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# Clinical Isolation and Resistance Patterns of and Superinfection with 10 Nosocomial Pathogens after Treatment with Ceftriaxone versus Ampicillin-Sulbactam

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**Isolation of pathogens from clinical cultures and their resistance patterns may be altered by antecedent antibiotic treatment. The objective of this study was to assess the influence of treatment with ceftriaxone versus that with ampicillin-sulbactam on recovery and superinfections with 10 nosocomial pathogens. The study was designed as a historical cohort study, using a propensity score to adjust for confounding by indication and multivariate survival analyses to adjust for other confounding. Two thousand four hundred forty-five patients were treated with ampicillin-sulbactam, and 1,308 were treated with ceftriaxone. The study analyzed two outcomes: (i) recovery of pathogens from clinical cultures and (ii) microbiologically documented infections. Data were obtained from administrative, pharmacy, clinical, and laboratory databases and by chart extraction. Following treatment, new isolation of at least 1 of the 10 target pathogens occurred for 244 patients. After adjustment, more infections occurred in the ampicillin-sulbactam group (hazard ratio [HR], 1.55; $P = 0.009$). This was observed with all gram-negative rods combined (HR, 3.6; $P < 0.001$) and with each genus of the family *Enterobacteriaceae*. No differences in isolation of gram-positive bacteria were evident ($P = 0.33$). Microbiologically documented superinfections occurred in 172 patients and were less frequent in the ceftriaxone group (3.8% versus 5%; HR, 1.6; $P = 0.015$). All the *Escherichia coli* and *Klebsiella* spp. isolates were susceptible to ceftriaxone, but half were resistant to ampicillin-sulbactam. The prevalence of oxacillin resistance among *Staphylococcus aureus* isolates was higher in the ceftriaxone group (63% versus 31%; odds ratio, 3.8; $P = 0.08$). Differences in the rates of superinfections and the likely causative organisms following treatment with ceftriaxone or ampicillin-sulbactam were evident. This may guide clinicians in empirical choices of antibiotics to treat superinfection.**

Nosocomial infections are associated with adverse outcomes and occur in 8% of hospitalized patients (8, 10). Many of the patients in whom nosocomial infections occur had previously been exposed to antibiotics either for prophylaxis or as a treatment. In such cases, these infections may appropriately be viewed as nosocomial superinfections. The rate and patterns of isolation of pathogens from clinical cultures, the resistance patterns, and the types of nosocomial infections caused by these organisms may be altered by antecedent antibiotic treatment. Antibiotic treatment can reduce the incidence of infections with certain organisms (prophylactic effect) but may not modify others and may even increase the incidence of infections with some organisms. These effects would be attributable to direct activity against the causative organism and/or to effects on competing microflora (5, 6, 11, 16, 17).

Variation in the spectrum of activity as well as pharmacodynamic factors may result in differences between agents in the rates and distribution of the microorganisms causing superinfection. Moreover, agents may differ in the propensity to select for bacterial strains resistant to antimicrobial drugs, a process that may have particularly severe consequences, resulting in increased mortality, morbidity, and costs (1, 9, 12).

Differences in effectiveness between antibiotic agents are studied in randomized prospective trials. These studies are usually not large enough to allow detection of differences in uncommon events, such as superinfections. Traditionally, these events have been examined by case control studies analyzing risk factors for infections with specific organisms. However, this study design is less adequate for assessing a spectrum of causative agents, since patients are recruited according to the presence of the outcome. Here we offer an alternative study design, a retrospective observational cohort study. This study design enables the enrollment of patients according to the specific antimicrobial treatment and allows comparison between a number of uncommon outcomes. Moreover, it allows better adjusting for confounding by indication for treatment, by using the propensity score method (3, 13, 14).

To assess the influence of antibiotic treatment on clinical isolation and superinfections with important nosocomial pathogens, we examined two agents that are used to treat a similar spectrum of clinical conditions, ceftriaxone and ampicillin-sulbactam. We compared the rates of isolation of bacteria from clinical cultures and superinfections following treatment with these two agents. We also examined which pathogens are likely to cause these events in each group and their resistance profiles.

## MATERIALS AND METHODS

The Beth Israel Deaconess Medical Center—West Campus is a 320-bed urban tertiary-care teaching hospital in Boston, Mass. It utilizes 24 intensive care unit (ICU) beds, and there are approximately 12,000 admissions per year.

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TABLE 1. Baseline characteristics of the 3,753 patients treated with ceftriaxone or ampicillin-sulbactam

| Variable | Value for group | | *P* value |
|---|---|---|---|
| | Ceftriaxone | Ampicillin-sulbactam | |
| Total no. of patients | 1,308 | 2,445 | |
| Follow-up (days) | 9,266 | 18,925 | |
| Age in mean years (95% confidence interval) | 66.5 (65.7–67.4) | 61.8 (61.2–62.5) | <0.0001 |
| No. female (%) | 633 (48%) | 936 (38%) | <0.0001 |
| Hospitalization until treatment (days) | 1 | 0 | |
| No. of patients (%) with: | | | |
| Cardiovascular disease | 955 (73) | 1,694 (69%) | 0.017 |
| Cancer | 151 (11) | 247 (10%) | 0.17 |
| Diabetes | 603 (46) | 1,639 (67%) | <0.0001 |
| Liver disease | 105 (8) | 473 (19%) | <0.0001 |
| Lung disease | 273 (21) | 215 (9%) | <0.0001 |
| ICU admission | 429 (33) | 290 (9%) | <0.0001 |
| Major surgery | 349 (27) | 996 (41%) | <0.0001 |

Data were collected from administrative, pharmacy, and laboratory computerized databases using a relational database management system (Access; Microsoft Corp., Redmond, Wash.). The databases and methods of data collection were described previously (15). The presence of infections (according to the CDC criteria, modified so as not to include asymptomatic bacteriuria) (7) was confirmed by reviewing medical records and laboratory, pathology, and radiology results.

Gram-positive organisms had been identified in clinical specimens submitted to the microbiology laboratory by using the Gram-positive Identification Panel (Dade International Inc., West Sacramento, Calif.). Gram-negative bacilli had been identified by using the Gram-negative Identification Panel Type II (Dade International Inc.). Susceptibility had been determined by microdilution broth testing (MicroScan; Dade International Inc.). Isolates with intermediate susceptibility were considered resistant in order to match better treatment decisions in clinical settings (definition of susceptibility for ceftriaxone, <16 μg/ml, and for ampicillin-sulbactam, <16 and 8 μg/ml for ampicillin and sulbactam, respectively).

**Definitions and study design.** The study is designed as a historical cohort study. Patients were included in the cohort if they had been treated with intravenous ceftriaxone or ampicillin-sulbactam during a hospital stay between 31 August 1994 and 1 September 1996. The patients were monitored from the start of the antibiotic treatment to discharge from the hospital or to the beginning of treatment with another antibiotic agent (except aminoglycosides, metronidazole, and clindamycin). We chose to examine two agents that are used for similar indications, but since ampicillin-sulbactam is active against many anaerobes and ceftriaxone is not, when ceftriaxone is used to treat mixed infections it is used in combination with metronidazole or clindamycin. To allow similar indications to be included, we did not exclude patients treated with these agents, and we adjusted for their use in the analysis.

The primary outcomes were isolation of a pathogen from a clinical specimen (colonization and infection) and superinfection by any of the study pathogens. Each case was evaluated to determine the development of superinfection caused by these pathogens. If an organism was isolated from the site of infection within the 30 days prior to the start of treatment and was isolated again during or after treatment, it was not assigned as related to treatment.

The 10 most prevalent nosocomial pathogens (excluding coagulase-negative *Staphylococcus*) were examined: *Staphylococcus aureus*, *Enterococcus* spp., *Escherichia coli*, *Enterobacter* spp., *Klebsiella* spp., *Proteus* spp., *Serratia* spp., *Citrobacter* spp., *Pseudomonas aeruginosa*, and *Stenotrophomonas maltophila*. The first two were grouped as gram positive, and the last eight were grouped as gram negative.

To explore for confounding, the following variables were analyzed: age, gender, underlying diseases as recorded by the admitting physician and weighted comorbidities (2), culture site, surgical procedures (considered major when performed in the operating room; not debridement or tracheostomy), ICU stays, the time interval between the hospital admission and treatment, and the bacterial pathogens that were isolated from the patient before treatment. All of these factors were considered baseline variables. Since no active surveillance had been performed during the study period, a score was constructed in order to adjust for the intensity of culturing. This score was calculated as the average numbers of cultures per day during the follow-up period.

**Statistical analysis.** Statistics were run on SAS (SAS Institute Inc., Cary, N.C.) and Stata (Stata Corp., College Station, Tex.) software. A propensity score was constructed to control for confounding by indication (3, 13, 14). The propensity score was constructed using the prediction probabilities of a logistic regression model. All baseline variables were candidates for the model and were selected for the model in a stepwise manner.

The outcomes of the study were examined using survival analysis in order to allow variable follow-up periods. Univariate and multivariate Cox proportional hazard models were used to address the outcomes (4). Variables with a *P* value of <0.2 in univariate analysis were considered candidates for multivariate analysis and added to a model including the study drugs to control for confounding. A forward stepwise procedure was used to select independent variables while forcing inclusion of study drugs and the propensity score into the model. Variables that were not retained in the model by this procedure were then tested for confounding by adding them one at a time to the model and examining their effects on the beta coefficients. Variables which caused substantial confounding (a change in the beta coefficient of more than 10%) were included in the final model. The proportional hazard assumption was examined for each of the variables included in the final Cox model.

All statistical tests were two-tailed. A *P* value of ≤0.05 was considered significant.

## RESULTS

During the study period, 5,447 patients were treated with the study drugs. Patients treated with another antibiotic before or simultaneously with the study drugs were excluded, but patients treated with combinations of the study agent and an aminoglycoside (1.5% of each group), metronidazole (1.9% of each group), or clindamycin (15% of the ceftriaxone group versus 0.5% of the ampicillin-sulbactam group) were not excluded. The study cohort included 3,753 patients, 2,445 of whom were treated with ampicillin-sulbactam and 1,308 of whom were treated with ceftriaxone. Sites of infections triggering antibiotic treatment included the respiratory tract (38.9% of the ceftriaxone group versus 27.3% of the ampicillin-sulbactam group), bone and soft tissue (26.4 versus 37.2%, respectively), intra-abdominal sites (11.8 versus 16.1%, respectively), urine (16.2% versus 14.4%, respectively) and blood (6.7 versus 5%, respectively). The study patients were followed for a total of 27,482 hospital days. The patients' characteristics are summarized in Table 1. The organisms isolated in clinical cultures from the study patients prior to treatment are shown in Table 2.

Using the patients' characteristics and the patterns of isolation of pathogens before treatment, a multivariate logistic re-

TABLE 2. Isolation of bacteria from the study patients prior to treatment with ceftriaxone or ampicillin-sulbactam

| Organism | No. of isolates (% of patients) for group | |
|---|---|---|
| | Ceftriaxone | Ampicillin-sulbactam |
| *S. aureus* | 103 (7.9) | 581 (23.8) |
| *Enterococcus* spp. | 122 (9.3) | 543 (22.2) |
| *Enterobacter* spp. | 49 (3.7) | 70 (2.9) |
| *Klebsiella* spp. | 165 (12.6) | 148 (6) |
| *E. coli* | 59 (4.5) | 100 (4.1) |
| *Proteus* spp. | 36 (2.7) | 111 (4.5) |
| *Serratia* spp. | 25 (1.9) | 45 (1.8) |
| *Citrobacter* spp. | 17 (1.3) | 16 (0.7) |
| *P. aeruginosa* | 50 (3.8) | 118 (4.8) |
| *S. maltophilia* | 10 (0.8) | 23 (0.9) |

gression model was developed to calculate the propensity score (3, 13, 14), a score that predicts the patient's probability of being treated with ceftriaxone based on the pretreatment characteristics. The model developed is shown in Table 3. The score had an area under the receiver operating characteristics curve of 80%, indicating excellent discrimination between patients in the two treatment groups. The ability of the propensity score to adjust for important covariates of treatment was evaluated by testing for differences in the covariates within quintiles of propensity.

New isolation of at least 1 of the 10 target nosocomial pathogens occurred in 244 patients. The risk of isolation of each pathogen according to the treatment group is summarized in Table 4. More events of nosocomial colonization and infection occurred in patients treated with ampicillin-sulbactam than in patients treated with ceftriaxone (hazard ratio [HR], 1.55; $P = 0.009$). This was observed with all gram-negative rods combined (HR, 3.6; $P < 0.001$) and with each genus of the family *Enterobacteriaceae* that was isolated in more than 10 patients (*Enterobacter* spp., *Klebsiella* spp., and *E. coli*). No differences in isolation of gram-positive bacteria were evident ($P = 0.33$).

In 172 of the study patients, a microbiologically documented nosocomial infection occurred following treatment. Fewer patients had nosocomial superinfections in the ceftriaxone group than in the ampicillin-sulbactam group (3.8% versus 5% of infected patients, respectively; HR, 1.6; $P = 0.015$). The sites of infection were soft tissue and bone for 68 patients (36% of the ceftriaxone group versus 41% of the ampicillin-sulbactam group), respiratory tract for 33 patients (22 versus 18%, respectively), abdomen for 31 patients (16 versus 20%), urinary tract for 30 patients (16 versus 15%), and bloodstream for 25 patients (15 versus 13%). No difference in the distribution of sites of infections was found between the treatment groups. Many of the infections were polymicrobial. The distributions of the causative pathogens according to the treatment group are summarized in Table 4. *Enterococcus* spp. constituted the most common nosocomial pathogen in the ceftriaxone group. The *Enterobacteriaceae* and *P. aeruginosa* were causative pathogens more frequently in the ampicillin-sulbactam group than in the ceftriaxone group, and *Enterococcus* spp. were less often the infecting organism in the ampicillin-sulbactam group.

The resistance patterns of pathogens isolated following antibiotic treatment are summarized in Table 5. All the *E. coli* isolates were susceptible to ceftriaxone, but half were resistant (20% were intermediately resistant) to ampicillin-sulbactam. Similar patterns were found for *Klebsiella* spp. The prevalence of oxacillin resistance among *S. aureus* isolates was high in both treatment groups and tended to be higher in the ceftriaxone group than in the ampicillin-sulbactam group (63 versus 31%; odds ratio, 3.8; $P = 0.08$). Resistance to ampicillin as well as resistance to vancomycin among *Enterococcus* spp. isolates did not differ between groups.

## DISCUSSION

Confounding by indication for treatment is a major obstacle in observational pharmacoepidemiological studies. While in case control studies it is adjusted for only indirectly, here using the retrospective observational cohort design we were able to address confounding by indication up front. In this observational cohort study, we tried to simulate a randomized clinical trial by using multivariable analysis to create the propensity score. The score allowed us to account for differences between characteristics of patients which influenced the clinicians' decision to treat with one study agent instead of the other, thus stimulating randomization (3, 13, 14). We further adjusted for other confounding variables occurring following treatment allocation which are related to the development of the outcomes. This design enabled us to include a larger number of patients than typically is included in antimicrobial randomized clinical trials. Thus, it had enough power to allow examination of uncommon outcomes, such as nosocomial superinfections, an outcome not usually addressed by randomized clinical trials. In contrast to case control studies that usually examine infections with a specific organism, the cohorts design enabled us to examine a large spectrum of pathogens.

We chose to examine two agents that are used for similar indications, but since ampicillin-sulbactam is active against many anaerobes and ceftriaxone is not, when ceftriaxone is used to treat mixed infections it is used in combination with metronidazole or clindamycin. To allow similar indications to be included, we did not exclude patients treated with the last two agents and adjusted for their use in the analysis.

Distinction between infecting and colonizing organisms detected in clinical culture can be difficult, particularly in polymi-

TABLE 3. Propensity score for patient's likelihood of being treated with ceftriaxone

| Pretreatment variable | Odds ratio | *P* value |
|---|---|---|
| Age | 1.0135 | <0.0001 |
| Days in hospital until treatment | 1.1177 | <0.0001 |
| Cardiovascular disease | 1.3 | 0.01 |
| Diabetes | 0.56 | <0.0001 |
| Lung disease | 2.1 | <0.0001 |
| ICU admission | 4.3 | <0.0001 |
| Major surgery | 0.36 | <0.0001 |
| Organism isolated: | | |
| *S. aureus* | 0.46 | <0.0001 |
| *Enterococcus* spp. | 0.5 | <0.0001 |
| *Enterobacter* spp. | 1.8 | 0.007 |
| *Klebsiella* spp. | 2.1 | <0.0001 |
| *Serratia* spp. | 1.6 | 0.09 |
| *Citrobacter* spp. | 2.1 | 0.09 |

TABLE 4. Isolation of nosocomial pathogens following treatment with the study agents and distribution of pathogens as the cause of the events of superinfections in each treatment group[a]

| Pathogen(s) | No. of isolates | Adjusted HR[b] (95% CI) | *P* value | % Superinfections[c] | | *P* value |
|---|---|---|---|---|---|---|
| | | | | Ampicillin-sulbactam | Ceftriaxone | |
| All | 244 | 1.55 (1.1–2.1) | 0.009 | | | |
| All gram positive | 130 | 0.81 (0.5–1.2) | 0.33 | | | |
| All gram negative | 141 | 3.6 (2.1–5.9) | <0.001 | | | |
| *S. aureus* | 44 | 1.6 (0.7–3.5) | 0.22 | 19 | 16 | 0.6 |
| *Enterococcus* spp. | 99 | 0.76 (0.5–1.2) | 0.25 | 26 | 64 | <0.0001 |
| *Enterobacter* spp. | 45 | 2.6 (1.1–5.8) | 0.02 | 28 | 20 | 0.2 |
| *Klebsiella* spp. | 37 | 14.4 (3.2–64) | <0.001 | 28 | 4 | 0.0002 |
| *E. coli* | 22 | >10 (2.5–∞) | <0.001 | 18 | 0 | 0.0006 |
| *Proteus* spp. | 6 | | | 5 | 0 | 0.18 |
| *Serratia* spp. | 6 | | | 4 | 2 | 0.6 |
| *Citrobacter* spp. | 8 | | | 5 | 4 | 0.6 |
| *P. aeruginosa* | 31 | 1.88 (0.6–5.6) | 0.26 | 21 | 10 | 0.08 |
| *S. maltophilia* | 13 | 1.5 (0.4–6.1) | 0.5 | 7 | 8 | 0.9 |

[a] Patients treated with ampicillin-sulbactam are at a higher risk for colonization and infection with nosocomial pathogens and in particular with *Enterobacteriaceae*.
[b] Ampicillin-sulbactam vs. ceftriaxone, adjusted for propensity score, having major surgery, combination treatment with aminoglycoside, and addition of an antianaerobic agent (metronidazole or clindamicin) and the intensity of culturing. CI, confidence interval.
[c] The total is more than 100%, since many patients had polymicrobial infections. The number of patients with a nosocomial infection following treatment was 122 for the ampicillin-sulbactam group and 50 for the ceftriaxone group.

crobial infections; it is definition dependent and subjective. Therefore, we decided to analyze two main outcomes: (i) the isolation of pathogens from clinical cultures, an objective but nonspecific outcome, and (ii) microbiologically documented infections, a specific but less-sensitive outcome. Indeed, infection was determined in 71% of the patients from whom pathogens were isolated.

We found that microbiologically documented nosocomial superinfections following treatment occurred in 4.6% of the treated patients at an incidence of 61 episodes per 10,000 patients per day. In 172 of the study patients, a microbiologically documented nosocomial infection occurred following treatment. Fewer patients had nosocomial superinfections in the ceftriaxone group than in the ampicillin-sulbactam group (3.8 versus 5% of infected patients, respectively; HR, 1.6; $P = 0.015$). What is the significance of this 1.2% risk difference? It represents a 32% increase in the unadjusted risk and a 60% increase in the adjusted risk of superinfection for patients treated with ampicillin-sulbactam. In other words, if all patients treated with ampicillin-sulbactam had been treated with ceftriaxone we would expect only 93 to develop superinfection, as opposed to the 122 cases of superinfection that actually occurred, and after controlling for confounding the expected number of patients with superinfection, the number would have been only 76.

The higher risk of superinfections among patients treated with ampicillin-sulbactam was observed primarily for superinfections caused by *Enterobacteriaceae*. Results of the analysis for clinical isolation were in concordance with those of the analysis of infections.

The higher rate of superinfections in the ampicillin-sulbactam group is probably related to differences in susceptibility. The most prominent difference among infecting organisms was in superinfections caused by *Enterobacteriaceae*, more of which are susceptible to ceftriaxone than to ampicillin-sulbactam. This explanation is also supported by the higher rate of polymicrobial infections caused by *Enterobacteriaceae* affecting patients in the ampicillin-sulbactam group. Only 1.5% of the patients were treated with an aminoglycoside combination, and no events occurred among these patients. When patients treated with aminoglycosides were excluded from the analysis, similar results were found. Therefore, we conclude that aminoglycosides did not play an important role in this study.

Residual confounding in an observational study should always be considered. In this study we did not adjust for hospital location or admitting service. Thus, different transmission patterns and differences in the endemicities of various pathogens may have played a role that was not fully controlled for.

Our results confirm and document the differences among the likely causative organisms in superinfections following treatment with ceftriaxone or ampicillin-sulbactam. This may guide a clinician in choosing an empirical antimicrobial regimen to treat superinfection.

When antibiotic choices are made, one should consider many variables, most importantly efficacy but also resistance patterns, adverse events, and cost. Here we suggest that differences in the incidence of superinfections exist between the ampicillin-sulbactam- and ceftriaxone-treated patient groups.

TABLE 5. Susceptibilities of selected isolates by treatment group[a]

| Isolate | Total no. tested | Antibiotic | Results[b] | | | |
|---|---|---|---|---|---|---|
| | | | SAM group ($n$ = 2,445) | | Ceftriaxone group ($n$ = 1,308) | |
| | | | No. S | No. R | No. S | No. R |
| *E. coli* | 22 | SAM | 10 | 12 | | |
| | | Ceftriaxone | 22 | | | |
| *Enterobacter* spp. | 45 | SAM | 9 | 26 | 1 | 9 |
| | | Ceftriaxone | 21 | 14 | 5 | 5 |
| *Klebsiella* spp. | 37 | SAM | 16 | 19 | 2 | |
| | | Ceftriaxone | 33 | 2 | 2 | |
| *S. aureus* | 43 | Oxacillin | 22 | 10 | 4 | 7 |
| *Enterococcus* spp. | 50 | Ampicillin | 7 | 10 | 17 | 13 |
| | | Vancomycin | 14 | 4 | 27 | 5 |

[a] SAM, ampicillin-sulbactam.
[b] $n$, no. of patients; S, susceptible; R, resistant.

Thus, the initial choice of an antibiotic agent has extensive consequences for the selection of nosocomial pathogens and for the resistance pattern, which can cause potentially costly and difficult-to-treat superinfections. Physicians should be aware of the impact of selecting an antibiotic agent for a patient. Further studies examining the factors leading to nosocomial superinfections and the outcomes of such events are warranted.

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## REFERENCES

1. **Carmeli, Y., N. Troillet, A. Karchmer, and M. Samore.** 1999. Health and economic outcomes of antibiotic-resistance in *Pseudomonas aeruginosa*. Arch. Intern. Med. **159:**1127–1132.
2. **Charlson, M. E., P. Pompei, K. L. Ales, and C. R. McKenzie.** 1987. A new method of classifying prognostic comorbodity in longitudinal studies: development and validation. J. Chronic Dis. **40:**373–383.
3. **Connors, A. F., Jr., T. Speroff, N. V. Dawson, C. Thomas, E. F. Harrell, Jr., D. Wagner, et al.** 1996. The effectiveness of right heart catheterization in the initial care of critically ill patients. SUPPORT Investigators. JAMA **276:**889–897.
4. **Cox, D. R.** 1972. Regression models and life tables. J. R. Statistical Soc. **B34:**187–220.
5. **Dubos, R. R., R. W. Schaedler, and M. Stephens.** 1963. The effect of antibacterial drugs on the fecal flora of mice. J. Exp. Med. **117:**231–243.
6. **Finegold, S. M., L. Ingram-Drake, R. Gee, J. Reinhardt, M. A. C. Edelstein, K. MacDonald, and H. Wexler.** 1987. Bowel flora changes in humans receiving cefixime (CL 284,635) or cefaclor. Antimicrob. Agents Chemother. **31:** 443–446.
7. **Garner, J. S., W. R. Jarvis, T. G. Emori, T. C. Horan, and J. M. Hughes.** 1998. CDC definitions for nosocomial infections. Am. J. Infect. Control **16:** 128–140.
8. **Haley, R. W., D. H. Culver, J. W. White, et al.** 1985. The nationwide nosocomial infection rate: a new need for vital statistics. Am. J. Epidemiol. **121:** 159–167.
9. **Holemberg, S. D., S. L. Solomon, and P. A. Blake.** 1987. Health and economic impact of antimicrobial resistance. Rev. Infect. Dis. **9:**1065–1078.
10. **Horan, T. C., D. H. Culver, R. P. Gaynes, et al.** 1993. Nosocomial infections in surgical patients in the United States, January 1986–June 1992. Infect. Control Hosp. Epidemiol. **14:**73–80.
11. **Meynell, G. G.** 1955. Some factors affecting the resistance of mice to oral infection by Salmonella typhimurium. Proc. R. Soc. Med. **48:**916–918.
12. **Phelps, C. E.** 1989. Bug/drug resistance: sometimes less is more. Med. Care **27:**194–203.
13. **Rosenbaum, P., and D. B. Rubin.** 1983. The central role of the propensity score in observational studies for causal effects. Biometrika **70:**41–55.
14. **Rubin, D. B.** 1997. Estimating causal effects from large data sets using propensity scores. Ann. Intern. Med. **127:**757–763.
15. **Samore, M. H., D. Lichtenberg, L. Saubermann, C. Kawachi, and Y. Carmeli.** 1997. A clinical data repository enhances hospital infection control, p. 56–60. JAMIA Proceedings of the American Medical Informatics Association Annual Fall Symposium, October, 1997.
16. **Vollaard, E. J., and H. A. L. Clasener.** 1994. Colonization resistance. Antimicrob. Agents Chemother. **38:**409–414.
17. **Vollaard, E. J., H. A. L. Clasener, A. J. H. M. Janssen, and H. J. A. Wynne.** 1990. Influence of cefotaxime on microbial colonization resistance in healthy volunteers. J. Antimicrob. Chemother. **26:**117–123.