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Selective decontamination of the digestive tract and prevention of infection in intensive care units

Infection is a major problem in the management of intensive care patients. Unfortunately, a generalized description of the problem is difficult because patterns of infection vary with the population served, the type of unit, and between different times of sampling within the same unit (Brown et al., 1985; Daschner, 1985). This review is primarily concerned with unit-acquired infection and its prevention, as encountered in unspecialized, medico-surgical intensive care units. An overall incidence of infection of 23–36% is frequently reported in units of this type (Thorp, Richards & Telfer, 1979; Potgeiter et al., 1987). There is a high incidence of unit-acquired infection; the proportion of infected patients increases remorselessly with duration of stay and may exceed 80% in patients admitted for five or more days (Thorp et al., 1979; Kerver et al., 1987). Once a cycle of reduced host defence, sepsis and organ failure is established conventional management is demonstrably inadequate and mortality exceeds 50% (Watt & Ledingham, 1984).

Urinary tract infection, septicaemia and soft-tissue infections are all common. However, respiratory tract infections constitute a particular problem in that they account for 30–60% of all reported infections, and there are often intractable difficulties in both diagnosis and treatment (Brown et al., 1985; Kerver et al., 1987).

A wide range of organisms is associated with intensive therapy unit (ITU) infections. However, most (60–80%) of the episodes in a medico-surgical unit are caused by a relatively restricted group of Gram-negative bacilli. These are the coliform bacilli (particularly Escherichia coli and Klebsiella, Proteus, Enterobacter and Serratia spp., Pseudomonas aeruginosa and, less commonly, Acinetobacter spp. (Northey et al., 1974; Potgeiter et al., 1987). In the context of ITU infections, the term, aerobic Gram-negative bacilli (AGNB) is a useful collective term for these organisms.

It may be surprisingly difficult to distinguish between infections present on admission and those acquired in the unit. This reflects the frequent occurrence at the time of admission of either subclinical infection or developing infection masked by some other pathology. Consequently, unit-acquired infections are often arbitrarily restricted to episodes first diagnosed after a duration of stay exceeding 48 h (Kerver et al., 1987). Unit-acquired infections are of particular interest because, unlike those present at admission, they are potentially preventable by unit practice. Unit-acquired infections were once assumed to be mainly exogenous (i.e. acquired directly or indirectly from other patients, attendants or the environment) and modern ITU practice is to a large extent conditioned by the need to prevent this mode of infection spread (Gaya, 1976). However, against the background of such practice, most unit-acquired infections are now recognized to be endogenous, with the patient's own oropharynx, stomach and intestines as the major source of infection (Van Saene et al., 1983; Kerver et al., 1987).

Whilst AGNB are an important cause of all types of ITU infection, they are particularly associated with unit-acquired, endogenous infection. In these circumstances, infection is frequently preceded by abnormal colonization of skin and mucosal surfaces with AGNB, a process that results from overgrowth of endogenous flora, acquisition of exogenous unit flora, or a combination of these phenomena (Northey et al., 1974; Van Saene et al., 1986). The importance of the progression from abnormal colonization at a surface to overt tissue infection is exemplified by the well-documented colonization with AGNB of stomach, oropharynx and trachea prior to the development of lower respiratory tract infection with these organisms (Atherton & White, 1978; LaForce, 1981; Driks et al., 1987).

Perhaps surprisingly, anaerobic bacteria are rarely described as a cause of unit-acquired infection, although they may be important in sepsis present on admission (Thorp et al., 1979). Infection (as distinct from abnormal colonization) due to yeasts is uncommon in a medico-surgical ITU.
Until recently (1984), prevention and management of ITU-infection could be described in terms of a combination of detailed clinical and microbiological surveillance, an antibiotic policy, and isolation procedures. Ideally, surveillance would allow early detection of infection or pre-infection states and identify the causal organisms, the antibiotic policy would combine restricted drug use (thus minimizing selective pressure for resistance) with early and intensive therapy when indicated, and wide-ranging isolation procedures would prevent the transmission of infection within the unit. Whilst successful in some respects, this approach to management has been associated with the very disappointing results described. It also only poorly addresses the perceived, major problem in current practice—unit-acquired infection with endogenously-derived AGNB. In contrast, a relatively new approach, selective decontamination of the digestive tract (SDD) is directly applicable to this type of problem. The clinical application of this technique to ITU patients is currently the subject of considerable interest and controversy.

The microbiological background to SDD has been extensively reviewed in this journal (Van Saene & Stoutenbeek, 1987) and elsewhere (Van Saene et al., 1983; Van der Waaij, 1987). Briefly, clinical regimens of SDD employ orally-administered antibiotics to eliminate or markedly reduce the number of AGNB (and usually of yeasts) in the gastrointestinal tract, thus directly reducing the risk of endogenous infection with these organisms. The highly selective action of the antibiotics used allows retention of the normally predominant anaerobic flora of the gastrointestinal tract, and this retained flora prevents colonization or overgrowth with organisms resistant to the drugs used for decontamination, a phenomenon termed colonization resistance. It should be emphasised that the clinical use of SDD is a specialized application of concepts derived from extensive experimental studies in mice (briefly reviewed by Van der Waaij, De Vries-Hospers & Welling, 1986), and considerable care is required when utilizing these experimental results to explain clinical data.

The clinical use of SDD regimens is not novel. The first explicit clinical application in the United Kingdom appears to have been the study of Guiot & Van Furth (1977) who described the use of ‘partial antibiotic decontamination’ in nine patients suffering from agranulocytosis. There have been numerous subsequent studies in neutropenic patients (e.g., Sleijfer et al., 1980; Kurrle et al., 1986), often with impressive results. However, the role of the technique in this complex and specialized field has still to be established.

The first application of SDD to ITU patients was reported from Groningen, Holland, by Stoutenbeek et al. in 1984. It should be emphasized that the prophylactic regimen employed in this important study combined three distinct elements: SDD applied throughout the duration of ITU stay, systemic cefotaxime administered during the first few days of admission only, and intensive microbiological monitoring throughout the admission. SDD was achieved with a mixture of tobramycin, polymyxin E and amphotericin B, applied as a sticky base to the oropharynx and as a fluid via a nasogastric tube to the stomach and more distal intestinal tract. SDD was supplemented with cefotaxime in order to provide additional broad-spectrum cover for the early period of admission. During this time SDD is only partially established, intubation and other invasive procedures are very common, and sub-clinical infection undiagnosed at admission may become manifest. Systemic cefotaxime has only minimal effects on the anaerobic flora of the gastrointestinal tract and is thus unlikely to impair colonization resistance. This prophylactic regimen did not prevent the therapeutic use of other systemic antibiotics when indicated by clinical and microbiological findings. However, drugs with minimal effects on the anaerobic flora of the gastrointestinal tract were employed (Van Saene et al., 1983).

This triple regimen (usefully described by the acronym SPEAR—selective parenteral and enteral antisepsis regimen) achieved a marked reduction in the colonization of the oropharynx and of the rectum with AGNB. The incidence of unit-acquired infection was also strikingly reduced—from 81% of 59 patients in a traditionally managed control group to 16% of 63 patients managed with SPEAR. Problems of antibiotic resistance were not encountered. Although SPEAR was primarily designed to prevent endogenous infection within individual patients, environmental studies (Miranda et al., 1983) suggested a major secondary affect on the bacterial ecology of the ITU, with a consequent reduction in the risk of exogenous infection with AGNB. These findings, together with the recognized complex inter-relationship between exogenous and endogenous infection, suggest that SPEAR should be viewed more in
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terms of manipulation of the patients total microbiological environment than as a prophylactic regimen confined to the individual. This view of SPEAR has major implications for the design of clinical trials to assess the technique.

Although the results described by Stoutenbeek et al. are impressive, they pertain only to a highly selected group of patients. Multiple trauma patients with a duration of ITU-stay exceeding four days who were neither infected nor receiving antibiotics at the time of admission. By contrast, a recent report from Glasgow, United Kingdom, (Ledingham et al., 1988), described the application of SPEAR to all the patients admitted to an unspecialized, medico-surgical ITU over a period of eight months. This prospective trial studied a control group of 161 patients who were managed traditionally followed by a test group of 163 patients managed with SPEAR. The SPEAR group showed a striking and consistent reduction in the colonization with AGNB of the oropharynx, stomach and rectum, and a statistically significant reduction (24% to 10%) in the incidence of unit-acquired infection. Mortality in certain categories of patient was also substantially reduced, but statistical significance could only be established in relation to trauma patients. Again, problems of drug resistance were not encountered. These results both confirm and significantly extend the findings of Stoutenbeek et al. (1984). In both studies, the bacteriological and morbidity data are consistent with the assumptions upon which SPEAR is based (although great care is required when drawing such conclusions from what are recognized to be very complex biological systems).

Taken together, the Dutch and Scottish studies describe the use of SPEAR in 226 patients, and the results suggest strongly that SPEAR represents a significant advance in the control of unit-acquired infection in an unspecialized medico-surgical ITU. This conclusion is further supported by the impressive results described in three other reports of the use of SPEAR or similar regimens in a total of 56 ITU patients (Aerdts & Van Dalen, 1987; Stoutenbeek et al., 1987a; Unertl et al., 1987).

If the efficacy of SPEAR is provisionally accepted, then the possible emergence of problems of drug resistance remains a major and legitimate concern. Problems may arise both from the complex selective pressures for resistance imposed by the regimen and, possibly, from the induction of β-lactamases in certain species of Gram-negative bacilli during the initial periods of cefotaxime therapy (Brun-Buisson et al., 1987; Livermore, 1987; Sanders & Sanders, 1987). However, the alternative of traditional management involves extensive use of a wide range of antibiotics (including cephalosporins) and hence, in some measure, the same potential problems. Moreover, the SDD component of SPEAR is specifically designed to prevent colonization or overgrowth with drug-resistant strains, and the extensive microbiological surveillance should allow early detection of problems and prompt institution of well-established control measures. More generally, a modern ITU environment exposed simultaneously to cefotaxime therapy and an effective SDD regimen represents a novel situation, and considerable care is therefore required when making predictions from data obtained under different conditions. In these circumstances, events in practice must be the final arbiter, and in this respect the results obtained with SPEAR are encouraging: significant problems of drug resistance have yet to be reported despite careful monitoring (Stoutenbeek, Van Saene & Zandstra, 1987b), and continuous use of the regimen at one centre for more than five years. Nevertheless, detailed and continuous microbiological surveillance must remain an essential component of SPEAR for the foreseeable future.

The use of SPEAR in ITU practice must be assessed in the context of the complex characteristics of unit-acquired infection and the well-documented limitations of traditional management. At present, an appreciable body of published evidence suggests strongly that SPEAR may represent a major advance in this previously intractable area. However, many important questions remain unanswered and further clinical and experimental studies are required. Meanwhile, the more widespread use of SPEAR in unspecialized medico-surgical ITU's is justified, but only in circumstances that allow rigorous application of the very detailed microbiological surveillance and drug dosage protocols.

STEPHEN R. ALOOCK**
IAIN McA. LEDINGHAM*
*Department of Bacteriology and Immunology and
**Department of Surgery,
Western Infirmary,
Glasgow, G11 6NT,
Scotland
*Corresponding author
References


**Cefuroxime axetil**

Cefuroxime axetil is a prodrug of cefuroxime, an injectable second generation cephalosporin with excellent activity *in vitro* (O'Callaghan et al., 1976), enhanced stability to many enterobacterial β-lactamases (Greenwood, Pearson & O'Grady, 1976) and favourable pharmacokinetic properties (Foord, 1976). However, Foord (1976) reported that cefuroxime is not absorbed after oral administration largely because it is highly ionised at physiological pH and therefore is poorly lipid soluble. Cefuroxime axetil is the 1-acetoxyethyl ester of cefuroxime, which after oral administration is rendered more lipophilic by esterification of the C4 carboxyl group of the molecule thus enhancing absorption. The absorbed ester is rapidly hydrolysed, within three to four minutes of absorption, in the intestinal mucosa and in the portal circulation (Harding et al., 1984). The products of de-esterification are active cefuroxime, acetaldehyde and acetic acid. It is not possible to detect cefuroxime axetil itself in the systemic circulation.

Cefuroxime axetil has been under development for a long time owing to a number of problems, many associated with the physico-chemical properties of the drug itself.

Clinical trials were started in 1981 with large, uncoated tablets (T), with consistent bioavailability and acceptable clinical results (Harding, Williams & Aryton, 1984; Sommers et al., 1984; Williams & Harding, 1984). These tablets were modified to reduce their size (RS) and film coated to mask the bitter taste. With subsequent pharmaceutical development, a second version (RS2) was released for clinical trials in 1983. Again, these appeared to have acceptable bioavailability (Ginsberg et al., 1985). However, reports began to appear suggesting that absorption was erratic and that this might affect clinical outcome (Adams et al., 1985; Carson et al., 1987).

A fascinating story now unfolds. Standard dissolution and disintegration tests failed to discriminate between batches that were well or poorly absorbed; more specifically batches could pass these standard tests and yet be poorly absorbed. The material forms a gel when suspended in water at 37°C and slow penetration of aqueous medium through the film-coat was found to cause occasional failure of the tablet to disintegrate rapidly. This is believed to have led to a significant proportion (about 13%) of the RS2 tablet failing to be adequately absorbed in volunteers, with a bimodal distribution of absorption, the upper band being satisfactory (about 50%) and as reported earlier. It was found that the nature and thickness of the film-coat were critical for allowing water into the tablet core and a further modification (RS3 tablet version), together with added disintegrant in the core, has overcome this problem and, in addition, has reduced the variability of absorption and improved the total absorption (Harding & Walton, 1987). A new pharmaceutical disintegration test has had to be developed—a film coat rupture time test—to control this process. Over 300 doses to healthy volunteers have revealed only one failure of absorption, an incidence similar to that with other orally absorbed drugs and not necessarily indicative of a formulation problem (Harding S. M. & Walton, C. A., personal communication).

Early clinical studies with this formulation have been successful with reproducible bioavailability.

A second unusual feature of cefuroxime axetil was also revealed. The bioavailability as measured by urinary recovery of cefuroxime was about 50% if the axetil was taken after food but only 30% if the same preparation was taken after overnight fasting (Williams & Harding, 1984; Ginsberg et al., 1983). This phenomenon is not seen with the oral administration of other cephalosporins (Ginsberg & McCracken, 1979; Welling & Tse, 1982), and it is not clear why it should occur with cefuroxime axetil. Possible explanations include the alteration of intragastric pH by food, an effect on gastric emptying time or gut motility, improved dispersion of drug or competition for esterase activity. Unfortunately, investigation in man is hampered by the lack of availability of suitable agents to alter or measure these factors (for example, esterase inhibitors) and, when raising pH, by the instability of cefuroxime axetil in the presence of alkali. Repeated dosing does not alter the amount of drug absorbed and the kinetics of absorption are independent of dose; the drug is equally well absorbed in men.