

# Antimicrobial Resistance of Gram-negative Bacilli in the Intensive Care Units of Phramongkutklao Hospital

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## Abstract

Many developing countries are facing the problem of antibiotic resistance especially in hospital acquired infection. Not only lacking of knowledge how to use antibiotic appropriately but also fail to control it effectively are the important reasons to explain why antibiotic resistance is growing as time goes by. This study demonstrated gram-negative bacilli such as *Pseudomonas aeruginosa* and other enterobacteriaceae were the most common isolates in ICUs and resistant to third and fourth generation cephalosporins, aminoglycosides, quinolones and carbapenem as well. Various mechanisms were found that can develop resistance such as chromosomal  $\beta$ -lactamase producing in *P. aeruginosa* or ESBL (extended spectrum  $\beta$ -lactamase) producing in *K. pneumoniae* and *E. coli*. These are two common mechanisms that jeopardize the use of cephalosporins which were the most common prescribed antibiotic in this hospital. (*J Infect Dis Antimicrob Agents* 1998; 15:9-14.)

## INTRODUCTION

There are several factors in the intensive care unit (ICU) setting for endemic nosocomial infections. Underlying diseases, severity of illness and invasive procedure are usually perceived as important risk factors. The emergence of bacterial multi-resistance during antimicrobial therapy has been recognized for many groups of antibiotics. Gram-negative organisms are the most common infecting bacteria among ICU patients.

Phramongkutklao Hospital is the tertiary care with one thousand and two hundred beds including 18 intensive care beds. The multi-resistant gram-negative bacilli have been continuously isolated from patients in ICUs. The frequency of cross-resistance and the development of resistance to antibiotics during antimicrobial therapy have not been well determined. To know the sensitivity pattern and understand to

which mechanism nosocomial resistance develop in this hospital will help physicians to improve strategy for controlling this problem.

## OBJECTIVE

To study the prevalence and antimicrobial susceptibility of gram-negative bacteria isolated from ICUs in Phramongkutklao hospital.

To analyze the resistance and cross-resistance patterns of gram-negative bacteria among the antibiotics used.

## MATERIALS AND METHODS

### Isolation

One hundred specimens of nosocomial bacteria were sequentially isolated from patient in ICUs during August to December 1995. The specimens were obtained from sputum, blood, urine, and wound

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specimens. Re-isolates from patients with persistent colonization were shown and excluded from analysis. Organisms were cultured and identified their species by the current techniques. Additional information, including patient identification, date of isolation, site of infection and antibiotic given within 48 hours before sampling were also recorded.

### Susceptibility testing

The minimum inhibitory concentration (MIC) for each isolate was determined by E test® AB-Biodisk. The breakpoint for susceptibility follows National Committee for Clinical Laboratory Standards (NCCLS). Twelve antibiotics from several classes were tested (Table 1). The TZ<sub>L</sub> (ceftazidime-clavulanate) strip was reserved for testing extended spectrum  $\beta$ -lactamase (ESBL) vs strains of *E. coli* and klebsiella. *Escherichia coli* (ATCC® 25922) and *Pseudomonas aeruginosa* (ATCC® 27853) were used as control strains.

Table 1. MIC range and breakpoints of ICU isolates.

|     | Antibiotics      | Range      | Breakpoints (mg/l) |
|-----|------------------|------------|--------------------|
| IPM | Imipenem         | 0.13 - 64  | 4                  |
| CAZ | Ceftazidime      | 0.25 - 128 | 8                  |
| TZL | Ceftaz / clavul. | 0.06 - 32  | ESBL indicator     |
| AZT | Aztreonam        | 0.25 - 128 | 8                  |
| CFT | Cefotaxime       | 0.25 - 128 | 8                  |
| CAX | Ceftriaxone      | 0.25 - 128 | 8                  |
| CPR | Cefpirome        | 0.25 - 128 | 8                  |
| FOX | Cefoxitin        | 0.25 - 128 | 8                  |
| PTz | Pip. / tazobact  | 1 - 128    | 16 (64)            |
| AUG | Amox. / clavul.  | 0.25 - 128 | 8                  |
| GM  | Gentamicin       | 0.25 - 128 | 4                  |
| AMK | Amikacin         | 1 - 128    | 16                 |
| CP  | Ciprofloxacin    | 0.06 - 32  | 1                  |

Breakpoint shown in parentheses is used only in the case of *P. aeruginosa*.

Table 4. Percentage of susceptibility of 77 isolates.

| Organisms            | # Isolates | Imipenem | Ceftazidime | Cefotaxime | Cefpirome | Cefoxitin | Pip+Taz | Amox+Clav | Amikacin | Ciprofloxacin |
|----------------------|------------|----------|-------------|------------|-----------|-----------|---------|-----------|----------|---------------|
| <i>P. aeruginosa</i> | 23         | 70       | 61          | 13         | 61        | 0         | 65      | 0         | 83       | 70            |
| <i>K. pneumoniae</i> | 12         | 100      | 33          | 50         | 75        | 83        | 67      | 58        | 67       | 83            |
| <i>A. baumannii</i>  | 9          | 100      | 44          | 0          | 44        | 0         | 44      | 44        | 44       | 44            |
| <i>E. coli</i>       | 8          | 100      | 63          | 75         | 63        | 100       | 50      | 38        | 75       | 63            |
| Ind. enterobac.*     | 14         | 86       | 29          | 43         | 71        | 0         | 43      | 8         | 79       | 64            |
| Others               | 11         | 82       | 82          | 64         | 73        | 45        | 64      | 45        | 73       | 73            |
| Total                | 77         | 86       | 53          | 36         | 65        | 32        | 58      | 29        | 73       | 66            |

\* Inducible *Enterobacteriaceae* - *Enterobacter* spp., *Serratia* spp.  
- *Providencia stuartii*, *Citrobacter freudii*, *Morganella morganii*

## RESULTS

A total of 99 isolates, separated into 77 initial isolates and 22 repeated strains, all were obtained from 38 patients. The polymicrobial infections were found 51 isolates from 16 patients (Table 2).

The most common site of isolation was from the respiratory tract (58%) as shown in Table 3.

Seventy-seven initial isolates were evaluated. The most common species were *P. aeruginosa* (30%), *K. pneumoniae* (16%), *A. baumannii* (12%), *E. coli* (10%), inducible enterobacteriaceae\* (18%) and other gram-negative bacilli (14%).

The prevalence of various species and susceptibility to antimicrobial agents tested are listed in Table 4 and non susceptible isolate distribution was shown in Fig. 1.

Table 2. Derivation of isolation by patient.

| Description             | Patients | Isolates |
|-------------------------|----------|----------|
| Infected site           |          |          |
| one species             | 15       | 15       |
| more than one species   | 16       | 51       |
| Persistent colonization | 7        |          |
| First isolation         |          | 11       |
| Repeated Isolation      |          | 22       |
| Initial isolates        |          | 77       |
| Total patients          | 38       |          |

Table 3. Sources of isolation.

| Site of isolation | Number (%) |
|-------------------|------------|
| Respiratory tract | 57 (58)    |
| Wound             | 25 (25)    |
| Blood             | 8 (8)      |
| Urinary tract     | 5 (5)      |
| Others            | 2 (2)      |

Cumulative percentage of isolates, gram-negative bacilli

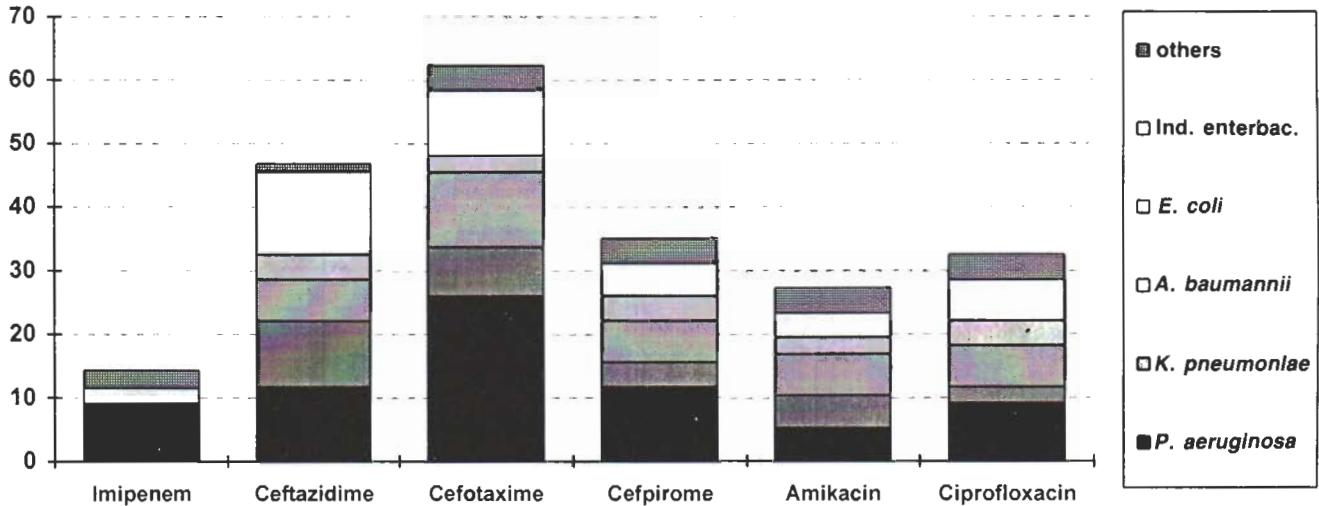


Fig. 1 Non susceptible isolate distribution among 77 isolates.

***P. aeruginosa***

The non-fermentater *P. aeruginosa* was the most common problematic pathogen and progressively less susceptible to anti-pseudomonal agents, ceftazidime (61%), piperacillin-tazobactam (65%), amikacin (83%), ciprofloxacin (70%) and imipenem (70%), concomitant resistance to other antibiotics were demonstrated not only elevated MICs to ceftazidime but also cefpirome, piperacillin-tazobactam, and ciprofloxacin (Table 5).

***K. pneumoniae* and *E. coli***

*K. pneumoniae* and *E. coli* were highly resistant to ceftazidime, cefotaxime, piperacillin-tazobactam, amikacin, cefpirome and moderately resistant to ciprofloxacin.

Indeed the MICs of cefotaxime, cefpirome, amoxicillin-clavulanate and amikacin correlated to ceftazidime resistant isolates which were contrary to MICs of imipenem, ceftazidime-clavulanate and cefoxi-

Table 5. Resistance pattern of 23 isolates of *Pseudomonas aeruginosa*.

| Isolate No. | SP                   | Imipenem | Ceftazidime | Cefotaxime | Cefpirome | Pip/Taz | Gentamicin | Amikacin | Ciprofloxacin |
|-------------|----------------------|----------|-------------|------------|-----------|---------|------------|----------|---------------|
| 0041        | <i>P. aeruginosa</i> | 4        | 128         | 128        | 128       | 32      | 128        | 512      | 32            |
| 0002        | <i>P. aeruginosa</i> | 32       | 128         | 128        | 128       | 512     | 128        | 512      | 32            |
| 0054        | <i>P. aeruginosa</i> | 8        | 128         | 128        | 128       | 512     | 128        | 128      | 32            |
| 0043        | <i>P. aeruginosa</i> | 2        | 128         | 128        | 64        | 512     | 8          | 16       | 0.25          |
| 0066        | <i>P. aeruginosa</i> | 64       | 128         | 128        | 128       | 512     | 128        | 8        | 32            |
| 0053        | <i>P. aeruginosa</i> | 2        | 32          | 128        | 128       | 512     | 128        | 16       | 32            |
| 0047        | <i>P. aeruginosa</i> | 2        | 32          | 128        | 4         | 512     | 128        | 16       | 32            |
| 0070        | <i>P. aeruginosa</i> | 64       | 16          | 128        | 64        | 512     | 128        | 512      | 1             |
| 0031        | <i>P. aeruginosa</i> | 2        | 16          | 128        | 64        | 256     | 8          | 16       | 4             |
| 0080        | <i>P. aeruginosa</i> | 8        | 8           | 128        | 32        | 32      | 128        | 16       | 0.13          |
| 0040        | <i>P. aeruginosa</i> | 2        | 4           | 16         | 4         | 8       | 8          | 16       | 0.25          |
| 0093        | <i>P. aeruginosa</i> | 4        | 4           | 32         | 4         | 8       | 16         | 16       | 0.25          |
| 0034        | <i>P. aeruginosa</i> | 2        | 4           | 16         | 4         | 8       | 8          | 8        | 0.50          |
| 0012        | <i>P. aeruginosa</i> | 2        | 4           | 16         | 4         | 4       | 128        | 8        | 0.25          |
| 0007        | <i>P. aeruginosa</i> | 8        | 4           | 16         | 4         | 8       | 8          | 8        | 0.25          |
| 0006        | <i>P. aeruginosa</i> | 2        | 4           | 16         | 2         | 4       | 4          | 4        | 0.13          |
| 0092        | <i>P. aeruginosa</i> | 64       | 2           | 32         | 8         | 8       | 16         | 16       | 0.13          |
| 0077        | <i>P. aeruginosa</i> | 2        | 2           | 32         | 4         | 16      | 8          | 8        | 0.13          |
| 0033        | <i>P. aeruginosa</i> | 2        | 2           | 8          | 4         | 8       | 0.25       | 8        | 0.25          |
| 0039        | <i>P. aeruginosa</i> | 2        | 2           | 16         | 4         | 4       | 8          | 8        | 0.25          |
| 0075        | <i>P. aeruginosa</i> | 2        | 2           | 8          | 2         | 4       | 4          | 4        | 0.13          |
| 0010        | <i>P. aeruginosa</i> | 2        | 2           | 16         | 2         | 8       | 4          | 4        | 0.25          |
| 0088        | <i>P. aeruginosa</i> | 2        | 1           | 8          | 2         | 2       | 4          | 4        | 0.13          |

tin (Table 6).

### *Acinetobacter baumannii*

The incidence of multidrug resistance of *A. baumannii* was about 60 percent, these include fourth generation cephalosporin, aminoglycoside and quinolone except imipenem (Table 7).

### Inducible enterobacteriaceae

The high percentage of isolates were resistant to ceftazidime (71%), cefotaxime (57%), ciprofloxacin (57%) and piperacillin-tazobactam (39%). High level of MIC more than 4 folds was observed in these re-

sistant strains.

The majority of highly ceftazidime resistant strains mostly correlated to cefotaxime, piperacillin-tazobactam, gentamicin but less resistant to amikacin and ciprofloxacin. Fortunately this cross resistance was not simultaneously present for imipenem (Table 8).

### DISCUSSION

All of the isolates in this study were obtained from patients in medical ICUs and surgical ICUs. They were considerably more resistant to antibiotics than those isolates from patients in the wards. The dramatic increasing in resistance of *Acinetobacter*,

**Table 6. Resistance pattern of 21 isolates of *E. coli* + *Klebsiella* species.**

| Isolate No. | SP                   | Imipenem | Ceftazidime | CAZ+Clav | Cefotaxime | Cefpirome | Cefoxitin | Pip/Taz | Amox/Cla | Amikacin | Ciprofloxacin |
|-------------|----------------------|----------|-------------|----------|------------|-----------|-----------|---------|----------|----------|---------------|
| 0030        | <i>K. pneumoniae</i> | 0.25     | 128         | 2        | 32         | 16        | 4         | 512     | 16       | 128      | 1             |
| 0027        | <i>K. pneumoniae</i> | 0.25     | 128         | 1        | 16         | 16        | 4         | 128     | 8        | 128      | 1             |
| 0098        | <i>K. pneumoniae</i> | 0.50     | 128         | 2        | 128        | 16        | 8         | 8       | 32       | 64       | 32            |
| 0013        | <i>K. pneumoniae</i> | 4        | 128         | 4        | 64         | 4         | 8         | 32      | 8        | 64       | 0.50          |
| 0068        | <i>E. coli</i>       | 0.25     | 128         | 2        | 32         | 32        | 4         | 32      | 32       | 32       | 8             |
| 0086        | <i>E. coli</i>       | 0.25     | 128         | 0.50     | 8          | 16        | 8         | 8       | 16       | 32       | 32            |
| 0051        | <i>E. coli</i>       | 0.25     | 128         | 1        | 16         | 16        | 4         | 256     | 32       | 16       | 2             |
| 0087        | <i>K. pneumoniae</i> | 0.50     | 128         | 4        | 8          | 4         | 8         | 8       | 16       | 8        | 16            |
| 0059        | <i>K. pneumoniae</i> | 0.25     | 128         | 2        | 16         | 4         | 4         | 4       | 8        | 2        | 0.06          |
| 0065        | <i>K. pneumoniae</i> | 0.25     | 128         | 1        | 8          | 4         | 2         | 4       | 4        | 1        | 0.06          |
| 0009        | <i>K. pneumoniae</i> | 0.50     | 64          | 16       | 16         | 1         | 128       | 32      | 128      | 16       | 0.50          |
| 0071        | <i>K. pneumoniae</i> | 1        | 8           | 8        | 4          | 0.50      | 128       | 8       | 64       | 8        | 0.50          |
| 0024        | <i>E. coli</i>       | 0.50     | 1           | 1        | 4          | 0.25      | 4         | 32      | 25       | 4        | 0.06          |
| 0090        | <i>E. coli</i>       | 0.25     | 0.50        | 0.50     | 0.25       | 0.25      | 4         | 4       | 4        | 4        | 0.06          |
| 0078        | <i>K. pneumoniae</i> | 0.50     | 0.50        | 1        | 0.25       | 0.25      | 4         | 4       | 4        | 4        | 0.13          |
| 0096        | <i>K. pneumoniae</i> | 0.50     | 0.50        | 0.50     | 0.25       | 0.25      | 4         | 4       | 8        | 2        | 0.06          |
| 0081        | <i>E. coli</i>       | 1        | 0.50        | 1        | 0.25       | 0.50      | 4         | 4       | 32       | 2        | 0.13          |
| 0023        | <i>K. pneumoniae</i> | 0.25     | 0.50        | 0.50     | 0.25       | 0.25      | 2         | 4       | 2        | 2        | 0.25          |
| 0003        | <i>E. coli</i>       | 0.50     | 0.50        | 0.50     | 0.25       | 0.50      | 4         | 512     | 32       | 2        | 0.06          |
| 0095        | <i>K. pneumoniae</i> | 0.25     | 0.25        | 0.50     | 128        | 0.25      | 4         | 4       | 2        | 2        | 0.06          |
| 0073        | <i>E. coli</i>       | 0.25     | 0.25        | 0.50     | 0.25       | 0.25      | 2         | 2       | 8        | 2        | 0.13          |

**Table 7. Resistance pattern of 9 isolates of *Acinetobacter baumannii*.**

| Isolate No. | Imipenem | Ceftazidime | Cefotaxime | Cefpirome | Pip/Taz | Gentamicin | Amikacin | Ciprofloxacin |
|-------------|----------|-------------|------------|-----------|---------|------------|----------|---------------|
| 0083        | 4        | 128         | 128        | 128       | 32      | 128        | 512      | 32            |
| 0089        | 0.13     | 128         | 128        | 128       | 32      | 128        | 512      | 32            |
| 0097        | 4        | 128         | 128        | 128       | 512     | 128        | 128      | 32            |
| 0017        | 1        | 128         | 128        | 128       | 512     | 128        | 64       | 32            |
| 0011        | 2        | 64          | 128        | 128       | 512     | 128        | 128      | 32            |
| 0044        | 0.50     | 8           | 16         | 4         | 16      | 2          | 4        | 0.25          |
| 0057        | 0.50     | 8           | 16         | 2         | 8       | 2          | 4        | 0.25          |
| 0079        | 0.25     | 8           | 16         | 4         | 8       | 1          | 2        | 0.25          |
| 0004        | 0.25     | 8           | 16         | 4         | 8       | 0.5        | 2        | 0.25          |

**Table 8. Resistance pattern of 14 isolates of inducible Enterobacteriaceae.**

| Isolate No. | SP                   | Imipenem | Ceftazidime | Cefotaxime | Cefpirome | Pip/Taz | Gentamicin | Amikacin | Ciprofloxacin |
|-------------|----------------------|----------|-------------|------------|-----------|---------|------------|----------|---------------|
| 0014        | <i>S. marcescens</i> | 32       | 128         | 128        | 32        | 512     | 128        | 512      | 16            |
| 0099        | <i>E. cloacae</i>    | 0.50     | 128         | 64         | 16        | 32      | 128        | 64       | 0.25          |
| 0046        | <i>S. marcescens</i> | 2        | 128         | 128        | 128       | 512     | 128        | 16       | 32            |
| 0069        | <i>Ent. spp.</i>     | 0.50     | 128         | 8          | 2         | 16      | 8          | 8        | 0.25          |
| 0016        | <i>S. marcescens</i> | 1        | 128         | 32         | 8         | 32      | 128        | 8        | 2             |
| 0020        | <i>S. marcescens</i> | 8        | 128         | 128        | 8         | 32      | 64         | 4        | 1             |
| 0061        | <i>Serratia spp.</i> | 1        | 128         | 32         | 4         | 32      | 32         | 2        | 4             |
| 0028        | <i>E. cloacae</i>    | 2        | 32          | 128        | 32        | 512     | 128        | 32       | 32            |
| 0029        | <i>E. cloacae</i>    | 1        | 16          | 8          | 0.50      | 16      | 128        | 16       | 0.25          |
| 0076        | <i>E. cloacae</i>    | 0.50     | 16          | 16         | 2         | 128     | 16         | 4        | 0.13          |
| 0035        | <i>E. cloacae</i>    | 1        | 8           | 4          | 4         | 4       | 16         | 8        | 0.50          |
| 0032        | <i>E. cloacae</i>    | 4        | 1           | 0.25       | 0.25      | 4       | 2          | 4        | 0.06          |
| 0001        | <i>E. cloacae</i>    | 0.50     | 0.50        | 0.25       | 0.25      | 4       | 1          | 2        | 0.06          |
| 0056        | <i>M. morgani</i>    | 2        | 0.25        | 0.25       | 0.25      | 1       | 1          | 1        | 0.06          |

*K. pneumoniae*, *P. aeruginosa* and inducible enterobacteriaceae was probably due to the increasing use of cephalosporin and  $\beta$ -lactamase inhibitor combinations and inappropriate use of antibiotic for treatment of infections.

In *P. aeruginosa* and inducible enterobacteriaceae, the amp C (Class I) chromosomal enzymes are the most important mean of resistance. Mutant of these species produce continuously high level of enzyme and resist to anti-pseudomonal penicillins and cephalosporins. The selection is favoured by labile weak inducer eg. cephalosporins, ureidopenicillin and monobactam (1). For *P. aeruginosa*, the alteration of DNA gyrase results in resistance to quinolones (2) and loss of D2 porin causes imipenem resistance (3). However, cross-resistance between quinolone agents and imipenem after quinolone therapy has been reported in *P. aeruginosa* (4).

In this study, though *P. aeruginosa* was highly susceptible to amikacin (83%) but MICs of amikacin at breakpoint (16  $\mu$ g/ml) were 35 percent of *P. aeruginosa* isolates (Table 5). So the risk of resistance was still high for amikacin monotherapy. The antimicrobial combination should be recommended for treatment of *P. aeruginosa* infections due to high level of MICs especially in immunocompromised host.

Sixty-seven percent of *K. pneumoniae* isolates were found to be resistant to ceftazidime and there was a significant relation of resistance to other antimicrobial classes (Table 6). The extended spectrum  $\beta$ -lactamase (ESBL) was identified by ceftazidime-clavulanate which all of ceftazidime resistant strains

were due to ESBL. Interestingly, even ceftazidime resistant *K. pneumoniae* was highly sensitive to ceftazidime-clavulanate but the combination of amoxicillin-clavulanate or piperacillin-tazobactam inhibited only 50 percent of ceftazidime resistant *K. pneumoniae*. Ceftazidime restriction and barrier precautions for colonized and infected patients are the effective control measures (5).

A number of clinical *E. coli* strains are highly resistant to the combination of amoxicillin-clavulanate and piperacillin-tazobactam. The mechanisms of resistance were described to be due to ESBL, the hyperproduction of small copy plasmid-determined TEM-1  $\beta$ -lactamase and a new TEM-type  $\beta$ -lactamase, TRI-1 and TRI-2 (TEM resistant to  $\beta$ -lactamase inhibitor) (6).

*A. baumannii* is emerging as an important nosocomial multidrug resistant pathogen and causing outbreaks of infection and colonization. Several mechanisms have been hypothesized for multi-resistant strain including the presence of aminoglycoside modifying enzymes, chromosomal cephalosporinase as well as plasmid  $\beta$ -lactamase enzymes (7). However, the mechanism of resistance has not been determined definitely.

## SUMMARY

Surveillance of antimicrobial resistance of gram-negative bacilli in the ICUs was conducted and found that many gram-negative bacteria increased resistance to third generation cephalosporins included ceftazidime, quinolones, aminoglycosides and imipenem as well.

*P. aeruginosa*, *K. pneumoniae*, *A. baumannii* were the three most sequential common isolates in ICUs and imipenem was the most active antibiotic to cover these organisms. The most effective strategy to reduce this problem therefore is to use antibiotics appropriately and purposefully reserved.

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