of nosocomial infection and 445 (84%) were culture positive for GNB. Sputum, urine and blood accounted for approximately 85% of isolates. *Pseudomonas aeruginosa* (*P. aeruginosa*), *Klebsiella pneumoniae (K. pneumoniae), Citrobacter spp* and *Enterobacter spp* were the predominant isolates from sputum, while from urine; it was *P. aeruginosa* and *K. pneumoniae.* The major isolate from bloodstream infection on the ICU was *Citrobacter spp.* Of the 10 antimicrobial agents, the least effective was ampicillin that showed 87.8% resistance, while the most effective against GNB were imipenem (94.2%), ciprofloxacin (93.9%) and piperacillin-tazobactam (88.5%). The most common isolate was *P. aeruginosa* which is sensitive to >82% of the antimicrobials. Antimicrobial consumption was 2282 grams and the most frequently prescribed drugs were ampicillin, cefuroxime and amoxicillin-clavulanic acid, with consumption of the beta-lactam antimicrobials being 87.3% of the total. There were 280 (24.1%) deaths on the ICU during the study period and 42.9% (120 of 280) were said to be due to, or associated with overall hospital-acquired infectious complications. Mortality associated with GNB infection was approximately 33%. All fatal cases were associated with pneumonia and bloodstream infections. The predominant organisms were *Citrobacter spp, Enterobacter spp, Acinetobacter spp* and *P. aeruginosa*, with *Citrobacter spp* associated with both pulmonary and bloodstream fatalities.

Conclusion: In general, the isolates were relatively antimicrobial susceptible. Imipenem, ciprofloxacin and piperacillin-tazobactam were found good empiric choices for treatment of most GNB infection in the ICU. The study showed that resistance among ICU pathogens depended on the site of infection and that increased drug consumption of any antimicrobial agent may lead to increase resistance to those drugs. The need for policies governing the prudent use of antimicrobial agents cannot be overemphasized. Many endeavors aimed at introducing an antibiotic policy have encountered repeated failure and attempts at rational prescribing through educational programs have met with limited success. Hope is seen however, in proper implementation of infection control procedures aimed specifically to curtail lateral transmission of resistant organisms.

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From the Department of Paraclinical Sciences, Faculty of Medical Sciences, Unit of Pathology and Microbiology, University of the West Indies, Trinidad and Tobago, *West Indies*.

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Address correspondence and reprint request to: Dr. Fitzroy A. Orrett, PO Box 371, Curepe Post Office, Curepe, Trinidad and Tobago, *West Indies*. Tel. +868 6821364. Fax. +868 6633797. E-mail: drfao4301@yahoo.com

Gram-negative bacteria are among the most common infectious agents isolated from patients admitted to an intensive care unit (ICU).[1-4] The dissemination of antimicrobial resistant organisms within the hospital has been related to the widespread use of antimicrobial agents, particularly within the ICU setting.[2] Several factors predispose to multi-resistance within the ICU. These include multiple and repeated invasive supportive measures, frequent administration of broad-spectrum antimicrobials and prolonged hospitalization.[2-4] Infections affecting patients in the ICU are usually severe and mostly gram-negative bacteria have been isolated. Antibiotics must therefore be prescribed before culture results become available and a rational choice of antibiotics may not be possible without knowledge of the infectious agents and their likely susceptibilities.

Most gram-negative bacteria harbor resistance plasmids that can spread to different strains and species.[5] Common hospital pathogens such as *Escherichia coli* (*E.coli)* and *Klebsiella pneumoniae* (*K. pneumoniae)* were first found in the mid-1980s to produce plasmid-mediated extended spectrum beta–lactamase (EBSL),[6] thus conferring resistance to most broad spectrum cephalosporins. Such plasmids have now been found in many hospitals throughout the world, and particularly in critical care facilities.[7,8] Resistance to the aminoglycosides, fluoroquinolones, carbapenems and monobactams has developed among *Pseudomonas aeruginosa*, *Citrobacter spp*, *Acinetobacter spp* and *K. pneumoniae*.[9,10] The monitoring of antimicrobial resistance is of paramount importance in the ICU where infection rates and consumption of antimicrobials are significantly higher than other wards. Knowledge of resistance patterns in the ICU will help clinicians to select the most appropriate antibiotic empirically, and increase cost-effective treatment of infections. The purpose of this study was to determine the prevalence of antimicrobial resistance among ICU gram-negative aerobic bacterial isolates at the San Fernando General Hospital and the outcome of infected patients.

Methods. From January 1998 to December 31, 2002 Gram-negative bacterial isolates were recovered from patients admitted to the general ICU of the San Fernando General Hospital (SFGH), which caters for all surgical and medical patients. The ICU has 4 beds (only 3 operational during the study period) and the hospital is the only major government institution serving a population of approximately 410,000 people. Trinidad is the larger of the twin-island Republic, Trinidad and Tobago, located about 11km off the northern coast of Venezuela in South America. The population of the Republic is approximately 1.25 million people. All bacterial strains were identified according to standard microbiological procedures.[11] Only gram-negative bacteria consecutively isolated from infected patients were included in the study. Repeated isolation of the same organism from the same patient was recorded as one isolate. The bacterial strains were tested for susceptibility using the Kirby-Bauer disc diffusion method[12] and the National Committee for Clinical Laboratory Standards criteria for interpretation.[13] The following antimicrobials and concentrations (in brackets) were used: ampicillin (10µg), amoxicillin-clavulanic acid (20/10 µg), cefuroxime (30µg), ceftazidime (30 µg), gentamicin (10µg), aztreonam (30µg), piperacillin (100µg), ciprofloxacin (5µg), imipenem (10µg) and piperacillin-tazobactam (110µg). Antimicrobial agents and the amount consumed by patients on the ICU for the study period were obtained from the Hospital Pharmacy records. Patients' admission to the ICU were obtained from the Records Office. Deaths on the ICU especially those associated with infectious complications were also obtained from the Records Office.

Results. From 1160 admissions to the ICU during the study period, clinical specimens were collected from 530 suspected episodes of infection. From these suspected cases 445 (84.0%) were culture positive for *Gram negative bacilli* (GNB). There were 280 deaths on the ICU during the study period, and of these, approximately 43% (120 of 280) were thought to be due to, or associated overall with hospital-acquired infectious complications and GNB was implicated in 39 deaths. Pneumonia and septicemia were the cause of death and *P. aeruginosa*, *Acinetobacter spp*, *Citrobacter spp* and *Enterobacter spp* were the principal isolates. Four hundred and forty-five GNB were consecutively isolated from the specimens. Sputum, urine, wound and blood accounted for almost 93% of all isolates. The bacterial strains isolated were *P. aeruginosa*, 157 (35.2%), *Citrobacter spp*, 93 (21.0%), *Enterobacter spp*, 75 (16.8%), *K. pneumoniae*, 57 (12.8%), *E. coli*, 32 (7.2%), *Acinetobacter spp*, 16 (3.6%), *P. mirabilis*, 9 (2.0%) and *Serratia marcescens*, 6 (1.3%). The most common isolates from sputum were *P. aeruginosa*, *Citrobacter spp* and *Enterobacter spp*. From urine, it was *P. aeruginosa* and *K. pneumoniae*; from wound, it was *P. aeruginosa* and *Enterobacter spp*. and from blood, the predominant isolate was *Citrobacter spp* (**Table 1**). The susceptibility pattern of the GNB to the commonly prescribed antimicrobials is shown in **Table 2.** More than 82% of *P. aeruginosa* strains remained sensitive to the anti-pseudomonal antibiotics. *Acinetobacter spp, Citrobacter spp* and *Enterobacter spp* were the most resistant organisms to ampicillin (>90%) and amoxicillin-clavulanic acid (>72%), but showed varying degrees of

Table 1 - Source of Gram-Negative Bacterial Isolates from intensive care unit patients at the San Francisco General Hospital, 1998-2002.

Isolates	Total isolates	N of isolates from sputum	N of isolates from urine	N of isolates from wound	N of isolates from blood	N of isolates from other*
Pseudomonas aeruginosa	**157**	47	43	47	7	13
Citrobacter spp	**93**	26	15	24	24	4
Enterobacter spp	**75**	24	11	32	6	2
Klebsiella pneumoniae	**57**	8	28	9	6	6
Escherichia coli	**32**	11	7	6	2	6
Acinetobacter spp	**16**	6	0	4	6	0
Proteus mirabilis	**9**	0	0	9	0	0
Serratia marcescensc	**6**	0	0	6	0	0
Total	**445**	**122**	**104**	**137**	**51**	**31**

*Genital tract 9, ear 5, colony stimulating factor 1, eye 1.

Table 2 - Prevalence (%) of Resistance of ICU Gram-negative bacilli at the SFGH, 1998-2002

Organisms	Total	AM n (%)	AMC n (%)	CXM n (%)	ATM n (%)	CAZ n (%)	PIP n (%)	TZP n (%)	IMP n (%)	CIP n (%)	GM n (%)
Pseudomonas aeruginosa	**84**	NT	NT	NT	16 (18.8)	16 (18.8)	12 (14.1)	8 (9.4)	6 (7.1)	5 (5.9)	5 (17.6)
Citrobacter spp	**50**	45 (90)	37 (74)	42 (84)	12 (24)	34 (68)	19 (68)	4 (8)	2 (4)	4 (8)	15 (28)
Enterobacter spp	**40**	37 (92.5)	29 (72.5)	18 (45)	16 (40)	12 (30)	16 (40)	6 (15)	6 (15)	6 (15)	6 (15)
Klebsiella pneumoniae	**30**	30 (100)	10 (33.3)	20 (66.7)	13 (43.3)	18 (60)	16 (53.3)	3 (10)	0	0	5 (16.7)
Escherichia coli	**17**	12 (70.6)	9 (52.9)	8 (47.1)	6 (35.3)	7 (41.2)	9 (52)	4 (23.5)	0	0	0
Acinetobacter spp	**8**	8 (100)	6 (75)	6 (75)	2 (25)	5 (62.5)	3 (37.5)	0	0	0	0
Proteus mirabilis	**5**	2 (40)	0 (0)	0	0	0	0	0	0	0	0
Serratia marcescensc	**3**	0	0 (0)	0	0	0	0	0	0	0	0

NT - not tested, AM - ampicillin, AMC - amoxicillin-clavulanic acid (augmentin), CXM - cefuroxime, ATM - aztreonam, CAZ - ceftazidime, PIP - piperacillin, TZP - piperacillin-tazobactam (zosyn), IMP - imipenem, CIP – ciprofloxacin, GM – gentamicin, ICU - intensive care unit, SFGH - San Fernando General Hospital

resistance to the cephalosporins, cefuroxime (45-84%) and ceftazidime (19-68%). Resistance of *E.coli* and *Acinetobacter spp* to imipenem, ciprofloxacin and gentamicin was zero. However, this resistance prevalence to the third generation cephalosporin, ceftazidime, by *K. pneumoniae* and *E.coli* maybe a result of extended spectrum beta-lactamase production (ESBLs). Resistance of the other GNB to the antimicrobials was also quite low. **Table 3** shows the overall prevalence of resistance to the 10 antimicrobials used in the study. The least effective was ampicillin that showed 87.8% of GNB to be resistant to this agent. The drug to which isolates were most sensitive was imipenem (94.2%) followed by ciprofloxacin (93.9%) and piperacillin-tazobactam (88.5%). The consumption of antibiotics on the ICU is shown in **Table 4.** The total amount of antibiotics consumed during the 5-year period was 2282 gm. The most frequently prescribed antimicrobials were ampicillin, cefuroxime and amoxicillin-clavulanic acid. The beta-lactam drugs accounted for 87.3%.

Table 3 - Gram-negative bacterial resistance in the intensive care unit to antimicrobial agents tested, 1998 - 2002.

Antimicrobial	Resistance n	(%)
Penicillins		
Ampicillin	253/288*	(87.8)
Amoxicillin-clavulanic acid	171/288	(59.3)
Piperacillin	124/445	(27.9)
Piperacillin-tazobactam	51/445	(11.5)
Cephalosporins		
Cefuroxime	177/288	(61.5)
Ceftazidime	173/237	(38.9)
Monobactam		
Aztreonam	122/445	(27.4)
Carbapenem		
Imipenem	26/445	(5.8)
Aminoglycoside		
Gentamicin	57/445	(12.8)
Fluoroquinolone		
Ciprofloxacin	27/445	(6.1)

*number of resistant over number of tested

Discussion. The frequency and susceptibility patterns of nosocomial isolates are major factors of any infection control program. Such surveillance monitoring would assist clinicians in empiric and prudent choices of antimicrobial agents in managing infections, especially in the ICU. Surveillance of nosocomial infections at the SFGH actually began in 1985 by the Caribbean Epidemiology Center, a regional branch of the Pan-American Health Organization (PAHO), which found a rate of 6.1% (unpublished data). No follow-up was carried out until the report of Orrett et al[14] 10 years later, which showed that over a 4-year period (1992-1995), 7158 nosocomial infections were identified from among 72,532 hospitalized patients (10 per 100 admissions). The highest rate of nosocomial infection was found on the ICU (67 per 100 admissions). Since that 1995 survey, the ICU has been carrying out focal surveillance from various specimens. Preliminary results had suggested significant differences in species mix, the predisposition of certain body sites to nosocomial infections and the varied resistance profiles of Gram-negative bacterial pathogens, according to the analyzed specimen. The present study showed that the major isolates from ICU were *P. aeruginosa, Citrobacter spp, Enterobacter spp,* and *K. pneumoniae*, all of which are either naturally resistant to antimicrobials or capable of acquiring resistance via various mechanisms. *P.aeruginosa* was the leading cause of nosocomial infection involving the lower respiratory tract (LRT) (38.5%), a discovery supported by reports from other countries. In Thailand,[4] Croatia,[15] and Oman,[2] *P. aeruginosa* was responsible for 25%, 33% and 60%,

Table 4 - Antimicrobial consumption on the intensive care unit at the San Francisco General Hospital, 1998-2002.

Antimicrobial agent	Amount in grams n	(%)
Penicillins		
Ampicillin	240	(10.5)
Cefuroxime	189	(8.3)
Piperacillin	209	(9.2)
Piperacillin-tazobactam	459	(20.1)
Amoxicillin-clavulanic acid	224	(9.8)
Cephalosporins		
Cefotaxime	229	(10)
Ceftazidime	209	(9.2)
Ceftrioxone	186	(8.2)
Macrolides		
Erythromycin	242	(10.6)
Roxithromycin	18	(0.8)
Aminoglycoside		
Gentamicin	30	(1.3)
Carbapenem		
Imipenem	47	(2)
Total	**2282**	**(100)**

for all LRT infections, with an associated mortality in ICU patients reported to be between 40-50%. *Pseudomonas aeruginosa* was also found to be the predominant isolate associated with other ICU nosocomial infections: infected urine (41.1%) and wounds (34.5%). All patients in our ICU had indwelling urethral catheters for the duration of their ICU stay, and despite appropriate preventative measures, almost all developed infections. Catheterization is frequently associated with urinary tract infection not only in hospitalized patients,[16,17] but also in those attending outpatient clinics.[18,19] Among bloodstream isolates, *Citrobacter spp* were the organisms most frequently recovered. These organisms have only recently been recognized as human pathogens of increasing clinical significance, particularly in nosocomial infections.[20] Two groups of persons are at highest risk for clinical disease due to Citrobacter, neonates and the elderly debilitated patients.[21,22] In this study as in others,[22,23] the urinary tract was the principal source of Citrobacter bacteremia and isolation from the blood is often associated with more than one organism.[24] Neonates occasionally develop sepsis with Citrobacter, and while some cases are attributable to mother-to-child transmission,[25,26] the majority of cases had unknown origins.[22] In one report from this institution, 132 of 627 admissions to the neonatal unit resulted in death. Sepsis was the cause of death in 21.2% of these infants and *P. aeruginosa* was the most common GNB isolated.[27] No neonatal death was attributable to Citrobacter organisms. Although the rate of isolation of Citrobacter was high in this study, it is not clear as to how many episodes of infections associated with these organisms were due cross infection or represents an outbreak of Citrobacter infections. However, although a high mortality has been associated with Citrobacter bacteremic patients, 22 this was not the case as observed in this study. Only 9 of the 24 Citrobacter bacteremic patients succumb to their infection. In a report by Drelichman and Band,[21] Citrobacter bacteremia was associated with 48% mortality. Their patients received appropriate antimicrobial therapy with either an aminoglycoside or another agent active against *Citrobacter spp, Enterobacter spp*, *Citrobacter spp* and *Acinetobacter spp* were among the most resistant to the cephalosporins, cefuroxime and ceftazidime, with more than 60% resistance being observed. These resistances co-exist with good activity of piperacillin-tazobactam, gentamicin, imipenem and ciprofloxacin. Resistance to the most frequently used antimicrobial agents was high in our ICU and this was correlated with the antimicrobial consumption (**Tables 3 and 4**). The exceptions were Imipenem and ciprofloxacin to which resistance was low in all types of infection. From an empiric therapeutic standpoint, only imipenem and ciprofloxacin would be efficacious for all types of nfections in the ICU.[28] Because the majority of patients in the ICU often receive antimicrobials for weeks at times, combinations of 3 or even 4 agents are not rare. Since most antimicrobials are often given before culture results are known, careful clinical assessment should give some indication of the source of the infection and allow a rational choice of the drugs. The most commonly used antimicrobials in the ICU are the ones to which most isolates are resistant. The study clearly shows that therapy with imipenem, ciprofloxacin and piperacillin-tazobactam are good empiric choices while awaiting culture reports. Although resistance was relatively low, the need for policies governing the use of antimicrobials in the hospital is important. Attempts at introducing an antibiotic policy and providing educational programs aimed at rational prescribing of antibiotics have met with limited success.

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