Selective decontamination of the digestive tract in intensive care

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SUMMARY

Nosocomial infection in intensive care unit (ICU) practice is a common problem and is associated with abnormal carriage of Gram-negative aerobic bacilli in the gastrointestinal tract, resulting in endogenous infections. Selective decontamination of the digestive tract (SDD) is a regimen aimed at preventing or eradicating this abnormal carriage.

A large number of trials examining SDD in ICU practice have been published, the vast majority showing a significant reduction in the incidence of nosocomial, Gram-negative infection. However, the impact on morbidity and mortality is much less certain. A recent meta-analysis has suggested a 10–20% reduction in mortality (3–6% absolute difference) with SDD. A discussion of these results is presented together with potential criticisms of SDD.

INTRODUCTION

Progress in intensive care medicine has enabled clinicians to keep extremely sick patients alive for considerable periods of time. These critically ill patients are vulnerable, and can succumb to even minor insults. Nosocomial infection is a particular problem, especially with long-stay patients: up to 80% of general intensive care unit (ICU) patients may have acquired infection after a stay of 5 days or more [1–3].

Although previously it was believed that infection was a major cause of death amongst these patients, recent thinking has swung away from this view towards the concept of death *with* infection rather than *of* infection [4]. This is obviously an oversimplification as we remain aware of the fact that even healthy people can die of virulent infections (e.g. Legionnaires' disease) and in at least one study nosocomial infection was associated with a threefold increase in mortality [5]. However, ICU patients commonly acquire infections from a relatively restricted set of organisms, often of low virulence, not normally seen in the general population. These organisms are predominantly Gram-negative aerobic bacteria (GNAB), and often originate from the patient's own gastrointestinal tract (GIT).

A well-documented progression is seen in long-stay ICU patients, with initial colonization of the GIT with GNAB, leading to an abnormal carrier state (a qualitative and quantitative change in the carriage of GNAB within the GIT). This is followed by colonization of major organ systems with these organisms and finally overt infection [6–8]. This 'abnormal carrier state' is almost invariable in

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critically ill patients after 2 or 3 days in ICU, and reflects the patient's weakened defences in critical illness.

Selective decontamination of the digestive tract (SDD) is a prophylactic regimen aimed at preventing or eliminating this abnormal carriage, thus preventing acquired infection. SDD is very successful at this: almost all trials of SDD to date have shown dramatic reductions of colonization rates and significant reductions in the incidence of infection. However, one of the reasons for the current view that ICU patients are dying with but not of infection comes from the fact that despite these reductions, SDD trials on the whole show less benefit in terms of reduced mortality. This point will be discussed in detail below.

PRINCIPLES AND AIMS OF SDD

SDD is founded on three principles: Firstly, most ICU-acquired infections are caused by GNAB. Secondly, colonization and infection of major organ systems usually occurs after prior colonization of the GIT. Thirdly, the normal (predominantly anaerobic) flora of the oropharynx and GIT rarely cause nosocomial infection and may even contribute to the defence against abnormal colonization.

SDD aims to prevent or eradicate the state of abnormal carriage of GNAB in the GIT and oropharynx whilst preserving the anaerobic flora. Most SDD regimens also include an antifungal agent, as fungal overgrowth may lead to systemic fungal infection in immunosuppressed patients. The primary goal of SDD is to abolish the abnormal carrier state; secondary goals are to reduce morbidity and mortality due to nosocomial infection.

THE SDD REGIMEN

The most widely studied regimen is polymyxin-E, tobramycin and amphoteracin B (PTA) as used in the original Groningen trial [9]. A mixture of these antibiotics is applied to the oropharyngeal mucosa in the form of the sticky paste or gel (to ensure prolonged mucosal contact) and an aqueous mixture of the same antibiotics is introduced into the stomach four times daily. Full details of the regimen can be found in a recent review [10]. In addition many centres add a systemic agent (usually cefotaxime) for the first few days.

The cefotaxime serves several purposes. Its broad spectrum includes Gram-positive organisms, which are responsible for many of the early ICU infections [6, 11], and it is a good 'best guess' antibiotic to treat any sub-clinical infections that may be developing. It also provides prophylaxis for the early period in ICU when most invasive procedures (for example endotracheal intubation and insertion of intravascular lines) are performed. It provides activity against GNAB until the topical agents have established an effect, which typically takes 2–3 days [11]. The magnitude of the contribution by cefotaxime to the overall effect of SDD is currently unresolved [12].

The use of other parenteral antibiotics should be avoided if possible, especially those with significant action against the anaerobic flora such as ampicillin and ureidopenicillins.

A third aspect of the SDD regimen is rigorous microbiological surveillance to ensure early detection of drug-resistant strains, and the prompt institution of well-

established control procedures if required. Surveillance is also essential to ensure that 'decontamination' has been achieved.

The ideal SDD regimen would cover all GNAB (including Enterobacteriaceae, pseudomonads, and *Acinetobacter* species) and yeasts whilst leaving the anaerobic flora intact. Ideal agents would be completely non-absorbable to avoid systemic toxicity and fluctuations in levels that may lead to resistance developing. The agents should not be inactivated by gastric acid, luminal enzymes or faeces.

The PTA regimen is not ideal, but does fulfil many of the above criteria. Polymyxin-E and tobramycin both cover a wide spectrum of GNAB and act synergistically, particularly against some pseudomonads [13]. Resistance to polymyxin-E is rare, whereas plasmid encoded resistance to aminoglycosides is a potential problem. However, polymyxin-E protects tobramycin from being destroyed by bacterial enzymes [13]. Notwithstanding there are a few gaps in the spectrum. Polymyxin-E is inactive against *Proteus* and *Morganella* spp., *Serratia* spp. and *Acinetobacter* spp. may be resistant to tobramycin. *Pseudomonas cepacia* is resistant to both tobramycin and polymyxin-E. In all about 10% of organisms are resistant to one or other of the agents, but significant problems with these organisms have yet to be described [14]. Even organisms partly resistant to the agents on standard disk testing are successfully eliminated due to the high local concentrations of the drugs. Enterococci are intrinsically resistant to both tobramycin and polymyxin-E, and although generally thought to be of low pathogenicity, there have been reports of serious enterococcal infections [15, 16].

Polymyxin-E is moderately inactivated by faeces and amphotericin B is substantially inactivated [13], but tobramycin is not. Some studies have substituted gentamicin for tobramycin [17–19] but gentamicin is more susceptible to inactivation by faeces.

THE PATIENTS

ICU patient populations vary significantly between units [20]. Although in the UK most units are mixed with medical, surgical and trauma patients, other units are specialized, catering only for cardiac surgery or neurosurgery patients for example. In mixed ICU's infection has been reported in between 18 and 36% of patients [1, 21], whereas in cardiac surgery ICU infection rates are much lower – in the order of 1–2% [22].

Humans are continuously exposed to potentially pathogenic microorganisms. These are encountered in the environment and large numbers are harboured within the GIT. These do not normally present a problem to the healthy individual because of the defences provided by normal anatomy, physiology and immunology. The ICU patient is vulnerable because many of these anatomical, physiological and immunological defences are disrupted. Immunity may be impaired by underlying diseases such as diabetes [23], alcoholic liver disease [24], malignancy (and its therapies) and malnutrition [25, 26]. Trauma, burns and major surgery have also been shown to impair the immune response [26–30].

Skin and mucosal surfaces are breached by traumatic, surgical or thermal wounds, intravascular lines and urinary catheters. Stasis occurs in the GIT. Normal physiological cleansing mechanisms such as chewing and swallowing are lost. The flow of saliva and gastric acid is reduced, no longer stimulated by food and hunger.

Lower respiratory tract infection poses the greatest problem, accounting for up to 50% of all episodes of infection [1, 22, 31]. Depression of the normal protective airway reflexes in obtunded patients can lead to aspiration of oropharyngeal contents [32]. Endotracheal intubation is a recognized risk factor for infection [33]. The actual process of intubation carries organisms from the oropharynx into the normally sterile lower airway. Even with the endotracheal tube cuff inflated it is recognized that seepage of oropharyngeal contents into ten lower airway occurs [34]. This may be a particular problem with the low-pressure, high-volume cuffs favoured for longer-term ventilation. Intubation also disrupts the normal mechanisms of coughing and mucociliary clearance, and endotracheal suction can damage the respiratory epithelium and mucociliary transport [35]. Many patients have nasogastric tubes, which can facilitate gastro-oesophageal reflex, encouraged by the supine position.

Atherton and White first stressed the role of gastric colonization in nosocomial pneumonia in 1978 [36]. Although gastric acid effectively kills GNAB [37], approximately 50% of critically ill patients have low levels of gastric acid production [8, 38], and many units still use H2 antagonists and antacids as prophylaxis against stress ulceration. A cut off at pH 4 appears to be clinically important, with high bacterial counts noted above this level [39].

The traditional view that lower respiratory tract infection is caused by aspiration of contaminated oropharyngeal contents has recently been questioned [40, 41]. Fiddian-Green suggests that ischaemic mucosal injury of the gut, allowing translocation of bacteria, may be a more important mechanism [41].

The normal anaerobic flora of the oropharynx and GIT have a role in the prevention of colonization by GNAB, so called 'colonization resistance' [42, 43]. The normal GIT flora also contribute to the maintenance of immunological homeostasis, and when abnormal can produce systemic depression of lymphocyte function [44]. There are important interactions between the GIT flora, the local immunological mechanisms (gut lymphoid tissue and liver Kupffer cells) and the systemic immune response. However, these are complex, and at present incompletely understood.

TRADITIONAL METHODS OF INFECTION CONTROL

ICU physicians are very aware of the fact that many of their patients are at risk of infection, both from the critical illness itself and from the invasive nature of intensive care treatment. Most modern units take great care to prevent transmission of infection to their patients. It is now well recognized that the hands and clothing of attending staff are potential vectors for the transmission of infection both from staff members and between patients. Hand washing and application of antiseptic solutions such as chlorhexidine in isopropyl alcohol are routine before and after patient contact in many units. Careful attention to asepsis and antisepsis during the insertion of intravascular lines and urinary catheters for example has been shown to reduce septic complications and to increase the time that these devices can be safely left in situ. In the past exogenously transmitted respiratory tract infections were a major problem for ventilated patients, but now the use of sterile disposable breathing circuits and humidifiers has rendered this once endemic problem one of historical interest only.

Despite these precautions, spread of exogenous infection from patient to patient does still occur, but can be minimized by the above-mentioned measures and also by increasing the distance between beds or the use of isolation rooms.

However, even with the most stringent of regimens, ICU patients still become infected [45]. These measures are only able to control exogenous infections, whereas the major source of acquired infection in ICUs is thought to be endogenous – i.e. from the patient's own colonizing bacterial flora.

DEFINITIONS OF COLONIZATION AND INFECTION

In order to compare different trials and protocols of SDD it is important to define end-points such as colonization and infection as accurately as possible. As there are obvious differences between different organ systems it is also necessary to specify in the definition to which organ system the definition pertains.

There has been a wide variety of definitions used in trials of SDD. For example, in defining respiratory tract infection, some workers have defined it purely on clinical grounds using non-specific evidence of infection such as fever and leukocytosis combined with organ specific clinical signs such as deterioration in gas exchange, purulent sputum and new infiltrates on chest X-ray. This definition of infection does not include a microbiologically proven diagnosis of infection, and thus could lead to overdiagnosis, as many of these features are also seen in ARDS (adult respiratory distress syndrome). Other workers have restricted the diagnosis of lower respiratory tract infection to those in whom samples obtained purely from the lower respiratory tract (by protected specimen brush or transthoracic fine needle aspiration) grow $> 10^3$ organisms per ml of at least one organism in combination with the above clinical features [46, 47].

Although we all intuitively understand the terms 'colonization' and 'infection' there is in fact a continuum between the two and the cut-off point is actually quite difficult to define accurately [48]. Colonization is generally defined as the persistent presence of microorganisms not normally found at a particular site isolated from the site in question in the absence of clinical signs of infection. Precision is required in the definition of persistence of an abnormal organism and this is usually taken as finding the organism(s) on at least two separate occasions separated by at least one week. The definition should also specify the number of organisms in the sample (for example between 10 and 10^3 organisms per ml or gram of sample). At first sight absence of clinical signs of infection may be thought of as easy to define but this becomes harder and more arbitrary in sites such as the respiratory tract and urinary tract where intubation or catheterization can themselves lead to an inflammatory response stimulating accumulation of leukocytes. An arbitrary cut-off level is needed such as the finding of < 25 white cells per low power field being defined as colonization. In the urinary tract it is generally agreed that more than 10^5 organisms per ml of urine is indicative of infection whereas the finding of lower numbers of bacteria is suggestive of colonization but again there is a continuum and the cut-off is also artificial and arbitrary. If the definition of infection includes systemic signs such as fever, tachypnoea and leukocytosis we can still be misled as many critically ill patients have a systemic inflammatory response in the absence of infection. Systemic inflammatory response syndrome (SIRS) is the latest terminology for the 'sepsis

syndrome', which recognizes the need for a wider, non-prejudicial definition to include conditions such as severe pancreatitis and extensive burns, with systemic manifestations indistinguishable from classical bacterial sepsis.

The diagnosis of bacteraemia is relatively straightforward in that the isolation of any organism from a blood sample can be considered as abnormal. However, difficulty may arise with the isolation of organisms such as *Staphylococcus epidermidis* which can be pathogenic in critical care patients but is also a common contaminant of blood culture samples. If there is any doubt it is usual to treat a blood culture positive with this organism only after two or more isolations of the organism from the blood.

Interpretation of microbiological cultures can be confused by prior administration of parenteral antibiotics (or even direct contamination of samples such as tracheal aspirates by topical antibiotics as used in SDD regimes), leading to false negative results.

Infections have been classified as exogenous (acquired from the environment) or endogenous (acquired from the patient's own flora). Endogenous infections can be subdivided into primary and secondary endogenous infections. Primary endogenous infections are due to organisms normally colonizing the patient whereas secondary endogenous infection follow a period of abnormal colonization prior to infection.

Standard international definitions of colonization and infection in critical care practice need to be agreed to aid interpretation of future trials in this field.

TRIALS OF SDD IN ICU

Since the first published trial of SDD in ICU patients in 1983 from Groningen [9] (using the PTA and cefotaxime regimen) there have been many other trials of SDD in ICU (at least 30 to date). The great majority of these show a significant reduction in colonization and respiratory tract infection in the treatment groups compared to the control groups. Impact on morbidity (as assessed by length of ICU stay for example) and mortality is much less certain, with most trials showing no significant difference. However, the numbers of patients in each trial are relatively small and most study designs did not have sufficient power to demonstrate a reduction in mortality. It is perhaps surprising then that several trials have actually shown a reduction in overall mortality [49–51], and others (admittedly usually only after post hoc analysis), a reduction in mortality in subgroups such as trauma patients [10, 19] and patients with mid-range APACHE scores [10, 47, 52]. Studies to date have not shown a statistically significant effect of SDD on length of ICU stay. However, a reduction of 2–3 days was apparent in several studies [3, 31, 47, 53].

Although SDD has its greatest impact on nosocomial pneumonia, it is probable that only a small proportion of ICU deaths are directly attributable to these infections, most deaths being related to the prognosis of the underlying condition [54]. It follows therefore that a large number of patients will be required to show a statistically significant reduction in mortality due to SDD. Meta-analysis has been used by two groups in an attempt to resolve this problem [55, 56]. However, comparison between the published trials is difficult: definitions of infection differ; the patient populations studied differ; the proportion of infected patients and the

unit mortality rates differ; the regimen and drugs used for SDD and the inclusion of a systemic agent have also varied considerably between centres. Therefore meta-analysis of these trials can at best give only a rough approximation of the effect on mortality of SDD.

Vandenbrouke-Grauls and Vandenbrouke [55] included 11 published studies from 1984–90 with 1489 patients; however, only 491 patients were in randomized (or alternate allocation) controlled studies. They did not use methodological selection criteria and accepted the results as published. They concluded that both the randomized controlled trials and the trials with historical controls showed that SDD had a significant ($p < 0.05$) protective effect on the risk of respiratory tract infection (odds ratio 0·12, 95% confidence limits 0·08–0·19 and odds ratio 0·21, 95% confidence limits 0·15–0·29, respectively), but no significant effect on mortality (odds ratio 0·70, 95% confidence limits 0·45–1·09 and odds ratio 0·91, 95% confidence limits 0·67–1·23, respectively).

The meta-analysis of Liberati and Brazzi [56] included 27 trials between 1984 and 1991 on 3587 patients, 2225 of which were in 16 prospective randomized trials. For their mortality analysis only the prospective randomized trials were reported. Full details of the patients were obtained from the principal investigators of 12 of these trials and 213 patients excluded from the published results were included in an 'intention to treat' analysis. From a total of 2438 patients there were 760 deaths, 335 in the SDD group and 425 in the control group, giving a significant 21% reduction in mortality (odds ratio 0·79, 95% confidence limits 0·65–0·95). However, after excluding an outlying study by Hünefeld [49] (which had a very high overall mortality of 77%) the reduction in mortality was not significant (11%, odds ratio 0·89, 95% confidence limits 0·73–1·09). Liberati recently updated this meta-analysis (CIPI-II, Nice, May 1992) to include 19 randomized studies (3444 patients). The treatment effect of SDD still showed a 21% reduction in mortality (odds ratio 0·79, 95% confidence limits 0·67–0·93). Excluding the Hünefeld study [49] gave an odds ratio of 0·87 (95% confidence limits 0·73–1·02).

This carefully conducted, on-going, meta-analysis suggests a 10–20% reduction (3–6% absolute difference) in mortality, attributable to SDD. For a single study to show a statistically significant reduction in mortality an enrolment of about 2000 patients would be required.

Stoutenbeek [3] has highlighted a potential problem with randomized controlled trials, in that the benefits of SDD may overflow to the control patients in the same unit, by altering the microbiological milieu of the unit and reduce the likelihood of cross infection. Such an effect has been reported [57]. Conversely, control patients may act as reservoirs of organisms, spilling over to continuously recolonize the SDD patients. Both of these possibilities would lead to an apparent reduction in the effect of SDD.

SDD AS A METHOD OF OUTBREAK CONTROL

Since the 1970s *Klebsiella* species with acquired plasmid-mediated resistance to multiple antibiotics have caused many hospital epidemics especially in ICU [58]. Intestinal colonization has been shown to be an important reservoir for these organisms and transfer from patient to patient is primarily via the hands of health care personnel.

Two centres have reported the successful control of outbreaks of multi-resistant *Klebsiella* species by means of SDD [57, 59]. In Taylor and Oppenheim's study [59] the outbreak was caused by *Klebsiella aerogenes* resistant to ceftazidime, cefuroxime, cefotaxime, ampicillin and piperacillin (but sensitive to amino-glycosides). The outbreak occurred in a busy general ICU over a 3-month period. When traditional infection control methods failed to eradicate the outbreaks, all patients were then treated with an SDD regimen. PTA gel was applied to the oropharynx, nose and rectum and a suspension of the same agents was also given via a nasogastric tube. Introduction of the SDD regimen resulted in rapid disappearance of the Klebsiella, with no evidence of super-infection or appearance of other resistant isolates. In the French study by Brun-Buisson and colleagues [57], control of the outbreak was achieved despite only half of the patients being treated with SDD. It would appear that the abolition of carriage of multi-resistant Klebsiella strains by SDD is associated with a significant reduction in its transmission, followed by the control of outbreaks. Clearly, there is no role for a parental agent in this situation, unless systemic antibiotics are otherwise clinically indicated.

MULTIPLE ORGAN FAILURE

Despite the use of SDD many critically ill patients still die of multiple organ failure (MOF), without evidence of infection – so called 'non-bacterial sepsis'. There is now increasing evidence to suggest that such patients are suffering from the absorption of mediators such as endotoxin from the GIT [44, 60]. If gut derived endotoxin is a major mediator, then SDD may have a role in reducing the gut endotoxin load, both by reducing GNAB colonization and directly by the binding of endotoxin to polymyxin-E [61]. In an experimental study of sterile peritonitis SDD has been shown to prevent bacterial translocation, endotoxaemia and death [62]. However, as presently administered the reduction in large bowel GNAB is both slow and often incomplete (particularly in post-operative patients), suggesting that other therapies such as gut irrigation may also be required if gut mediated MOF is to be avoided.

CRITICISMS OF SDD

SDD is still regarded with suspicion by many ICU physicians, especially in North America. There are several reasons for this: foremost of these is the impact of SDD on mortality and morbidity, hotly debated but still unresolved.

Long-term use of prophylatic antibiotics has raised concern over the selection of resistant organisms. However it must be borne in mind that parenteral antibiotic usage in traditional ICUs is already very high [11], and that SDD may actually lead to a reduction in the need for other therapeutic antibiotics [11, 31]. Problems with resistant organisms have yet to be described, but rigorous microbiological surveillance must remain an integral part of any SDD regimen.

Another major concern is the cost of the regimen, not only in terms of the cost of the drugs themselves (which vary considerably between countries), but also the extra burden on the ICU staff in administering them and collecting the surveillance culture samples. The workload of the microbiologists in processing the surveillance cultures also needs to be considered. These may be offset by savings on diagnostic

procedures, therapeutic antibiotics and intravascular line changes due to lower infection rates. Any gains in terms of mortality or length of ICU stay would obviously contribute greatly to the cost-benefit analysis.

CONCLUSIONS

Before SDD becomes generally accepted and incorporated into universal ICU practice there are questions to be answered. Despite overwhelming evidence to suggest that SDD can reduce colonization and nosocomial infection, its effects on mortality and morbidity are as yet unproven. The significance of the contribution of the systemic agent to the overall effect is still open to debate, as is the best choice of antimicrobial agents.

Whether the full benefits of SDD are only seen when all patients in a unit receive it or whether it can be fully efficacious when applied selectively to those patients most likely to benefit, requires further evaluation.

Audit is becoming increasingly important especially in critical care. With scarce financial resources and costly new treatments such as monoclonal antibodies competing for them, accurate cost-benefit analysis for SDD is essential.

It is vital that these questions are answered definitively. If this potentially useful weapon can be shown convincingly to have a role in the treatment of the critically ill it will have an important place in ICU practice, probably in selected patient groups.

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