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Selective decontamination in intensive care practice: a review of clinical experience

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Abstract. Acquired infection is a common problem in intensive care and in a general ICU the infection rate can exceed 80% in patients ventilated beyond 5 days. SDD, adapted from regimes used in neutropenic patients, was first introduced to the ICU situation in Groningen. This article reviews 10 published trials of SDD in ICU. The trial designs vary but all show a significant reduction in both colonisation rates and acquired infection rates. Infection rates were reduced from 10%–78% to 3%–10% in the SDD treated groups. Of the 10 trials 2 showed an overall reduction in mortality 2 showed a reduction in infection-related mortality and 1 showed a reduction in mortality amongst trauma patients. Although further evaluation of trials is required SDD now appears to be of proven efficacy in certain groups of high risk patients within ICU.

Key words: Selective decontamination of the digestive tract (SDD) – Nosocomial infection – Multiple organ failure

There is a large background of literature dealing with the successful use of selective decontamination of the digestive tract (SDD) in severely immuno-compromised patients [1–3]. This background work, the concept of "colonisation resistance", the reasoning behind the introduction of SDD and the choice of drugs for SDD regimens have all been discussed elsewhere in this edition of the journal. This chapter will deal solely with the introduction of SDD into the intensive care setting and will review current clinical experience with the regime in intensive care.

Infection rates of 18%–36% have been reported for intensive therapy units [4–7]. There is a high incidence of unit-acquired infection and surveys have shown that the incidence of unit-acquired infection increases with the length of stay, exceeding 80% in patients admitted for 5 or more days [4]. This high incidence of infection appears to be associated with increased mortality [8] and, until recently, it was thought that infection contributed directly to multiple organ failure in many instances [9], though this latter statement is now open to debate. Nosocomial pneumonia is a particularly troublesome problem in intensive care and accounts for up to 60% of all episodes of infection [4, 6, 10], endotrachael intubation and ventilation being the major risk factor.

It is difficult to make precise statements regarding the pathogenesis of ICU infections because of the complexity of the problem. However, most unit-acquired infections are now thought to be endogenous, with abnormal colonisation of the patient's gastrointestinal tract with gram-negative aerobic bacilli (GNAB) preceding colonisation and infection of the major organ systems [11–13]. A wide range of organisms may be involved in intensive care infection but GNAB (particularly *Escherichia coli Klebsiella*, *Proteus*, Enterobacter and *Pseudomonas species*) are by far the commonest infecting organisms [4, 10, 14].

The incidence of infection in different types of ICU can vary widely [6, 7]. Clearly a regime such as SDD may be appropriate in a general-surgical ICU with an infection rate above 30% but would clearly be inappropriate in a coronary care unit or cardiac surgical ICU with an infection rate below 2%. In the following text ICU should be taken to mean a general medical/surgical ICU with a high proportion of trauma patients or post-operative surgical patients, many of whom are ventilated.

Pattern of colonisation and infection under traditional infection control

In a traditionally manged ICU, control of colonisation and infection is based on aseptic technique and a restrictive antibiotic policy. Antibiotics tend to be withheld until good clinical and microbiological evidence of infection exists. An appropriate antibiotic is then given according to sensitivity testing. The principle of careful aseptic technique is clearly a good one, since regardless of wheth-

er infections are endogenously or exogenously acquired it should in theory be possible to prevent them by good aseptic technique and thus avoidance of initial bacterial contamination. However, it is patently obvious from the high infection rates already quoted that such regimes fail to control colonisation and infection in a large proportion of patients admitted. Colonisation of the GI tract with GNABs occurs rapidly following admission to ICU, usually within 48–72 hours [15].

In day to day life the GI tract is constantly exposed to large quantities of potentially pathogenic GNABs. Except in situations of extremely high bacterial concentrations, a variety of factors, together constituting "colonisation defence" act to prevent colonisation of the mucosal surfaces of the digestive tract. In health, motility and an anatomically intact mucosal surface are probably the most important factors. Colonisation and infection defence factors have been fully described elsewhere [16] but in a typical ICU patient these important lines of defence against colonisation and infection are deficient. A typical ICU patient should be thought of as an immuno-deficient host and it is worth considering in a little detail the various reasons why such a patient is so prone to abnormal colonisation and infection:

Nature of presenting disease

A patient's host defence can be adversely affected by a number of underlying diseases such as diabetes [17], renal and liver failure [18] and malnutrition [19, 20]. In addition, patients suffering from physical trauma show impaired host defence, regardless of whether the trauma is skeletal, thermal or following major surgery [21–24].

Use of broad spectrum antimicrobial agents

It has long been postulated that the widespread use of broad-spectrum antibiotics can predispose to colonisation by GNABs as a result of alterations in the normal indigenous flora. Such an effect was shown to occur after large dose penicillin therapy [25] and the same authors were able to prevent abnormal colonisation by inducing a state of resistance in the normal flora of the GI tract [26]. More recently increasing importance has been attached to the role of anaerobic flora, which are numerically predominant, in the preservation of colonisation resistance of the GI tract [27].

Effect of age

There is some evidence to suggest that colonisation resistance is decreased in elderly patients, with GNAB colonisation being found in a proportion of this group, especially if they are institutionalised [28].

Invasive intrumentation

Medical interventions such as endotrachael intubation, bladder catheterisation and the insertion of intravascular lines predispose to infection by breaching mechanical barriers. The presence of an endotrachael tube can lead to abrasion of the mucosal membrane thus increasing the risk of bacterial adherence and colonisation.

Abnormal gut motility

Lack of oral food intake, the inability of an intubated patient to swallow or chew and decreased or absent peristalsis all tend to predispose to abnormal colonisation. In paralytic ileus fluid accumulates within the bowel and stagnant fluid in this situation, as in any other, tends to become heavily colonised.

Gastric pH>4

Many patients have a gastric pH>4 even in the absence of therapy with antacids or H_2 receptor antagonists.

Gastric pH, colonisation and nosocomial pneumonia

Gastric colonisation as a preceding and predisposing factor for tracheal colonisation was shown as early as 1978 [11]. Du Moulin et al also demonstrated that gastric colonisation can precede tracheal conlonisation [12]. They showed that antacid therapy was a predisposing factor for gastric colonisation. It has been shown that patients with peptic ulcer disease will show significant bacterial colonisation of gastric aspirate after one month on cimetidine [29]. This would suggest a significant relationship between pH and bacterial counts. Other studies have shown the same relationship between pH and gastric colonisation in critically ill patients [30] with an apparent cut-off at a pH of 4; colonisation being rare when the pH is <4. Colony counts greater that 10^5/ml are common in situations with pH>4.

Interest in the role of gastric pH with regard to colonisation and subsequent risk of nosocomial pneumonia has been heightened by the introduction of mucosal protective agents such as sucralfate. Two recent controlled studies comparing sucralfate with antacids and/or H_2 blockers have provided strong evidence for an association between gastric pH, gastric colonisation and nosocomial pneumonia [31, 32]. The study by Tryba [31] showed a significantly higher rate of nosocomial pneumonia in a group treated with antacids than in a group treated with sucralfate, though this only reached statistical significance after excluding primary thoracic trauma and patients with pneumonia on admission. In the antacid group 90% of patients had a pH above 4 while in the sucralfate group only 53% had a pH above 4. Drik's study [32] showed a nosocomial pneumonia rate twice as high in an antacid/H_2 blocker group compared with a sucralfate group. This difference was not statistically significant although the authors did claim statistical significance after excluding patients in whom the initial treatment had been changed by the consulting physician. The obvious conclusion to be taken from these and other studies is that a gastric pH above 4 is the major risk factor for colonisation and carries a subsequent risk of nosocomial pneumonia. However, sucralfate itself has been shown to have a pH dependent antibacterial effect [33].

One additional point worthy of comment is that critically ill patients frequently have a pH>4 even in the absence of antacid or H_2 blocker therapy. In a recent study

comparing sucralfate versus SDD, in a group of cardiac surgery patients, it was noted that gastric pH was less than 4 in only 23% of sucralfate treated patients, leaving the majority without the benefit of gastric acidity as a barrier to bacterial overgrowth in the stomach [34]. This study showed that gastric colonisation with GNABs was significantly less likely in the SDD group than in the sucralfate group (12% v. 55% $p<0.001$). The rate of gram negative infection was also significantly lower in the SDD group (6% v. 20% $p = 0.02$). The antibacterial efficacy of sucralfate in this study may have been hindered by the small proportion of patients with a low gastric pH, but the study serves to underline the fact that gastric pH is often elevated in ICU patients even in the absence of antacid therapy.

Combining sucralfate with SDD would be an attractive proposition but some recent work (unpublished data) has suggested that sucralfate may bind and inactivate the SDD agents within the stomach.

Trials of SDD in ICU

The first report of an SDD regime applied to a group of ICU patients was published by Stoutenbeek et al [35]. They studied a group of long stay trauma patients. Since the publication of this group's original results, the authors are aware of nine other centres who have published their data in either a complete or a preliminary form (Table 1).

Trial designs

As can be seen from Table 1 most of the trials examined a mixture of patients in a general medical/surgical ICU. Stoutenbeek looked at trauma patients only; a population who, in general, are young, with no underlying disease process and no infection on admission. Thülig [37] and Unertl [38] used several specialist ICU's on the same campus and considerable numbers of "clean" cases, such as cardiac and neurosurgery, were included.

Four of the studies [35, 36, 38, 43] excluded all patients who were infected on admission. Ledingham [15] and Guillaume [42] analysed all patients admitted to the ICU regardless of length of stay, while the other studies set out to examine only patients who required, or were expected to require, prolonged ventilation. The early studies [15, 35, 36] utilised a consecutive trial design; two [35, 36] having retrospective control groups while the third [15] was prospective. The reasons for adopting a consecutive trial design have been fully discussed elsewhere [15]. All the subsequent studies were prospective studies with concurrent control groups. In studies conducted by Thülig [37] and Guillaume [42], two separate ICU areas were utilised with one unit using SDD while the other followed the control protocol. Cross-over was effected after the first period in each study.

Of the 10 studies listed in Table 1 six followed the original SDD regime described by Stoutenbeek et al [35]. This standard regime consists of the local application of tobramycin, polymixin E and amphotericin B as a paste to the oro-pharynx and as an aqueous solution down the naso-gastric tube. Variations on this original regime were used in four of the studies – Aerdts' group [39] used the quinolone norfloxacin in place of tobramycin. In Unertl's study [38] the regime differed in several ways: gentamicin was used in place of tobramycin; an aqueous solution of drugs was used and not a paste; gentamicin and polymyxin was applied to the naso pharynx, oro-pharynx and stomach while amphotericin was applied only to the oropharynx. In Guillaume's study [42], both SDD and control groups received amphotericin enterally and also oropharyngeal and naso-pharyngeal disinfection with Povidone iodine. In addition the SDD group received tobramycin and polymyxin enterally. Cockerill [43] used nystatin in place of amphotericin and gentamicin was substituted for tobramycin.

Preliminary work by Stoutenbeek [44] had shown a high incidence of early infections with community flora and as a result eight of the ten studies employed short term parenteral prophylaxis with cefotaxime, usually only for the first few days of admission. However, in the two studies by Unertl [38] and Guilluame [42] no systemic prophylaxis was given. Although the term prophylaxis has been used here, in studies such as that conducted by Ledingham [15], in which many of the patients were infected on admission, the parenteral agent is actually being used as a treatment in a proportion of cases.

Definitions used for the diagnosis of infection were broadly comparable in all studies. For precise definitions reference should be made to the original publications. As already noted above some of the studies excluded patients with infection present on admission. The majority of others sought to differentiate between infections occurring early or late after admission to ICU.

In Aerdts' study [39] two separate control groups were followed. When infection was diagnosed one group received systemic antibiotics which were deemed to have an effect on "colonisation resistance" while the other group received antibiotics that were in theory "colonisation resistance indifferent". This was an attractive trial design but the numbers enrolled were too small to allow any conclusion to be drawn.

Table 1. Published reports of SDD in intensive care

Authors	Study center	Patient numbers		Patient type
		Control	SDD	
Stoutenbeck CP et al. [35]	Groningen	59	63	Trauma
Ledingham I McA et al. [15]	Glasgow	161	163	Mixed
Sydow M et al. [36]	Göttingen	48	45	Mixed
Thülig B et al. [37]	Münster	100	100	Mixed
Unertl K et al. [38]	Munich	20	19	Mixed
Aerdts SJA et al. [39]	Nijmegen	18/21[a]	17	Mixed
Konrad F et al. [40]	Ulm	83	82	Mixed
Kerver AJH et al. [41]	Utrecht	47	49	Mixed
Guillaume C et al. [42]	Lyon	61	68	Mixed
Cockerill FR et al. [43]	Rochester (Mayo)	50	45	Mixed

[a] 2 control groups (see text)

Colonisation rates

Despite the variations in trial design, there has been a remarkable consistency in the results reported. All the studies confirm the rapid increase in GNAB colonisation of the upper GI tract in the control groups, rising from 10% – 40% on admission to 50% – 100% colonisation by 1 week. SDD achieved a consistent reduction in colonisation with GNABs, usually within 48 h, and all studies reported a colonisation rate of 0% – 5% by seven days. Unertl's group [38] found a percentage of gentamicin resistant organisms amongst these isolates but this has not been reported from any of the trials utilising tobramycin.

Rectal colonisation with GNABs was also consistently reduced but this required considerably longer to achieve, particularly in trials containing large numbers of post-operative patients in which paralytic ileus meant that rectal colonisation with GNABs was not abolished for in excess of 2 weeks [15]. This may be an important point when it comes to considering mortality since the lower GI tract in such patients continues to act as a potential source for endotoxaemia, which will be discussed later in this text. This is in stark contrast to the experience of Stoutenbeek where a fall in rectal contamination rates was found to be related to the time of first defaecation [35] and in general rectal decontamination occurred much more rapidly.

Infection rates

SDD has had a statistically significant, beneficial effect on infection rates in all the studies reported. The greatest impact has been on gram-negative respiratory tract infections (Table 2) though infection rates in other organ systems are also reduced. The incidence of unit-acquired respiratory tract infection in control group patients varied from 10% – 78% whereas the incidence amongst SDD treated groups was 3% – 10% (20% in Unertl's study [38]).

Mortality

In contrast to the significant and consistent improvements in colonisation and infection rates, the results pertaining to mortality have been much less consistent (Table 3). Sydow [36] and Guillaume [42] both appear to show a significant reduction in mortality in their SDD groups but the remaining 8 trials show no significant difference in *overall* mortality. However, in two trials (Unertl [38] and Kerver [41]) where infection related deaths were examined separately, both trials showed a significant reduction in mortality in the SDD groups. In addition, Ledingham's results [15] showed a significant improvement in mortality amongst the sub-group of patients suffering from trauma, with SDD reducing the mortality from 35% to 0%. There was also an apparent improvement in mortality in patients with mid-range APACHE scores and in those remaining in the unit for more than seven days. However, these 2 patient groups had not been prospectively stratified, and in addition they were not mutually exclusive; as a result the authors of this study did not claim any statistical significance in these latter groups.

Cost implications

Only Stoutenbeek's group have studied the effects of SDD on the running costs of an ICU or the workload and costs of the supporting laboratory services [45]; they reported large savings following the introduction of SDD. Estimates of the additional drug costs using SDD vary from £ 6000 to £ 50000 per annum (unpublished data). Ledingham retrospectively, carefully calculated the cost difference and it is at the lower end of the above scale. However, the use of SDD does reduce the requirements for other therapeutic parenteral antibiotics [15, 41]. By reducing the incidence of infection there is also a potential saving in laboratory time and the use of disposable items such as venous lines and pulmonary artery catheters. The workload of the microbiology service appears to be decreased as the large numbers of surveillance samples taken for culture show a high proportion of "no-growth" results and do not take up further time with sensitivity testing and typing [45]. There is also a reduction in the number of clinically ordered samples submitted to microbiology [46].

Table 2. Infection rates (acquired) in SDD trials (%) (control – SDD)

Study	Respiratory tract	Urinary tract	Bacteraemia
Stoutenbeek CP et al. [35]	59-8	32-2	42-3
Ledingham I McA et al. [15]	18-3	3-1	11-8
Sydow M et al. [36]	75-7	30-10	8-6
Thülig B et al. [37]	46-10	16-10	–
Unertl K et al. [38]	70-21	–	–
Aerdts SJA et al. [39]	78/62-6[a]	33/38-35	28/38-6
Konrad F et al. [40]	42-6	8-0	–
Kerver AJH et al. [41]	40-6	6-3	57-30
Guillaume C et al. [42]	21-3	–	–
Cockerill FR et al. [43]	Total infections	62-4	

[a] 2 control groups (see text)

Table 3. Mortality rates in SDD trials (%)

Study	Control	SDD	*p* value
Stoutenbeek CP et al. [35]	8	3	NS
Ledingham I McA et al. [15]			
(Overall)	24	24	NS
(Trauma)	26	0	0.002
Sydow M et al. [36]	14	0	<0.05
Thülig B et al. [37]	Not stated		NS
Unertl K et al. [38]	30	24	NS
(Infection related deaths)	15	0	<0.05
Aerdts SJA et al. [39]	22/10	12	Ns
Konrad F et al. [40]	22	30	NS
Kerver AJH et al. [41]	32	29	NS
(Infection related deaths)	Not stated (SDD < control)		<0.05
Guillaume C et al. [42]	18	6	<0.05
Cockerill FR et al. [43]	Not stated		NS

One might reasonably expect that the significant reduction in acquired infection produced by SDD should result in a reduction in days of ventilation and length of unit stay. In the trials reviewed this has not universally been the case; in fact only 2 studies [35, 41] report a decrease in ventilator days (of 3–4 days). It is interesting to note that Stoutenbeek [35] dealt solely with trauma patients and that trauma patients comprised a large part of the patients studied in Kerver's study [41]; infection is known to be the major cause of late morbidity and mortality in trauma patients. The patient groups studied in the other trials were more mixed.

Microbial resistance

All of the centres employing SDD have been careful to monitor for the emergence of organisms resistant to the antimicrobial agents used. To date no resistance of clinical importance has been noted. All the units have isolated GNABs which are resistant to one or other of the agents used. However, these do not persist and tend to disappear without changing the antibiotic regime. Sydow [36], Thülig [37] and Konrad [40] all noted an increase in oropharyngeal colonisation by resistant gram-positive organisms in the SDD treated patients but these did not give rise to infection. (Stoutenbeek in a separate publication [47] studied the pattern of microbial resistance arising in SDD treated patients over a 30 month period. He reported no increase in resistance to any of the agents used). Eastaway [48] studied patients who had undergone SDD for 5 or more days and subsequently returned to general wards within the hospital. A non-significant increase in the incidence of rectal carriage of cefotaxime and tobramycin resistant organisms was found. No infections were identified resulting from these organisms but it was speculated that these may become important if the patient's condition relapsed or a new disease process developed.

Comment

Following the early publications many people worried about the widespread development of microbial resistance as a result of the routine administration of large quantities of antibiotics. This worry was based on a false premise since in a traditionally managed ICU very considerable quantities of parenteral antibiotics are used therapeutically and it is not a case of comparing the SDD regimen against a situation in which antibiotics are not used. In fact, the reduced application of *therapeutic* parenteral agents under the SDD regime [15, 41] may actually reduce the selection pressure for resistance – since fluctuating antibiotic levels within the GI tract following parenteral administration is one of the commonest causes for the emergence of resistance. In addition, it is quite likely that the elimination of GNABs from the GI tract actually protects against the development of resistance to parenterally administered agents.

The SDD regime was introduced to the ICU setting because of the very high incidence of acquired infection seen in this area of practice. There can be no doubt that SDD is successful in largely preventing acquired gram-negative infections in ICU, with all 10 trials showing a significant reduction.

The impact on mortality has been less dramatic but 2 trials report a significant reduction in mortality, 2 further trials report a significant reduction in infection-related mortality and 1 reported decreased mortality in trauma patients. There may be a number of reasons why the other trials have failed to show a significant impact on mortality. Many of the trials include relatively small numbers of patients. In some studies patients from cardiac and neurosurgical intensive care areas are included and such patients have a very low incidence of infection and are thus unlikely to benefit from SDD. In Ledingham's large study [15] all admissions were included and many of these patients (40%) left ICU within 72 hours and these too are unlikely to benefit from SDD, which takes 2–3 days to establish its effect on colonisation, However, regardless of these points the inescapable fact is that patients in this and other studies still died of multiple organ failure (MOF) in the absence of infection. The previously observed link between infection and MOF was clearly not a causative one. Patients still die of MOF secondary to "non-bacterial sepsis" whilst treated with SDD. There is now increasing evidence to suggest that such patients are suffering from absorption of mediators such as endotoxin from the GI tract [49]. If gut-origin endotoxin is the major mediator involved as has been suggested [50], then SDD may have a role in reducing the gut load of endotoxin, by reducing GNAB colonisation in the GI tract. However, as presently administered this reduction of lower bowel GNAB with SDD is both slow and incomplete (particularly in post-operative surgical patients) suggesting that further synergistic therapy may be required to achieve a worthwhile effect [50, 51].

There are currently a number of large, stratified, concurrent, controlled studies in progress and it is to be hoped that they will answer some of the remaining questions about the use of SDD in ICU. The impact of SDD on survivor morbidity needs to be carefully assessed and an accurate estimate of the running costs under traditional and SDD regimes needs to be calculated. Finally, further trials should specifically examine the effect of SDD on MOF and adjuvant therapeutic techniques should be included in order to more rapidly eliminate the risk of absorption from the gut endotoxin pool in "at risk" groups.

Conclusions

It would appear that SDD does have a significant role to play in ICU. All 10 clinical trials reviewed here have shown a significant improvement in the overall infection rates. Currently, SDD should probably be applied to selected groups only; there would appear to be clear evidence of significant benefits in trauma patients and a strong suggestion that other long-stay groups in general ICUs would also benefit. SDD should not be utilised in low risk ICU areas such as cardiac and coronary care units (at least not as an infection prevention regime).

To date there has been no significant problem encountered with antibiotic resistance. However, careful and continuous microbiological surveillance must remain a part of the regime in any unit adopting SDD. Resistance developing to the SDD drugs can then be treated early by withdrawal of the regime and isolation of the patient.

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