Reduction in the Incidence of Methicillin-Resistant *Staphylococcus aureus* and Ceftazidime-Resistant *Klebsiella pneumoniae* Following Changes in a Hospital Antibiotic Formulary

David Landman, Mira Chockalingam, and John M. Quale

From the Section of Infectious Diseases, Department of Veterans Affairs Medical Center at Brooklyn, and the Division of Infectious Diseases, S.U.N.Y. Health Science Center at Brooklyn, Brooklyn, New York

In 1995, changes in our hospital formulary were made to limit an outbreak of vancomycin-resistant enterococci and resulted in decreased usage of cephalosporins, imipenem, clindamycin, and vancomycin and increased usage of β-lactam/β-lactamase-inhibitor antibiotics. In this report, the effect of this formulary change on other resistant pathogens is described. Following the formulary change, there was a reduction in the monthly number (mean $\pm$ SD) of patients with methicillin-resistant *Staphylococcus aureus* (from 21.9 $\pm$ 8.1 to 17.2 $\pm$ 7.2 patients/1,000 discharges; $P = .03$) and ceftazidime-resistant *Klebsiella pneumoniae* (from 8.6 $\pm$ 4.3 to 5.7 $\pm$ 4.0 patients/1,000 discharges; $P = .02$). However, there was an increase in the number of patients with cultures positive for cefotaxime-resistant *Acinetobacter* species (from 2.4 $\pm$ 2.2 to 5.4 $\pm$ 4.0 patients/1,000 discharges; $P = .02$). Altering an antibiotic formulary may be a possible mechanism to contain the spread of selected resistant pathogens. However, close surveillance is needed to detect the emergence of other resistant pathogens.

In the past decade, outbreaks of emerging resistant pathogens (e.g., vancomycin-resistant enterococci and Enterobacteriaceae having extended-spectrum β-lactamases) have been described [1–7], and established pathogens (e.g., methicillin-resistant *Staphylococcus aureus*) have persisted [8–10] and infiltrated the community [9, 10]. Guidelines have emphasized aggressive infection-control measures to limit the spread of resistant bacteria within hospitals [11, 12]. However, it is troubling that many of these outbreaks have occurred in the era of universal precautions, and investigations describing the failure of a variety of infection-control measures have been reported [1–3, 8, 9, 13, 14]. Clearly, new approaches are needed to limit the nosocomial spread of resistant bacteria.

See editorial response by Rice on pages 1067–70.

In 1993, infection-control measures were instituted at our hospital to limit the spread of vancomycin-resistant enterococci. When the failure of these measures was realized [2], we attempted to control the outbreak by changing the hospital formulary. In May 1995, the use of β-lactam/β-lactamase-inhibitor antibiotics was emphasized and the use of third-generation cephalosporins, vancomycin, and clindamycin was restricted. The success of this intervention to limit the spread of vancomycin-resistant enterococci and *Clostridium difficile* has been previously reported [15]. In this study, we examined the effect of this intervention on other nosocomial pathogens.

Methods

The Department of Veterans Affairs Medical Center at Brooklyn is a university-affiliated tertiary care facility. Microbiology records from 1 January 1993 through 30 April 1997 were reviewed to identify all patients whose cultures yielded the following bacteria: methicillin-resistant *S. aureus,* ceftazidime-resistant *Klebsiella pneumoniae,* ceftazidime-resistant *Enterobacter* species, ceftazidime-resistant *Pseudomonas aeruginosa,* ticarcillin-resistant *P. aeruginosa,* and cefotaxime-resistant *Acinetobacter* species. These organisms were selected to assess the impact of formulary changes on the major nosocomial pathogens at our institution. Only patients whose cultures of blood or other sterile body fluids or of wound, respiratory tract, or urinary tract specimens yielding the targeted pathogens were included. The number of new patients each month who had a positive culture was recorded. For each pathogen, patients were included only once. All isolates were identified with standard microbiological methods, and susceptibility testing was performed according to the guidelines of the National Committee for Clinical Laboratory Standards [16]. Of the antipseudomonal penicillins, only ticarcillin was routinely used in susceptibility testing. In 1996, the laboratory tested the susceptibility of selected resistant isolates to piperacillin/tazobactam.

In May 1995, approval by an infectious diseases physician was required prior to the administration of third-generation cephalosporins, clindamycin, and vancomycin. Ampicillin/sul-

Received 16 March 1998; revised 8 December 1998.

Presented in part at the 35th Annual Meeting of the Infectious Diseases Society of America, held in September 1997 in San Francisco.

Reprints or correspondence: Dr. John M. Quale, Division of Infectious Diseases, Box 77, S.U.N.Y. Health Science Center at Brooklyn, 800 Poly Place, Brooklyn, New York 11203 (jquale@netmail.hscbklyn.edu).

Clinical Infectious Diseases 1999; 28:1062–6

1058–4838/99/2805–0017$03.00

bactam and piperacillin/tazobactam were added to the formulary, and their use was suggested in place of the cephalosporins. In addition, pharmacy records from 1 January 1993 through 31 December 1996 were reviewed to determine the overall antibiotic usage per month. The usage and expenditures for the following antibiotics were reviewed: ampicillin, penicillin, piperacillin, nafcillin, ampicillin/sulbactam, piperacillin/tazobactam, cefazolin, cefoxitin, cefotaxime, ceftazidime, imipenem, ciprofloxacin, vancomycin, clindamycin, metronidazole, amikacin, and gentamicin. To adjust for fluctuating prices, antibiotic costs were calculated with use of 1996 prices.

Infection-control measures directed against vancomycin-resistant enterococci were initiated in April 1993, as previously described [2]. In May 1995, in addition to the changes in the hospital antibiotic formulary, contact precautions were expanded to also include patients with *C. difficile* colitis and diarrhea of unknown etiology [15]. No specific precautions were undertaken for patients whose cultures yielded any of the bacteria studied in this investigation.

Statistical analysis. The incidence of each nosocomial pathogen is reported as the number of new patients with a positive culture per 1,000 discharges per month from the medical and surgical services. The usage of antibiotics is reported as grams utilized per month. Results are expressed as mean ± SD. Student's *t* test and χ^2 analysis were used to compare preintervention and postintervention data. Stepwise multiple linear regression analysis was performed to determine any correlation between the number of patients with cultures yielding methicillin-resistant *S. aureus* or ceftazidime-resistant *K. pneumoniae* and the following variables: number of discharges, average length of stay, and the usage of vancomycin, clindamycin, and third-generation cephalosporins. All data were analyzed with use of TRUE EPISTAT software (Epistat Services, Houston). A two-tailed *P* value of $\leq .05$ was considered significant.

Results

Usage of the three targeted antibiotics (cefotaxime, clindamycin, and vancomycin) significantly decreased following the intervention in May 1995. Monthly usage of cefotaxime fell from 1,432 ± 283 to 164 ± 78 g/mo ($P < .001$), that of clindamycin from 594 ± 167 to 108 ± 62 g/mo ($P < .001$), and that of vancomycin from 588 ± 136 to 313 ± 98 g/mo ($P < .001$). In addition, significant reductions in the use of four antibiotics not targeted by the intervention were observed: cefazolin (from 724 ± 187 to 531 ± 209 g/mo [$P = .002$]), ceftazidime (from 677 ± 197 to 229 ± 117 g/mo [$P < .001$]), imipenem (from 136 ± 57 to 89 ± 47 g/mo [$P = .004$]), and gentamicin (from 43.8 ± 14.1 to 30.6 ± 6.9 g/mo [$P < .001$]). Administration of the two β-lactamase-inhibitor combination antibiotics dramatically increased: that of ampicillin/sulbactam to 3,326 ± 853 g/mo and that of piperacillin/tazobactam to 1,898 ± 761 g/mo. Total antibiotic costs before and after the intervention did not vary significantly ($29,457 ± $3,866 vs. $28,085 ± $5,749 per month [$P = .3$]).

For the 29 months before the intervention, the monthly incidence of new patients with cultures positive for methicillin-resistant *S. aureus* was 21.9 ± 8.1 per 1,000 discharges (figure 1). For the 23 months following the intervention, this decreased to 17.2 ± 7.2 patients per 1,000 discharges ($P = .03$). The incidence of new patients with ceftazidime-resistant *K. pneumoniae* also decreased, from 8.6 ± 4.3 to 5.7 ± 4.0 per 1,000 discharges ($P = .02$; figure 1). Susceptibility testing of the isolates from the 50 patients identified just prior to the intervention in May 1995 revealed that only 6% were resistant to cefotaxime and cefoxitin, suggesting the presence in most isolates of a β-lactamase that could be inhibited by sulbactam, tazobactam, and clavulanate. Of the isolates from the 50 patients identified immediately following the intervention, 10% were resistant to cefotaxime and cefoxitin ($P = .07$).

Compared with that in the baseline period, there was no change in the incidence of new patients with ceftazidime-resistant *Enterobacter* species (5.3 ± 3.2 vs. 4.1 ± 2.0 per 1,000 discharges [$P = .10$]) or ceftazidime-resistant *P. aeruginosa* (3.8 ± 2.9 vs. 3.3 ± 2.8 per 1,000 discharges [$P = .5$]). Similarly, there was no difference in the incidence of new patients with ticarcillin-resistant *P. aeruginosa* before and after the intervention (11.4 ± 4.7 vs. 12.2 ± 4.2 [$P = .5$]). However, the incidence of new patients with cultures positive for cefotaxime-resistant *Acinetobacter* species rose significantly (figure 1), from 2.4 ± 2.2 to 5.4 ± 4.0 per 1,000 discharges before and after the intervention, respectively ($P = .02$). Of 25 isolates collected in 1997, all but one were resistant to piperacillin/tazobactam.

The number of hospital discharges from the medical and surgical services averaged 569 ± 50 per month before the intervention. Following the intervention, this decreased to 513 ± 50 per month ($P < .001$). In addition, the average length of stay on the acute care services also decreased, from 15.0 ± 1.5 to 13.2 ± 1.8 days ($P < .001$). Multiple regression analysis revealed that only usage of third-generation cephalosporins was significantly correlated with the number of patients with methicillin-resistant *S. aureus* ($P = .003$) and ceftazidime-resistant *K. pneumoniae* ($P < .001$). The number of new patients requiring contact isolation (those with *C. difficile* or vancomycin-resistant enterococci) also decreased following the intervention, from 10.7 ± 4.7 patients per month to 6.2 ± 4.5 patients per month ($P = .002$).

Review of microbiological records revealed that 61% of 2,447 *S. aureus* isolates collected from 1993 through 1995 were susceptible to methicillin; in 1996, 65% of 678 isolates were susceptible ($P = .04$). For *K. pneumoniae,* 66% of 1,374 isolates received by the microbiology laboratory from 1993 through 1995 were susceptible to ceftazidime, compared with 88% of 336 isolates collected in 1996 ($P < .001$). The percentage of isolates of *P. aeruginosa* susceptible to ceftazidime also increased, from 92% of 1,560 isolates collected from 1993

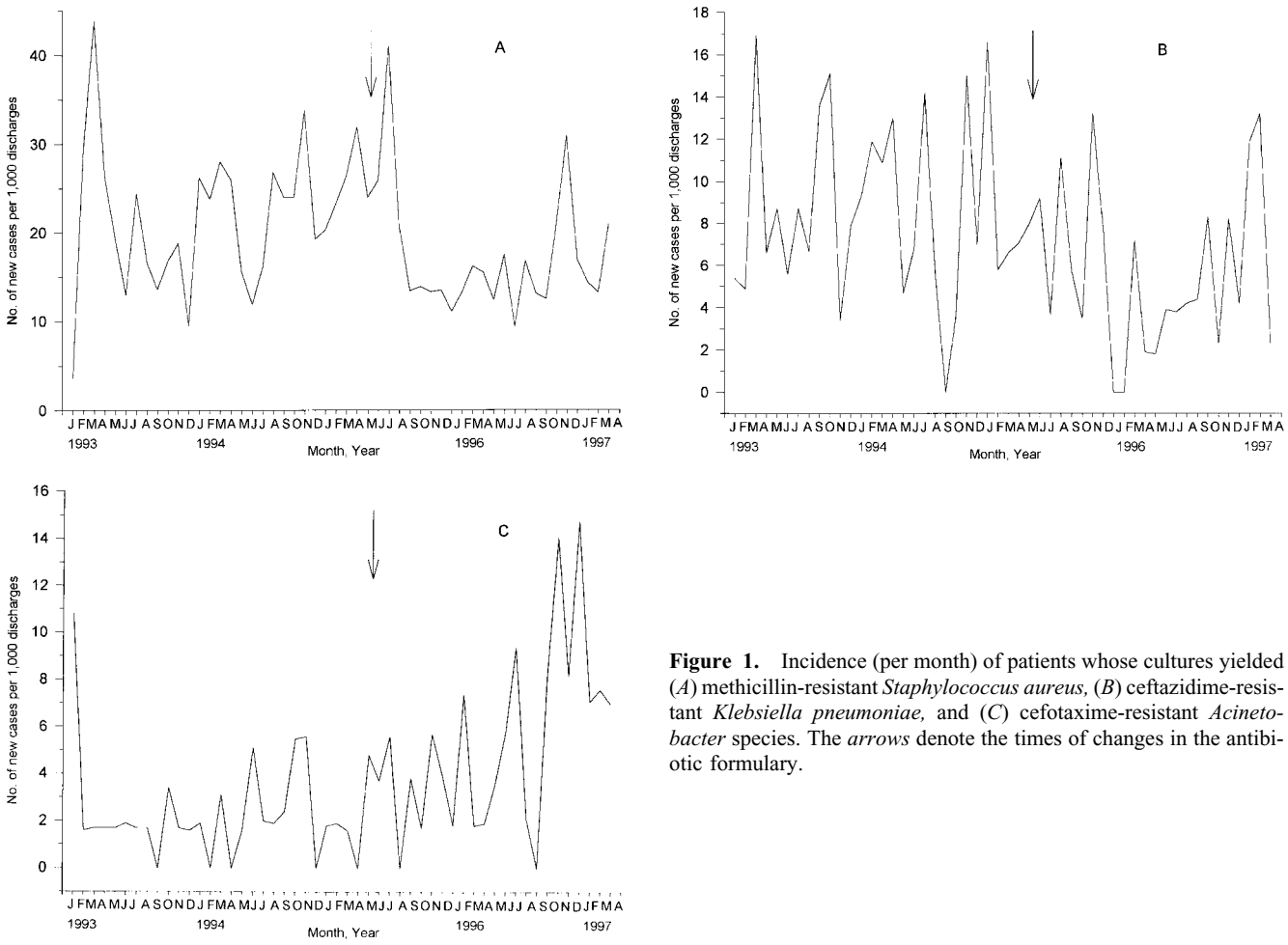

Figure 1. Incidence (per month) of patients whose cultures yielded (*A*) methicillin-resistant *Staphylococcus aureus,* (*B*) ceftazidime-resistant *Klebsiella pneumoniae,* and (*C*) cefotaxime-resistant *Acinetobacter* species. The *arrows* denote the times of changes in the antibiotic formulary.

through 1995 to 96% of 438 isolates collected in 1996 ($P = .003$). There was no change in the percentage of *Enterobacter* species isolates susceptible to ceftazidime or in the percentage of *P. aeruginosa* isolates susceptible to ticarcillin. There was a significant decrease in the percentage of *Acinetobacter* species isolates susceptible to cefotaxime, from 51% of 392 isolates collected from 1993 through 1995 to 37% of 155 isolates collected in 1996 ($P = .005$).

Discussion

There is an increasing trend for nosocomial infections to be caused by more-resistant pathogens [17], and as new antimicrobial agents have been developed, bacteria have acquired new mechanisms of resistance [18]. Although infection-control protocols may help limit the spread of nosocomial pathogens, once introduced into the hospital, pathogens are often difficult to eradicate [1–3, 8–10, 13, 14]. The emergence of a particular pathogen may be enhanced by the selective pressures exerted by the antibiotics used at a hospital. Changing the antibiotic usage may be an effective method for limiting the spread of resistant pathogens.

Methicillin-resistant *S. aureus* is a frequent nosocomial pathogen [19]. We noted a significant decline in the incidence of patients with cultures positive for methicillin-resistant *S. aureus* following a reduction in vancomycin, clindamycin, and cephalosporin usage and an increase in ampicillin/sulbactam and piperacillin-tazobactam usage. Although most methicillin-resistant *S. aureus* isolates are resistant to β-lactamase-inhibitor combination antibiotics, negating the effect of penicillinase restores much of the activity of ampicillin [20–22]. β-Lactam/β-lactamase-inhibitor antibiotics have shown activity in the treatment of experimental endocarditis due to methicillin-resistant *S. aureus* [20–22], although high levels may be required [22, 23]. Therefore, colonization with methicillin-resistant *S. aureus* may be less likely to occur in a patient receiving a β-lactam/β-lactamase-inhibitor antibiotic (than in one receiving a cephalosporin). Emphasizing this class of antibiotics may reduce the incidence of infection with this pathogen.

K. pneumoniae strains having extended-spectrum β-lactamases have been isolated with increasing frequency [4], and hospital outbreaks have been described [5–7]. Some of these outbreaks have involved strains with β-lactamases inhibited

by β-lactamase inhibitors [5–7]. Many of our isolates were susceptible to cefoxitin or cefotaxime, a trait characteristic of *K. pneumoniae* with β-lactamases effectively inhibited by clavulanate, sulbactam, or tazobactam [5, 7, 24–26]. Experimental infections involving such strains have been successfully treated with β-lactam/β-lactamase inhibitors [27], although increasing levels of the inhibitor may be required [28–30].

The decreasing incidence of patients with ceftazidime-resistant *K. pneumoniae* following our intervention is likely due to the ability of the β-lactamase-inhibitor antibiotics to prevent colonization or infection with these pathogens. Similar decreases were not noted for ceftazidime-resistant *Enterobacter* species or *P. aeruginosa,* which are more likely to carry chromosomal β-lactamases unaffected by β-lactamase inhibitors [18, 25, 31].

Unfortunately, a significant increase in resistant *Acinetobacter* isolates was noted following this intervention; virtually all were resistant to β-lactamase-inhibitor antibiotics. Therefore, while our intervention had a significant impact on the number of patients with methicillin-resistant *S. aureus* and ceftazidime-resistant *K. pneumoniae,* close surveillance is needed to detect the emergence of other resistant pathogens.

Other factors may have contributed to the decline in the number of patients with methicillin-resistant *S. aureus* and ceftazidime-resistant *K. pneumoniae.* It is unlikely that this decline was related to infection-control practices, since the number of patients in isolation actually decreased following the intervention. Consistent with a nationwide trend, there has been a significant decrease in the average length of stay at our hospital. Shorter hospital stays may reduce the likelihood that patients will be exposed to nosocomial pathogens. However, despite the shorter length of stay, the number of patients with other ceftazidime-resistant pathogens remained the same (or increased). We found it compelling that the only isolation of methicillin-resistant *S. aureus* and ceftazidime-resistant *K. pneumoniae,* microorganisms inhibited by β-lactamase-inhibitor antibiotics, decreased. Moreover, multiple linear regression analysis supported the observation that the change in the formulary, and not the length of stay, was associated with the number of patients with these two pathogens.

Changes in antibiotic usage have contributed to the control of outbreaks of *C. difficile* [13, 15], vancomycin-resistant enterococci [15], and ceftazidime-resistant *K. pneumoniae* [7, 32]. A recent report noted a significant decline in infections due to resistant *Klebsiella pneumoniae* when third-generation cephalosporin use decreased and imipenem and piperacillin/tazobactam use increased [32]. If surveillance reveals the emergence of a resistant pathogen at a particular hospital, the overall susceptibility trends and antibiotic usage should be reviewed. Altering the antibiotic formulary on the basis of this information may be a possible mechanism to contain the spread of the pathogen.

References

1. Morris JG Jr, Shay DK, Hebden JN, et al. Enterococci resistant to multiple antimicrobial agents, including vancomycin: establishment of endemicity in a university medical center. Ann Intern Med **1995**;123:250–9.
2. Quale J, Landman D, Atwood E, et al. Experience with a hospital-wide outbreak of vancomycin-resistant enterococci. Am J Infect Control **1996**;24:372–9.
3. Wells CL, Juni BA, Cameron SB, et al. Stool carriage, clinical isolation, and mortality during an outbreak of vancomycin-resistant enterococci in hospitalized medical and/or surgical patients. Clin Infect Dis **1995**; 21:45–50.
4. Burwen DR, Banerjee SN, Gaynes RP. Ceftazidime resistance among selected nosocomial gram-negative bacilli in the United States. J Infect Dis **1994**;170:1622–5.
5. Naumovski L, Quinn JP, Miyashiro D, et al. Outbreak of ceftazidime resistance due to a novel extended-spectrum beta-lactamase in isolates from cancer patients. Antimicrob Agents Chemother **1992**;36:1991–6.
6. Brun-Buisson C, Legrand P, Philippon A, Montravers F, Ansquer M, Duval J. Transferable enzymatic resistance to third-generation cephalosporins during nosocomial outbreak of multiresistant *Klebsiella pneumoniae.* Lancet **1987**;2:302–6.
7. Meyer KS, Urban C, Eagan JA, Berger BJ, Rahal JJ. Nosocomial outbreak of *Klebsiella* infection resistant to late-generation cephalosporins. Ann Intern Med **1993**;119:353–8.
8. Cohen SH, Morita MM, Bradford M. A seven-year experience with methicillin-resistant *Staphylococcus aureus.* Am J Med **1991**;91(suppl 3B): 233–7.
9. Linnemann Jr CC, Moore P, Staneck JL, Pfaller MA. Reemergence of epidemic methicillin-resistant *Staphylococcus aureus* in a general hospital associated with changing staphylococcal strains. Am J Med **1991**; 91(suppl 3B):238–44.
10. Layton MC, Hierholzer WJ Jr, Patterson JE. The evolving epidemiology of methicillin-resistant *Staphylococcus aureus* at a university hospital. Infect Control Hosp Epidemiol **1995**;16:12–7.
11. Anonymous. Guidelines for the control of epidemic methicillin-resistant *Staphylococcus aureus:* report of a combined working party of the Hospital Infection Society for Antimicrobial Chemotherapy. J Hosp Infect **1986**;7:193–201.
12. Centers for Disease Control and Prevention. Recommendations for preventing the spread of vancomycin resistance. Recommendations of the Hospital Infection Control Practices Advisory Committee (HICPAC). MMWR Morb Mortal Wkly Rep **1995**;44(RR-12):1–13.
13. Pear SM, Williamson TH, Bettin KM, Gerding DN, Galgiani JN. Decrease in nosocomial *Clostridium difficile*–associated diarrhea by restricting clindamycin use. Ann Intern Med **1994**;120:272–7.
14. Nelson DE, Auerbach SB, Baltch AL, et al. Epidemic *Clostridium difficile*–associated diarrhea: role of second- and third-generation cephalosporins. Infect Control Hosp Epidemiol **1994**;15:88–94.
15. Quale J, Landman D, Saurina G, Atwood E, Ditore V, Patel K. Manipulation of a hospital antimicrobial formulary to control an outbreak of vancomycin-resistant enterococci. Clin Infect Dis **1996**;23:1020–5.
16. National Committee for Clinical Laboratory Standards. Performance standards for antimicrobial disk susceptibility tests: approved standard. NCCLS document M2-A5. Villanova, Pennsylvania: National Committee for Clinical Laboratory Standards, **1993**.
17. Schaberg DR, Culver DH, Gaynes RP. Major trends in the microbial etiology of nosocomial infection. Am J Med **1991**;91(suppl 3B):72–5.
18. Gold HS, Moellering RC Jr. Antimicrobial-drug resistance. N Engl J Med **1996**;335:1445–53.
19. Wenzel RP, Nettleman MD, Jones RN, Pfaller MA. Methicillin-resistant *Staphylococcus aureus:* implications for the 1990s and effective control measures. Am J Med **1991**;91(suppl 3B):221–7.
20. Cantoni L, Wenger A, Glauser MP, Bille J. Comparative efficacy of amoxicillin-clavulanate, cloxacillin, and vancomycin against methicillin-sensitive and methicillin-resistant *Staphylococcus aureus* endocarditis in rats. J Infect Dis **1989**;159:989–93.
21. Franciolli M, Bille J, Glauser MP, Moreillon P. Beta-lactam resistance mechanisms of methicillin-resistant *Staphylococcus aureus.* J Infect Dis **1991**;163:514–23.

22. Hirano L, Bayer AS. Beta-lactam-beta-lactamase-inhibitor combinations are active in experimental endocarditis caused by beta-lactamase-producing oxacillin-resistant staphylococci. Antimicrob Agents Chemother **1991**;35:685–90.
23. Chambers HF, Kartalija M, Sande M. Ampicillin, sulbactam, and rifampin combination treatment of experimental methicillin-resistant *Staphylococcus aureus* endocarditis in rabbits. J Infect Dis **1995**; 171:897–902.
24. Bauernfeind A, Chong Y, Schweighart S. Extended broad spectrum beta-lactamase in *Klebsiella pneumoniae* including resistance to cephamycins. Infection **1989**;17:316–21.
25. Moosdeen F. The evolution of resistance to cephalosporins. Clin Infect Dis **1997**;24:487–93.
26. Jacoby GA, Carreras I. Activities of beta-lactam antibiotics against *Escherichia coli* strains producing extended-spectrum beta-lactamases. Antimicrob Agents Chemother **1990**;34:858–62.
27. Rice LB, Carias LL, Shlaes DM. In vivo efficacies of beta-lactam-beta-lactamase inhibitor combinations against a TEM-26-producing strain of *Klebsiella pneumoniae.* Antimicrob Agents Chemother **1994**;38:2663–4.
28. Leleu G, Kitzis MD, Vallois JM, Gutmann L, Decazes JM. Different ratios of the piperacillin-tazobactam combination for treatment of experimental meningitis due to *Klebsiella pneumoniae* producing the TEM-3 extended-spectrum beta-lactamase. Antimicrob Agents Chemother **1994**; 38:195–9.
29. Mentec H, Vallois JM, Bure A, Saleh-Mghir A, Jehl F, Carbon C. Piperacillin, tazobactam, and gentamicin alone or combined in an endocarditis model of infection by a TEM-3-producing strain of *Klebsiella pneumoniae* or its susceptible variant. Antimicrob Agents Chemother **1992**;36: 1883–9.
30. Caron F, Gutmann L, Bure A, et al. Ceftriaxone-sulbactam combination in rabbit endocarditis caused by a strain of *Klebsiella pneumoniae* producing extended–broad spectrum TEM-3 beta lactamase. Antimicrob Agents Chemother **1990**;34:2070–4.
31. Jacoby GA, Medeiros AA. More extended-spectrum beta-lactamases. Antimicrob Agents Chemother **1991**;35:1697–704.
32. Pena C, Pujol M, Ardanuy C, et al. Epidemiology and successful control of a large outbreak due to *Klebsiella pneumoniae* producing extended-spectrum *B*-lactamases. Amtimicrob Agents Chemother **1998**;42:53–8.