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Colonization and Infection with *Enterococcus faecalis* in Intensive Care Units: The Role of Antimicrobial Agents

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We studied the influences of antimicrobial agents on the colonization of the respiratory tract and infection with *Enterococcus faecalis* in intensive care unit (ICU) patients receiving mechanical respiration for at least 3 days. In a matched-cohort analysis, patients receiving topical antimicrobial prophylaxis (TAP) of the oropharynx and stomach with antimicrobial agents not treating *E. faecalis* were compared with patients not receiving TAP. Patients were matched with controls on the basis of their duration in the ICU, their use of systemic antibiotics treating and not treating *E. faecalis*, the administration of TAP, their APACHE II score, and surgical procedures they had undergone. In all, 276 patients were analyzed. The colonization of the oropharynx and/or trachea by *E. faecalis* at admission was demonstrated for 43 patients (16%). Twenty patients (9%) acquired tracheal colonization and 91 patients (40%) acquired oropharyngeal colonization with *E. faecalis*. In the matched-cohort analysis, 43 patients receiving TAP were matched to two controls each. TAP patients more frequently acquired tracheal colonization (15 of 43 versus 2 of 86 patients, *P* < 0.0001) and infections with *E. faecalis* (6 of 43 versus 1 of 86 patients, *P* < 0.01). The use of topical antibiotics not treating *E. faecalis* increased the risk for colonization and infection with *E. faecalis*.

Enterococci have become a significant cause of nosocomial infections in recent years (6, 17). According to the National Nosocomial Infection Surveillance Survey, which was based on studies in U.S. hospitals between 1986 and 1989, enterococci were the second most common type of microorganism recovered from nosocomial infections (6). In addition, other recent studies have demonstrated the pathogenic potential of enterococci, despite the general assumption that these microorganisms are second-rate pathogens belonging to the normal human flora (8, 9, 15). The genus *Enterococcus* can be divided into several species, of which *Enterococcus faecalis* and *Enterococcus faecium* are most important (19).

An increasing incidence of enterococcal infection in recent decades, as reported by some, has been related to an increased use of broad-spectrum antibiotics, especially second- and third-generation cephalosporins (18, 20). These agents lack activity against enterococci and may provide the microorganism with a selective growth advantage. Many regimens used for the selective decontamination of the digestive tract (SDD) include a short course of administration of systemic cephalosporins (22). Furthermore, colonization and infection with enterococci might be stimulated by topical antimicrobial prophylaxis (TAP) directed against gram-negative bacteria and *Staphylococcus aureus* but not against enterococci. For instance, the regimens commonly used for SDD generally do not include drugs that treat enterococci in their antimicrobial spectrum (22). An association between the use of SDD and an increase in the incidence of enterococcal infections has been reported (5, 7, 10, 21), although others have failed to confirm this observation (11). Because of the increasing importance of enterococci as nosocomial pathogens and the problems of treating infections caused by these bacteria, we studied risk factors for the colonization of the upper respiratory tract and for infections with *E. faecalis* in patients treated in intensive care units (ICUs) with mechanical respirators.

The results of this study were presented at the Interscience Conference on Antimicrobial Agents and Chemotherapy held October 1994 in Orlando, Fla.

**MATERIALS AND METHODS**

**Study design.** The study was performed in two general ICUs at the University Hospital of Maastricht, The Netherlands. The study period extended from 1 September 1991 until 1 January 1994. Patients on mechanical respirators were analyzed with regard to the colonization of their upper respiratory tracts and infection with *E. faecalis*. Patient characteristics and clinical parameters were recorded on admission and monitored during their ICU stay. The APACHE II score was determined on the first day of admission as described elsewhere (13). Patients were eligible for analysis if they were older than 16 years and were on mechanical respirators for at least 3 days. Informed consent was obtained from all patients or, if this was not possible because of the clinical condition of the patient, from their relatives.

**TAP.** During the course of two studies, 61 patients received TAP. In the first study, eligible patients were included consecutively, whereas patients were chosen at random in the second study. The results of both studies have been published elsewhere (2, 4). TAP medication consisted of (i) a suspension of tobramycin (8 mg/ml) and colistin (5 mg/ml), 1 ml of which was administered in each nostril and 5 ml of which was administered through a nasogastric tube; (ii) an application of tobramycin-colistin-ampicillin (B [2%]) in Orabase to the oropharynx; (iii) a suspension of amphotericin B (100 mcg/ml), of which 0.5 ml was administered in each nostril and 2.5 ml was administered through a nasogastric tube; and (iv) 1 g of sulfadiazine suspension through a nasogastric tube. This regimen was given four times daily.

**Antimicrobial therapy.** Antimicrobial agents administered systemically in our ICU study were divided into two groups according to their activity against *E. faecalis*. The group of antimicrobial agents not treating *E. faecalis* contained cephalosporins, aminoglycosides, fluoroquinolones, clindamycin, and metronidazole. The group of antibiotics treating *E. faecalis* contained amoxicillin (with and without clavulanic acid), piperacillin, vancomycin, erythromycin, cotrimoxazole, ciprofloxacin, and imipenem. In case a patient received therapy with both an aminoglycoside and amoxicillin (with or without clavulanic acid) or piperacillin, the combination was considered active against enterococci.

**Microbiological monitoring.** Colonization was assessed by culturing oropharyngeal swabs and tracheal aspirates on admission and twice weekly thereafter. Colonization was analyzed semiquantitatively with sheep blood, cysteine lactose electrolyte deficient, and chocolate agar plates. All media were incubated at 35°C.
for 18 to 48 h. Samples obtained by bronchoalveolar lavage and protected specimen brush were cultured quantitatively. Urine specimens were cultured twice weekly by following routine microbiological procedures. Tips of all urine catheters and intravascular devices were cultured routinely, also by routine microbiological procedures.

Colonization with *E. faecalis*. Colonization was defined as the isolation of *E. faecalis* from oropharyngeal swabs or tracheal aspirates in the absence of infection. Colonization on admission was established on the basis of a positive culture obtained within 24 h after admission to the ICU. Although 48 to 72 h is generally used as the cutoff point for nosocomial infections, we used 24 h since colonization was analyzed. Colonization was considered acquired if positive cultures of the same species of microorganism were present in at least two consecutive samples, the first of which was taken no sooner than 24 h after admission to the ICU.

**Infections with *E. faecalis***. All diagnoses of infection, with the exception of pneumonia, were established by the criteria formulated by the Centers for Disease Control and Prevention. (26) Pneumonia was considered to have been acquired in the ICU if a patient developed a clinical condition fulfilling the criteria for pneumonia after being in the ICU for at least 3 days. In the case of a clinical suspicion of pneumonia, tests were performed by bronchoalveolar lavage and protected specimen brush. The diagnosis of pneumonia was established according to the criteria described previously (3). These included that at least three of the following conditions be met: (i) a rectal temperature above 38.0°C or below 35.5°C, (ii) blood leucocytosis (>10.10⁴/mm³), and/or left shift or blast transformation, (iii) <3.0 leucocytes per high-power field in a Gram stain of a tracheal aspirate, and (iv) a positive culture from a tracheal aspirate. The criteria for a diagnosis of pneumonia also included a new or progressive infiltrate on a chest radiograph and a positive quantitative culture of samples obtained by bronchoalveolar lavage (>10¹⁰ CFU/ml) or protected specimen brush (≤10⁹ CFU/ml) or positive cultures from blood or pleural fluid culture unrelated to another source and obtained within 48 h before and after respiratory sampling.

**Analysis of antimicrobial agents as a risk factor for colonization**. Because the administration of TAP was not performed after patients were chosen at random, a matched-cohort analysis was performed in order to determine the risk of the administration of antimicrobial agents for acquired colonization with *E. faecalis*. Only patients not colonized with *E. faecalis* on admission were included in this analysis. Patients receiving TAP were matched with patients not receiving TAP. The following variables were used for matching individual cases: (i) the administration of systemic antimicrobial agents not treating *E. faecalis*; (ii) the administration of systemic antimicrobial agents treating *E. faecalis*; (iii) an APACHE II score calculated within the first 24 h of admission to the ICU (the score of the control had to be higher or <5 points lower than the matched case; the APACHE score was calculated without the points for age, because this was a separate matching variable); (iv) the date of birth (the control patient was not allowed to differ in age by more than 10 years from the age of the matched patient); (v) the surgical procedures each patient underwent (no surgery, abdominal surgery, or thoracic surgery). To ensure the same duration of exposure to risk, an additional variable required that each matched patient who did not receive TAP had a total length of stay in the ICU equal to or greater than the ICU stay of the matched patient receiving TAP before colonization with *E. faecalis* occurred. Potential patients for matching were reviewed for the best possible match on the basis of (in order of priority) the duration of their exposure to risk, the administration of systemic antimicrobial agents, surgical procedures, simplified acute physiology score, and age. When more than two potential patients could be matched to a patient receiving TAP, the patient with a date of admission nearest that of the patient receiving TAP was selected.

**Statistical analysis**. In the matched-cohort analysis, differences between both groups were tested by chi-square statistics or the Fisher exact test when appropriate.

**RESULTS**

**Study population.** During the study period, 276 patients (median age 65 years; range, 15 to 95 years) were included, of which 179 were male and 97 were female. The status of the patients was categorized as surgical (n = 112), medical (n = 110), multiple trauma (n = 33), or neurological (n = 21). The median duration of hospitalization before admission to the ICU was 4 days, and 52 patients were directly admitted to the ICU. The median APACHE II score was 19, with a range from 1 to 46. All patients were on mechanical respirators and had an ICU stay of at least 3 days, with a median of 9 days, ranging from 3 to 203 days.

**Colonization with *E. faecalis* on admission.** Forty-three patients (16%) showed *E. faecalis* colonization in the upper respiratory tract on admission to the ICU; 42 patients showed colonization in the oropharynx, and 3 showed colonization in the trachea. Colonized patients had a duration of hospitalization prior to their ICU admission of 18.0 ± 31.4 days, and noncolonized patients were hospitalized for a mean of 8.7 ± 14.4 days before being admitted to the ICU (P = 0.062, by Student’s t test).

**Acquired colonization with *E. faecalis***. Patients not colonized with *E. faecalis* in the upper respiratory tract on admission were analyzed for acquired colonization with *E. faecalis* in the oropharynx and trachea. In addition, some data were missing from 8 patients, so a total of 225 patients were included in this analysis. Acquired colonization with *E. faecalis* was demonstrated in the oropharynxes of 91 patients (40%) after a mean of 7.0 ± 3.8 days and in the tracheae of 20 patients (9%) after a mean of 9.6 ± 5.4 days.

**Infections.** In all, 11 patients (4%) developed an ICU-acquired infection in which *E. faecalis* was involved. Eight of these patients received TAP, of whom six developed an episode of respirator-associated pneumonia. The infection was polymicrobial in all cases. Of those patients not receiving TAP, three developed bacteraemia with *E. faecalis*, most probably from an abdominal focus in two patients and from a colonized intravascular device in the other patient.

Cultures positive for *E. faecalis* from urine specimens were obtained from 29 patients (11%), of whom 11 received TAP. In 57 patients (21%), 17 of whom received TAP, *E. faecalis* was cultured from the tips of urine catheters. Cultures from intravascular devices positive for *E. faecalis* were obtained from 19 patients (7%), of whom 10 received TAP.

**Matched-cohort analysis.** In the matched-cohort analysis, 43 patients receiving TAP were matched to two patients each (controls) who did not receive TAP. The length of time the patient was at risk and the factors relating to the administration of systemic antimicrobial agents treating and not treating *E. faecalis* were matched completely. Five controls could not be matched completely for surgical procedures. The APACHE II scores could be matched successfully for 80 controls (95%). Overall, successful matching was achieved for 419 of 430 (97%) variables. The clinical characteristics of the patients included in the analysis are depicted in Table 1. Eighty-seven patients (29 case patients and 58 controls) received antibiotics not treating *E. faecalis* for a median number of 4 days in both groups (P = 0.6, by Student’s t test). A group of 63 patients, of whom 21 were case patients and 42 were controls, received antibiotics treating *E. faecalis* for a median of 4 and 5 days, respectively (P = 0.3, by Student’s t test). Control patients had

**Table 1. Clinical characteristics of the patients included in the matched-cohort analysis**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients (n = 43)</th>
<th>Controls (n = 86)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>62</td>
<td>65</td>
<td>NS</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>13</td>
<td>16</td>
<td>NS</td>
</tr>
<tr>
<td>Days of exposure to risk</td>
<td>5</td>
<td>7</td>
<td>0.07</td>
</tr>
<tr>
<td>Medical categories</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>14</td>
<td>34</td>
<td>NS</td>
</tr>
<tr>
<td>Trauma</td>
<td>6</td>
<td>14</td>
<td>NS</td>
</tr>
<tr>
<td>Medical</td>
<td>22</td>
<td>31</td>
<td>NS</td>
</tr>
<tr>
<td>Neurology</td>
<td>1</td>
<td>7</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Members of this group were patients on mechanical respirators receiving TAP of the oropharynx and stomach with colistin, tobramycin, and amphotericin B.
* Controls represented patients on mechanical respirators who did not receive TAP.
* Values expressed are median values.
* NS, not significant.
TABLE 2. Colonization, infection, and clinical cultures positive for *E. faecalis* in the matched-cohort analysis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients (%) Controls (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acquired colonization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oropharynx and/or trachea</td>
<td>27 (63)</td>
<td>33 (38)</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>26 (60)</td>
<td>32 (37)</td>
</tr>
<tr>
<td>Trachea</td>
<td>15 (35)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Infections</td>
<td>6 (14)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>4 (9)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Positive vascular catheter</td>
<td>8 (19)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Positive urine specimen</td>
<td>10 (23)</td>
<td>10 (12)</td>
</tr>
<tr>
<td>Positive urine catheter</td>
<td>12 (28)</td>
<td>21 (24)</td>
</tr>
</tbody>
</table>

* Members of this group were patients on mechanical respirators receiving TAP of the oropharynx and stomach with colistin, tobramycin, and amphotericin B. N = 43.
* Controls represented patients on mechanical respirators who did not receive TAP. N = 86.

The data underscore the relationship between the use of TAP and increased rates of colonization and infection with *E. faecalis*. These data agree with other ICUs, since it was based on in vitro susceptibilities of isolates in our department.

Furthermore, to exclude the influence of other variables, a univariate and multivariate analysis was performed first in order to identify possible risk factors. Of 11 possible risk factors evaluated, the administration of TAP and a long ICU stay were most important for colonization of the respiratory tract with this species (data not shown). Therefore, in the matched-cohort analysis, patients were matched for the length of their ICU stay, the use of antibiotics, the severity of illness on admission, and surgical procedures performed. The matched-cohort analysis demonstrated that the use of TAP was associated with increased levels of tracheal and oropharyngeal colonization and higher infection rates with *E. faecalis*.

DISCUSSION

The main finding of this study is that the use of TAP of the oropharynx and stomach with antibiotics that do not treat *E. faecalis* increased colonization rates of the upper respiratory tract with this species of microorganism. Moreover, TAP with these antibiotics was associated with a higher incidence of respirator-associated pneumonia and bacteremia in which *E. faecalis* was involved.

Most nosocomial infections caused by enterococci are urinary tract infections or intra-abdominal infections (8). Although colonization of the upper respiratory tract with enterococci in patients on mechanical respirators occurs fairly often (17), this species rarely caused infection of the lungs (1). Recently we reported high colonization rates and six cases of polymicrobial pneumonia in which *E. faecalis* had an etiologic role (5). These cases occurred among patients receiving TAP with colistin, tobramycin, and amphotericin B, which do not treat *E. faecalis*. All cases of pneumonia were diagnosed by means of a protected specimen brush, bronchoalveolar lavage, or positive blood cultures, thereby confirming the etiologic role of this species in the infection. However, colonization and infection were not studied in a random fashion, and therefore no definite conclusions regarding the influence of TAP could be drawn. The present study was designed to study the hypothesized relationship between antibiotic use and colonization and infection with *E. faecalis* more accurately. Since a trial based on random inclusions of patients was not feasible, we performed a matched-cohort analysis in a large study population to identify risk factors for *E. faecalis* colonization and infection. Our major concern was to control the use of antibiotics, both topically and systemically. For this purpose, systemic antibiotics were divided into two groups, on the basis of the susceptibility patterns seen in our hospital. Therefore, β-lactam antibiotics such as amoxicillin (with and without clavulanic acid) and piperacillin, as well as vancomycin, were grouped among the agents treating *E. faecalis*. The group of antibiotics not treating this microorganism was mainly composed of cephalosporins and aminoglycosides, when not administered simultaneously with amoxicillin or piperacillin. It should be noted that this classification may not be adequate for other ICUs, since it was based on in vitro susceptibilities of isolates in our department.

Furthermore, to exclude the influence of other variables, a univariate and multivariate analysis was performed first in order to identify possible risk factors. Of 11 possible risk factors evaluated, the administration of TAP and a long ICU stay were most important for colonization of the respiratory tract with this species (data not shown). Therefore, in the matched-cohort analysis, patients were matched for the length of their ICU stay, the use of antibiotics, the severity of illness on admission, and surgical procedures performed. The matched-cohort analysis demonstrated that the use of TAP was associated with increased levels of tracheal and oropharyngeal colonization and higher infection rates with *E. faecalis*.

These data underscore the relationship between the use of TAP and increased rates of colonization and infection with gram-positive microorganisms which are not affected by the regimen. This has been suggested by others (7, 10, 21, 25) and by us (4, 5). Two placebo-controlled SDD trials, using colistin and tobramycin for topical prophylaxis, reported increased rates of infection with gram-positive cocci in patients receiving SDD (7, 10). Gastinne et al. (7) reported a similar incidence of pneumonia in patients receiving SDD and placebo medication. However, the number of gram-negative respiratory tract infections was lower in SDD patients but infections due to staphylococci were observed more frequently (10). In the study by Hammond et al., oropharyngeal colonization with methicillin-resistant *Staphylococcus aureus* was observed more frequently in SDD-treated patients (10). In a recent report, SDD with amphotericin B, polymixin E, and norfloxacin was associated with five cases of endocarditis caused by *E. faecalis* (21). In contrast, others have failed to demonstrate a relationship between SDD and rectal carriage with enterococci (11).

A relation between the systemic use of antibiotics not treating *E. faecalis* (such as cephalosporins) and increased rates of nosocomial endocardial infections has been reported previously (12, 14, 16, 27). Pallares et al. demonstrated a relation between the occurrence of nosocomial *E. faecalis* bacteremia and the use of second- and third-generation cephalosporins during a 6-year period (20). In that study, 156 cases of nosocomial *E. faecalis* bacteremia were matched to appropriate controls. In the univariate analysis, the presence of a urinary catheter, mechanical respiration, and cephalosporin use were associated with enterococcal bacteremia. By a logistic regression model, only the presence of a urinary catheter and the use of cephalosporins remained significantly associated with this infection (20). The influences of mechanical respiration and
the presence of a urinary catheter on *E. faecalis* colonization and infection could not be studied for our population, because all patients were mechanically respiration and had a urinary catheter in situ.

Six of eleven infections due to *E. faecalis* occurring in our study population were polymicrobial. However, none of the cases of bacteremia were polymicrobial. Several studies reported simultaneous bacteremia with enterococci and other microorganisms. In these studies, 18 to 38% of cases of enterococcal bacteremia were polymicrobial (8, 9, 15, 28). However, since only a few ICU patients were studied and since neonates and granulocytopenic patients were included (8, 9), the populations under study were not comparable to our population. Under normal circumstances, *E. faecalis* seldom causes infection of the respiratory tract (17). This is also our observation. However, the six cases diagnosed with quantitative cultures by bronchoalveolar lavage and/or protected specimen brush strongly suggest an etiologic role for this microorganism in the pathogenesis of pneumonia. Although all cases of pneumonia were polymicrobial, three cases were accompanied by *E. faecalis* bacteremia without another evident focus. To our knowledge, only Berk and Verghese have described two cases of enterococcal pneumonia in debilitated patients who received broad-spectrum antibiotic therapy (1), and Torres and coworkers sporadically found *E. faecalis* among pathogens causing respirator-associated pneumonia (23, 24).

*E. faecalis* colonization and infection have been assumed to originate from endogenous sources (19). In a previous study we demonstrated that *E. faecalis* colonization of the upper respiratory tract was frequently preceded by gastric colonization, thereby suggesting that colonization occurred via the so-called gastropulmonary route (3). On the other hand, several studies have clearly demonstrated the possibility of cross-acquisition of this microorganism (28, 29). The latter possibility might be important when multiresistant strains of enterococci are endemic in the ICU. During the period of this study, all isolates of *E. faecalis* in our ICU were susceptible to β-lactam antibiotics and vancomycin and high-level resistance to gentamicin was demonstrated in approximately 20% of isolates.

In conclusion, the results of this study demonstrate that the topical use of antibiotics that do not treat *E. faecalis* in the oropharynx and stomach increased colonization rates of the respiratory tract with this microorganism. Moreover, the use of TAP in the oropharynx and stomach was associated with an increased incidence of infection, especially pneumonia, in which *E. faecalis* was involved. Therefore, infections with *E. faecalis* should be considered side effects of the use of TAP with agents not treating enterococci.

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