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# Association of antibiotic utilization measures and reduced incidence of infections with extended-spectrum β-lactamase-producing organisms

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With the overuse of expanded-spectrum cephalosporins, especially ceftazidime, outbreaks of extended-spectrum β-lactamase (ESBL)-producing *Klebsiella pneumoniae* and *Escherichia coli* infections have been reported. In this prospective observational study, we demonstrated that the addition of piperacillin/tazobactam to the formulary and the restriction of ceftazidime were associated with a decrease in the percentage of ceftazidime-resistant isolates. When the use of ceftazidime decreased by 96.43%, and the use of piperacillin/tazobactam increased by over 50% during the 9-month study period, a concomitant decrease was found in the percentage of colonization and infection by ESBL-producing *E. coli* or *K. pneumoniae* in patients admitted to the intensive care unit. Results from this 9-month intervention study support the concept that levels of local and institutional use of ceftazidime are of substantial importance to the emergence and persistence of endemic ceftazidime-resistant *K. pneumoniae*.

**Key words:** Ceftazidime, extended spectrum β-lactamase, *Klebsiella pneumoniae*, piperacillin/tazobactam

Strains of *Enterobacteriaceae*, especially *Klebsiella pneumoniae*, that produce extended-spectrum β-lactamases are becoming increasingly prevalent in healthcare institutions such as medical centers and nursing homes [1,2]. Risk factors for the emergence of these strains include increased overall use of ceftazidime during hospitalization and, for individual patients, prolonged hospital stay, prior treatment with antimicrobials, and a stay in intensive care units [3]. Limited data exist on optimal strategies for controlling outbreaks of colonization and infection with these strains. One outbreak in a chronic care setting appeared to subside as a result of restrictions on the use of ceftazidime [4]. A second large outbreak in an acute care hospital in New York was aborted after approval for ceftazidime use was obtained from infectious diseases physicians and barrier precautions for colonized or infected patients were instituted [3].

In general, the common plasmid-mediated ESBLs that confer resistance to ceftazidime do not confer resistance to the β-lactam-β-lactamase inhibitor combinations [1]. The β-lactam-β-lactamase inhibitor combinations have the further advantage of not being in the cephalosporin class, and data had showed that the addition of piperacillin/tazobactam to the hospital formulary and educational efforts focused on minimizing the administration of ceftazidime were associated with a marked decrease in the drug's use and a concomitant decrease in the percentage of ceftazidime-resistant isolates [5].

This prospective observational study was conducted to evaluate the effectiveness of using piperacillin/tazobactam in reducing ESBL-producing *E. coli* or *K. pneumoniae* colonization and infection. A significant decline in widespread colonization with ESBL-producing *E. coli* or *K. pneumoniae* was found, which was attributed to this change in the hospital antibiotic formulary and in the prescribing habits of the physicians.

## Materials and Methods

### Study setting

The study was conducted in Tien Sheng Memorial Hospital, a regional hospital with 340 inpatient medical and surgical beds. There are 2 intensive care units (ICU), one for surgical and one for medical patients. The

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medical ICU was chosen for this study.

### Duration of study

Starting in April 2001,a 3-month Phase 1 (pre-intervention phase) period and a 6-month Phase II (intervention and postintervention phase) period were instituted. There were 58 patients enrolled in the Phase I (preintervention) period and 122 patients in the Phase II (last 3 months; postintervention) period. A total of 48 patients completed the Phase I period and 107 patients completed the Phase II period.

### Selection criteria

Inclusion criteria were patients of either sex, 18 years of age or older admitted to the medical ICU. Exclusion criteria were history of clinically significant bleeding tendencies or blood dyscrasia, cystic fibrosis and mononucleosis, ulcerative colitis or Crohn's disease, as well as women who were pregnant or nursing.

### Study procedure

#### *Preintervention period (Month 0-3)*

Upon admission to the ICU, patients' demographic data including age, sex, underlying disease, and cause of admission to the ICU were recorded. Medical history was taken, including prior treatments. Laboratory evaluations were done, including blood urea nitrogen (BUN), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and serum creatinine. Patients underwent rectal swab for detection of ESBL and non-ESBL pathogens by double-disc diffusion within and after 48 h of admission. Concomitant antibiotics taken during the study period were recorded. Rectal swab was done every 7 days for patients who stayed in the ICU longer than 1 week. Before discharge from the ICU, both laboratory evaluation and rectal swab study were done.

#### *Intervention period (First 3 months)*

Routine ICU procedures were done, and no screening culture was done in this period. Piperacillin/tazobactam was the main antibiotic used (at least 50% replacement of ceftazidime). Aminoglycosides was combined for patients only when multidrug resistant *Enterobacter* sp., *Acinetobacter* sp., and *Pseudomonas aeruginosa* were suspected or had been isolated. Other antibacterial drugs available as alternatives were ciprofloxacin, vancomycin, teicoplanin, and macrolides. Use of third-generation cephalosporins (ie ceftazidime, ceftriaxone), and fourth-generation cephalosporins (ie cefepime) was reduced by allowing their use only for patients in whom bacterial susceptibility had been proven and with isolates shown to be resistant to piperacillin/tazobactam.

#### *Intervention period (Last 3 months)*

The following procedures were done and data recorded upon admission of patients to the ICU: demographic data, medical history, prior treatments, and laboratory evaluation as in Phase I. Patients underwent rectal swab for detection of ESBL and non-ESBL pathogens by the double-disk diffusion method within and after 48 h of admission. Piperacillin/tazobactam was the primary antibiotic used (at least 50% replacement of ceftazidime). Aminoglycosides were combined for patients only when multidrug resistant *Enterobacter* sp., *Acinetobacter* sp., or *P. aeruginosa* was suspected or had been isolated. Other antibacterial drugs available as alternatives were ciprofloxacin, vancomycin, teicoplanin, and macrolides. Use of third-generation cephalosporins was reduced to less than 50% of that in the Phase I period. The latter drugs were allowed only for patients in whom bacterial susceptibility had been proven but with resistance to piperacillin/tazobactam. Concomitant antibiotics taken during the study period were recorded. The consumption of various antibiotics was compared between Phase I and II.

The rectal swab acquisition rate of ESBL-producing *E. coli* or *K. pneumoniae* was assessed based on the number of participants in each phase who either had no *E. coli* or *K. pneumoniae* isolated from rectal swab at the time of enrollment, or had either *E. coli* or *K. pneumoniae* isolated from rectal swab at the time of enrollment but recovered during their stay in the ICU. If the participant did not complete the discharge visit, but had at least one examination within 48 h after enrollment, data from the last examination was used to evaluate the participant's acquisition rate.

### Statistical methods

All available data were categorized by treatment phase. All statistical tests were 2-sided and evaluated at the 0. 05 level of significance. All confidence intervals were 95%. The primary analysis for efficacy endpoints was performed based on the intent-to-treat population. Descriptive statistics such as number of observations, mean, median, standard deviation, minimum and 95% confidence interval were used to summarize continuous variables. Frequency and proportion were used to summarize categorical variables. Fisher's exact test was used for between-treatment phase comparison.

## Results

There were 48 patients enrolled in the Phase I

**Table 1.** Overall duration in ICU for patients in different phases

| Statistics | Period | | Difference |
|---|---|---|---|
| | Phase I (n = 48) | Phase II (n = 107) | |
| Mean ± SD | 14.2 ± 4.8 | 9.1 ± 1.1 | 5.10 |
| Median | 8.0 | 5.0 | |
| Range | 1.0-61.0 | 1.0-64.0 | |
| CI | 10.3-18.0 | 7.1-11.1 | 0.69-9.37 |
| *p* | | | 0.024 |

Abbreviation: ICU = intensive care unit

(preintervention) period and 107 patients in the Phase II (last 3 months, postintervention) period. As shown in Table 1, the mean duration of stay in ICU was significantly longer for Phase I (14.2 ± 14.8) than for Phase II (9.1 ± 11.1) ($p<0.05$).

As shown in Table 2, the rectal swab acquisition rate for ESBL-producing *E. coli* or *K. pneumoniae* was significantly higher in Phase I (41%) than in Phase II (22%) ($p<0.05$).

Consumption of antibiotics during the 3 months of Phase I and the first and second 3 months of Phase II period were compared. In comparison with Phase I, the consumption of third-generation cephalosporins in Phase II was reduced by 96.45% and the reduction rate of ceftazidime was reduced by 96.43%, which was in accordance to protocol criteria. The consumption of fourth-generation cephalosporins, carbapenems, and piperacillin/tazobactam were increased, especially piperacillin/tazobactam, which was over 50% at the end of the Phase II (Table 3).

The reduction of ESBL-producing *E. coli* or *K. pneumoniae* was obvious in the first month of intervention and the overall trend in the isolation of ESBL-producing *E. coli* or *K. pneumoniae* was correlated with the use of ceftazidime and piperacillin/tazobactam, as shown in Fig. 1.

**Table 2.** Rectal swab acquisition rate for ESBL-producing *E. coli* or *K. pneumoniae*

| ESBL production | Period | | *p* |
|---|---|---|---|
| | Phase I n = 48 (%) | Phase II n = 107 (%) | |
| Positive | 20 (41) | 24 (22) | 0.020 |
| Negative | 28 (59) | 83 (78) | |

Abbreviation: ESBL = extended-spectrum β-lactamases

Neither clinically significant laboratory abnormalities nor adverse events were observed during the study period, which supports that piperacillin/tazobactam was well tolerated in these patients. To compare the antibiotic susceptibilities of the leading gram-negative organisms between the study phases, all positive bacteria culture data were collected and their antibiotic susceptibilities were compared. No significant increase of cephalosporin and imipenem resistance was found among the most common gram-negative organisms (Table 4). No nosocomial outbreak of *Candida* infection was noted during the study.

## Discussion

In the past decade, following the overuse of the expanded-spectrum cephalosporins, several outbreaks of ESBL-producing *K. pneumoniae* or *E. coli* have been reported. Several studies suggest that the implementation of rigorous restriction of their use, usually combined with a reinforcement of infection control measures, can decrease the prevalence of ESBL-producing *K. pneumoniae* [3,4,6]. When the use of ceftazidime decreased by over 50% and the use of piperacillin/tazobactam increased during the same period of time, a concomitant decrease in the percentage of ceftazidime-resistant *K. pneumoniae* isolates was observed, from 28% to less than 10% [5]. A similar

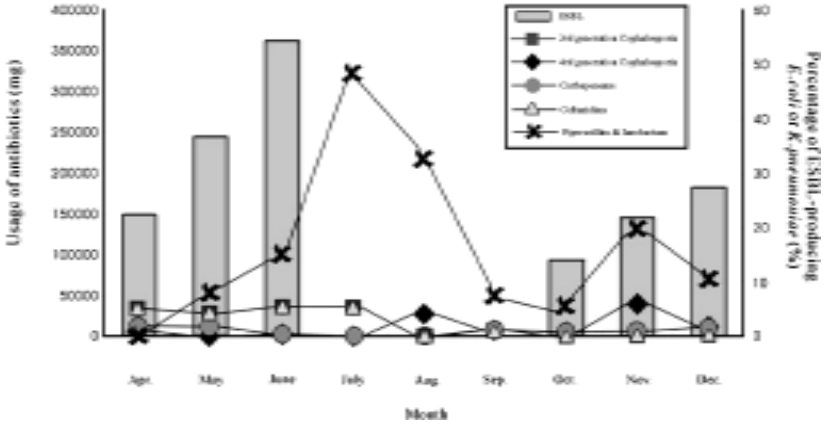


**Fig. 1.** ESBL-producing *E. coli* or *K. Pneumoniae.*

**Table 3.** Extent of use of major antibiotics in total amount (g) by study phase

| Antibiotic | Phase I Period (baseline) | Phase II to first 3 months | % change from baseline (phase II to first 3 months) | Phase II to Last 3 months | % change from baseline (phase II to last 3 months) |
|---|---|---|---|---|---|
| 3rd-generation cephalosporin[a] | 84 500 | 42 000 | –50.30 | 3000 | –96.45 |
| 4th-generation cephalosporin[b] | 3500 | 30 000 | 757.14 | 58 500 | 1571.4 |
| Carbapenems | 18 500 | 11 750 | –36.49 | 22 000 | 18.92 |
| Ceftazidime | 84 000 | 34 000 | –59.52 | 3000 | –96.43 |
| Piperacillin-tazobactam | 157 500 | 609 750 | 287.14 | 236 250 | 50.00 |

[a]Includes ceftazidime, ceftriaxone, cefotaxime.
[b]Cefepime.

observation was also reported where ceftazidime-resistant *K. pneumoniae* isolates were significantly reduced from 22% to 15% at hospital A and from 10% to 5% at hospital B.

Although it is possible that the decreased appearance of ceftazidime-resistant isolates in clinical laboratory specimens represents the failure to suppress competing flora with the widespread use of ceftazidime rather than a decrease in colonization with resistant strains, we consider this scenario unlikely. The spectrum of piperacillin/tazobactam is at least as broad as that of ceftazidime, therefore the use of piperacillin/tazobactam is unlikely to result in reestablishment of susceptible microflora.

Data from this 9-month intervention study support the concept that the levels of local and institutional use of ceftazidime are of substantial importance in the emergence and persistence of endemic ceftazidime-resistant *K. pneumoniae*.

By decreasing the level of ceftazidime use, we achieved a dramatic reduction in the incidence of colonization with ceftazidime-resistant strains. The relatively rapid segregation of these resistance determinants once ceftazidime use decreases suggests that they may confer an evolutionary disadvantage once the selective pressure of ceftazidime is eliminated.

The selection of piperacillin/tazobactam as the extended-spectrum antibiotics of choice has several

**Table 4.** Antimicrobial susceptibility test of GNB in ICU by disk diffusion test

| Microorganism | Phase | n | Susceptible rate (%) to antimicrobial agent | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | AN | CAZ | CRO | CZ | FOX | GM | IPM | MI | OFX | PIP | SAM | TZP | AM | FEP | SXT |
| *Acinetobacter baumanii* | Pre | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 100 | 50 | 0 | 0 | 100 | 0 | 0 | 50 | 0 |
| | Post | 5 | 0 | 50 | 0 | 0 | 0 | 0 | 100 | 100 | 0 | 0 | 100 | 50 | 0 | 0 | 0 |
| *Citrobacter freundii* | Pre | 4 | 100 | 100 | 100 | 0 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 0 | 100 | 100 |
| | Post | 6 | 100 | 100 | 100 | 0 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 0 | 100 | 100 |
| *E. coli* | Pre | 10 | 88 | 63 | 63 | 50 | 63 | 50 | 100 | 50 | 63 | 13 | 38 | 100 | 13 | 86 | 25 |
| | Post | 9 | 100 | 100 | 83 | 83 | 100 | 67 | 100 | 83 | 67 | 33 | 83 | 100 | 33 | 83 | 33 |
| *Enterobacter aerogenes* | Pre | 4 | 0 | 100 | 0 | 0 | 100 | 0 | 100 | 100 | 100 | 0 | 0 | 100 | 0 | 0 | 0 |
| | Post | 2 | 0 | 100 | 0 | 0 | 100 | 0 | 100 | 100 | 100 | 0 | 0 | 100 | 0 | 100 | 0 |
| *Enterobacter cloacae* | Pre | 5 | 100 | 100 | 100 | 0 | 0 | 100 | 100 | 100 | 100 | 100 | 50 | 100 | 0 | 100 | 100 |
| | Post | 2 | 100 | 100 | 100 | 0 | 0 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 0 | 100 | 100 |
| *Haemophilus influenzae* | Pre | 3 | | 100 | 100 | | 100 | | | | | | | | 100 | | 0 |
| | Post | 5 | | 100 | 100 | | 100 | | | | | | | | 100 | | 0 |
| *K. pneumoniae* | Pre | 9 | 100 | 75 | 75 | 50 | 50 | 50 | 100 | 100 | 100 | 50 | 50 | 100 | 0 | 75 | 50 |
| | Post | 8 | 50 | 50 | 50 | 50 | 50 | 50 | 100 | 75 | 75 | 25 | 50 | 100 | 0 | 50 | 0 |
| *Proteus mirabilis* | Pre | 5 | 100 | 100 | 100 | 0 | 100 | 0 | 100 | 100 | 100 | 0 | 0 | 100 | 0 | 100 | 100 |
| | Post | 6 | 33 | 100 | 100 | 67 | 100 | 33 | 100 | 67 | 100 | 33 | 100 | 100 | 33 | 100 | 0 |
| *P. aeruginosa* | Pre | 12 | 86 | 100 | 71 | 0 | 0 | 71 | 100 | 0 | 57 | 86 | 0 | 100 | 0 | 100 | 0 |
| | Post | 13 | 89 | 100 | 78 | 0 | 0 | 78 | 100 | 22 | 78 | 89 | 0 | 89 | 0 | 100 | 11 |
| *Serratia marcescens* | Pre | 3 | 75 | 100 | 50 | 0 | 50 | 0 | 100 | 100 | 100 | 0 | 0 | 50 | 0 | 75 | 50 |
| | Post | 2 | 0 | 67 | 0 | 0 | 33 | 0 | 67 | 100 | 67 | 0 | 0 | 100 | 0 | 67 | 67 |

Abbreviations: GNB = gram-negative bacillus; ICU = intensive care unit; Pre = preintervention phase; Post = postintervention phase; AN = amikacin; AM = ampicillin; CAZ = ceftazidime; CRO = ceftriaxone; CZ = cefazolin; FOX = cefoxitin; FEP = cefepime; GM = gentamycin; IPM = imipenem; MI = minocycline; OFX = tarivid; PIP = piperacillin; SAM = Unasyn; SXT = bakter; TZP = piperacillin/tazobactam

advantages. First, the use of cephalosporins will be decreased, which should decrease the emergence of other troublesome resistant organisms, most notably enterococci and *Enterobacter* species [3,8,10]. As previously reported, imipenem and meropenem, members of the carbapenems class of β-lactam antibiotics, were considered to obtain a similar antimicrobial activity as piperacillin/tazobactam, and are among the most active antibiotics available for systemic use in humans [11,12].

Second, the consumption of carbapenems antibiotics was low in total amount compared with the consumption of piperacillin/tazobactam in this study. Similar observations were also made on the use of fourth-generation cephalosporins. Although the use of imipenem in an outbreak in New York was associated with the emergence of multiresistant *Acinetobacter baumannii* [3,14], there was no significant increase of multidrug resistant *Acinetobacter* spp., *Pseudomonas* spp., and other gram-negative non-fermenters in this study (Table 4). This could be due to the low consumption of carbapenems and fourth-generation cephalosporins compared with the consumption of piperacillin-tazobactam. A previous study found no increase in the prevalence of piperacillin/tazobactam-resistant *K. pneumoniae* in the 20-month study period when this agent was used [5,9]. The potential emergence of resistance to piperacillin /tazobactam in the absence of resistance to ceftazidime remains a significant concern.

The results of this study suggest that antibiotic-use measures are important in combination with traditional infection control measures for preventing the emergence of multidrug-resistant pathogens. Rice *et al* [13] noted no emphasis or increase in compliance with infection control measures, suggesting that antibiotic use measures were the most important intervention in their clonal outbreak. Antibiotic use intervention may be particularly important to control of multidrug-resistant *K. pneumoniae*, regardless of whether emergence is either clonal or polyclonal [16].

## References


1. Jacoby GA, Medeiros AA. More extended-spectrum β-lactamases. Antimicrob Agents Chemother 1991;35:1697-704.
2. Burwen DR, Banerjee SN, Gaynes RP .Ceftazidime resistance among selected nosocomial gram-negative bacilli in the United States. J Infect Dis 1944;170:1622-5.
3. Meyer KS, Urban C, Eagan JA, Raha JJ. Nosocomial outbreak of infection resistant to late-generation cephalosporins. Ann Intern Med 1933;119:353-8.
4. Rice LB, Willey SH, Papanicolaou GA, Medeires AA, Eliopoulou GM, Moellering RC Jr, Jocoby GA. Outbreak of ceftazidime resistance caused by extended-spectrum β-lactamases at a Massachusetts chronic-care facility. Antimicrob Agents Chemother 1990;34:2193-9.
5. Rice LB, Ecktein EC, De Vente J, Shlaes DM. Ceftazidime-resistant *Klebsiella pneumoniae* isolates recovered at the Cleveland Department of Veterans Affairs Medical Center. Clin Infect Dis 1996;23:118-124.
6. Naumovki L, Quinn JP, Miyashiro D, Patel M, Bush K, Singer SB, Graves D, Palekill T, Arvin AM. Outbreak of ceftazidime resistance due to a novel extended-spectrum β-lactamase in isolates from cancer patients. Antimicrob Agents Chemother 1992;36:1991-6.
7. Patterson JE, Hardin TC, Kelly CA, Garcia RC, Jorgensen JH. Association of antibiotic utilization measures and control of multiple-drug resistance in *Klebsiella pneumoniae*. Infect Control Hosp Epidemiol 2002;21:455-8.
8. Pallares R, Pujol M, Pena C, Ariea J, Martin R, Gudiol F. Cephalosporins as a risk factor for nosocomial *Enterococcus faecalis* bacteremia: a matched case-control study. Arch Intern Med. 1993;153:1581-6.
9. Piroth L, Aube H, Doise JM, Vincent-Martin M. Spread of extended-spectrum β-lactamase-producing *Klebsiella pneumoniae*: are β-lactamase inhibitors of therapeutic value? Clin Infect Dis 1998;27:76-80.
10. Rice LB, Carias LL, Shales DM. *In vivo* efficacies of β-lactamase inhibitor combinations agent a TEM-26-producing strain of *Klebsiella pneumoniae*. Antimicrob Agents Chemother 1994;38:2663-4.
11. Hellinger WC, Brewer NS. Carbapenems and monobactams: imipenem, meropenem and aztreonam. Mayo Clin Proc 1999; 74:420-34.
12. Nathwani D, Wood MJ. Penicillins: a current review of their clinical pharmacology and the therapeutic use. Drugs 1993; 45:866-94.
13. Monnet DL, Buddke JW, EdwardsJR, Culver DH, Tolson JS, Martone WJ, Tenover FC, Gaynes RP. Evidence of interhospital transmission of extended-spectrum β-lactam resistant *Klebsiella pneumoniae* in the United States1986 to 1993. Infect Control Hosp Epidemiol 1997;18:492-8.
14. Sader HS, Pfaller MA, Jones RN. Prevalence of important pathogens and the antimicrobial activity of parenteral drugs at numerous medical centers in the United States II: study of the intra- and inter-laboratory dissemination of extended-spectrum β-lactamase-producing *Enterobacteriaceae*. Diagn Microbiol Infect Dis 1994;20:203-8.
15. Shannon K, Stapleton P, Xiang X, Johnson A, Beattie H, EI Bakri F, Cookson B, French G. Extended spectrum β-lactamase producing *Klebsiella pneumoniae* strains causing nosocomial outbreaks of infection in the United Kingdom. J Clin Microbiol 1998;36:3105-10.
16. Chanal CM, Sirot DL, Petit A, Labia R, Morand A, Sirot JL, Cluzel RA. Multiplicity of TEM-derived β-lactamases from *Klebsiella pneumoniae* strains isolated at the same hospital and relationships between the responsible plasmids. Antimicrob Agents Chemother 1989;33:1915-20.