Cefotaxime Combined with Selective Decontamination in Long Term Intensive Care Unit Patients
Virtual Absence of Emergence of Resistance

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Summary

Emergence of bacterial resistance to antimicrobial agents was studied during a period of 30 months of continuous use of parenteral cefotaxime combined with oral non-absorbable polymyxin E and tobramycin (selective decontamination) in a surgical intensive care unit (ICU). No increase in drug-resistant micro-organisms was found. Colonisation of the oropharyngeal cavity or intestine or both by strains resistant to polymyxin E occurred in 8% of patients (invariably Proteus and Morganella species). Tobramycin-resistant strains (Escherichia coli, Acinetobacter and Pseudomonas species) were found in 4% of patients. Intestinal colonisation with cefotaxime-resistant bacilli (e.g. Enterobacter, Pseudomonas and Acinetobacter species) occurred in 10% of patients, but in most patients these strains were eliminated by therapy with the topical antibiotics within one week.

The control of emergence of resistance has major implications for the antibiotic policy in the ICU: firstly, the number of different antimicrobials used is sharply reduced since the switching of antibiotics to treat superinfections is seldom necessary; secondly, it is possible to use a third generation cephalosporin such as cefotaxime for systemic prophylaxis, without risk of induction of resistance.

Intensive care units (ICU) commonly have problems with the emergence of resistant strains of micro-organisms. Patients who need long term mechanical ventilation usually suffer severe underlying disease (e.g. multiple trauma, malignancy, surgery). These serious conditions often need medical interventions such as dialysis, devices, H₂-antagonists, chemotherapeutic agents and antibiotics. This combination of factors decreases the defence mechanisms of the host, making the ICU patient at high risk of acquisition of ICU-associated micro-organisms (often multiresistant Serratia, Pseudomonas and Acinetobacter species). Acquisition is readily followed by colonisation and infection. The contaminated environment and, more particularly, the colonised and infected long stay ICU patients are the major sources.

Traditional control measures have relied on efforts to decrease transmission between patients, to eliminate environmental sources and to restrict antibiotic use (Weinstein & Kabins 1981). However, these strategies have not resulted in any significant decrease in colonisation or infection rates in critically ill patients (Donowitz et al. 1982).

The ICU of the Groningen University Hospital has adopted a prophylactic antibiotic regimen which
consists of topical application of non-absorbable antibiotics to the oral cavity and gastrointestinal tract, combined with a parenteral third generation cephalosporin. Polymyxin E (colistin) and tobramycin are given orally to prevent acquisition and colonisation with ICU-associated micro-organisms and to suppress the endogenous aerobic Gram-negative flora. Amphotericin B is also given to prevent overgrowth with yeasts (selective decontamination). Parenteral prophylaxis with cefotaxime is used to prevent early respiratory and urinary tract infections by *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Escherichia coli* (van Saene et al. 1983). This regimen has resulted in a dramatic reduction in colonisation and infection (Stoutenbeek et al. 1984, 1987a; van Uffelen et al. 1987).

However, the major concern of using tobramycin and a third generation cephalosporin for prophylaxis has been the possible emergence of resistance to these agents. The present study was designed to evaluate the incidence of acquisition, colonisation and infection with Gram-negative bacilli resistant to the prophylactic antibiotics used during a 30-month period.

### 1. Methods

#### 1.1 Antibiotic Regimens

Patients with multiple trauma who required prolonged mechanical ventilation and stayed 5 days or longer in the ICU were included in the study. Patients were divided into the 5 consecutive groups detailed in table 1. All groups were treated with topical non-absorbable antibiotics. A 10ml suspension of polymyxin E 100mg (Dumex), tobramycin 80mg (Eli Lilly) and amphotericin B 500mg (Squibb) was administered through the nasogastric tube 4 times daily. Gastric suction was discontinued for 1 hour after administration. A sticky paste (Orabase, Squibb) containing polymyxin E 2%, tobramycin 2% and amphotericin B 2% was applied to the buccal mucosa 4 times daily. Parenteral prophylaxis with cefotaxime (50 to 100 mg/kg per day intravenously) was started immediately on admission and continued for 4 days, in all groups except group I. This group did not routinely receive prophylactic cefotaxime.

#### 1.2 Bacterial Surveillance

Specimens – oropharyngeal swab, rectal swab or faeces, urine, tracheal aspirate and wound swabs – were cultured on admission and then 3 times weekly. All specimens were cultured in a qualitative and semi-quantitative manner. Enterobacteriaceae were identified by the API 20E system (Murray 1978). The sensitivity of individual strains to polymyxin E, tobramycin and cefotaxime was tested by the agar diffusion method (Kirby-Bauer). The breakpoints for resistance to cefotaxime and tobramycin were an inhibition zone of less than 24mm. For polymyxin, 19mm was taken as breakpoint because of the poor diffusibility of polymyxin in agar (van Saene et al. 1983).

#### 1.3 Definitions

*Acquisition* was defined as isolation of a new strain not present in any of the samples taken in the first 3 days (baseline). *Colonisation* was defined as isolation of the same species from 2 or more consecutive cultures from the same site without clinical signs of infection. Colonisation was termed 'primary' if the colonising bacteria were present in the baseline samples and 'secondary' if colonisation occurred later by acquired bacteria. *Secondary infection* was the term used for a clinical diagnosis (by standard criteria) of infection by acquired bacteria.

#### 1.4 Statistical Analysis

The incidence of resistance was evaluated statistically by the chi-squared test (with Yates' correction). A level of $p < 0.05$ was considered significant.

### 2. Results

164 patients were treated with the antibiotic regimen for a mean duration of 14 days. The total number of cultures evaluated was 5251 (mean of