Increased Resistance among
*Staphylococcus epidermidis* Isolates in a Large Teaching Hospital over a 12-Year Period

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The prevalence of drug resistance among clinically significant blood isolates of *Staphylococcus epidermidis* (n = 464) and consumption of antibiotics at a tertiary care teaching hospital (Meilahti Hospital, Helsinki) were analysed for the period 1983–1994. Resistance to methicillin increased from 28 to 77%. Simultaneously, usage of third-generation cephalosporins increased nearly sevenfold (from 8.6 kg to 56.4 kg/year). A significant correlation was found between percentages of methicillin resistance and usage of penicillinase-stable β-lactam agents, including cloxacillin, imipenem, and first-, second-, and third-generation cephalosporins (r = 0.737, p < 0.0062). The increase in ciprofloxacin resistance occurred soon after the introduction of ciprofloxacin. Moreover, there was a remarkable increase in resistance to fusidic acid (from 10 to 40%) and rifampin (from 0 to 23%) despite the low usage of these agents. Overall, the rate of multiply resistant isolates roughly tripled (from 20 to 71%) and, by 1994, the frequency of isolates susceptible to vancomycin only was as high as 11%, which remarkably limits options for therapy.

Currently, coagulase-negative staphylococci (CNS), in particular the species *Staphylococcus epidermidis*, are the preeminent cause of nosocomial bacteraemia in large teaching hospitals, especially in patients with intravascular catheters (1–3). Resistance in nosocomially acquired *Staphylococcus epidermidis* isolates to several antibiotics, including methicillin, is common (2–5). These isolates are cross-resistant to all β-lactam antibiotics, regardless of in vitro susceptibility (3). In addition, methicillin resistance in *Staphylococcus epidermidis* is often linked with resistance to other antibiotics, particularly the aminoglycosides and macrolides (2). High rates of resistance to an antibiotic can usually be explained by large consumption of the same antibiotic. The use of some antibiotics can also exert a selective pressure that favours the emergence of drug-resistant organisms that accumulate in the hospital environment and community (6–10). Moreover, these resistant isolates of *Staphylococcus epidermidis* have been proposed to be a potential reservoir for antibiotic resistance genes in hospitals (10, 11).

The present study was undertaken to determine how the drug resistance of *Staphylococcus epidermidis* and the consumption of antibiotics have changed during the last decade in a tertiary care teaching hospital and whether the use of certain antibiotics is associated with the increased resistance in *Staphylococcus epidermidis*. The material comprised all clinically significant blood culture isolates of *Staphylococcus epidermidis* obtained at Meilahti Hospital in the period 1983–1994. The consumption of all antibiotics at Meilahti Hospital during the same period was recorded.

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Materials and Methods

Setting. Meilahti Hospital is a 700-bed acute-care university hospital for adult patients with medical, surgical, neurological, and pulmonary diseases in Helsinki. The hospital has two critical care units and is the site of the heart, lung, and bone marrow transplantations performed in Finland.

Bacteria. All bacteraemic isolates of Staphylococcus epidermidis growing in more than one blood culture bottle or culture set and obtained from patients with fever or other symptoms compatible with bacteraemia between January 1983 and December 1994 were included in the study. Duplicate isolates from a bacteraemic episode of the same patient were excluded. Blood samples were taken by venipuncture (not through catheters) after careful cleansing of the skin.

Identification of Bacteria. Staphylococcus epidermidis isolates were identified by standard laboratory methods at the Department of Bacteriology and Immunology, University of Helsinki. The tests used to differentiate Staphylococcus epidermidis from other CNS included fermentation of mannitol and trehalose as well as the urease test. When appropriate, the API Staph 20 ID system (bioMérieux, France) was employed.

Antimicrobial Susceptibility. The antibiotic susceptibility of the bacteraemic isolates of Staphylococcus epidermidis was investigated at the time of isolation by a disk diffusion test (Rosco Diagnostica, Denmark). The Kirby-Bauer methodology and susceptibility interpretative criteria were applied as described by the disk manufacturer.

Antibiotic Usage. Data on antibiotic consumption at Meilahti Hospital per year in 1983–1994 were obtained from the records of the hospital pharmacy. Grams (g) were used as a unit of measurement except for benzylpenicillin, which was measured in international units (IU).

Analysis and Statistics. Resistance percentages for different antibiotics were calculated for each year. Resistance patterns of isolates were counted once per bacteraemic episode. If the susceptibility pattern varied between isolations, the most resistant one was noted. When calculating resistance percentages both resistant (R) and intermediately susceptible (I) isolates were considered resistant. The isolates were considered to be multiply resistant when they were resistant to methicillin and at least two antibiotic classes other than β-lactams. Pearson correlation coefficients (and p values) were calculated over the 12 years for the relationship between the percentages of resistant isolates and antibiotic consumption.

Results

A total of 464 bacteraemic Staphylococcus epidermidis isolates (median 40, range 26–49 per year) obtained at the hospital during the period 1983–1994 fulfilled the criteria for clinical significance; 297 of 761 were considered contaminants. During the period 1983–1990 the annual rate of admissions varied from 22,558 to 23,768, but by 1994 it increased to 30,772. The length of stay decreased from 10.8 days in 1983 to 5.5 in 1994. The rates of Staphylococcus epidermidis bacteraemia in relation to admissions at Meilahti Hospital are presented in Figure 1.

Percentages of methicillin resistance and data on antibiotic consumption of the most commonly used penicillinase-stable β-lactam agents (cloxacillin, imipenem, and first-, second-, and third-generation cephalosporins) per year are presented in Figure 2. The occurrence of methicillin resistance increased from 28 to 77% during the observation period. Simultaneously, there was a remarkable increase in the usage of third-generation cephalosporins (8.6 kg/year in 1983 to 56.4 kg/year in 1994), but the use of the other agents, except imipenem, was stable or decreased. The correlation between percentages of methicillin resistance and antibiotic consumption in grams per year was established by means of simple regression analyses for cloxacillin, imipenem, and first-, second-, and third-generation cephalosporins separately as well as for all five agents to-