Selective decontamination of the digestive tract: time to implement it in all UK intensive care units? Maybe not yet

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In this issue, a survey of UK intensive care units (ICUs) is described and the uptake of selective decontamination of the digestive tract (SDD) within these units is reported. Impressively, the authors achieved a 100% response from all the units contacted, but out of the total of 250, only three reported using a full SDD protocol including i.v. antibiotics, 10 more (13 in total) reported using SDD protocols without the i.v. component. The SDD protocols when used were applied variably; some units used them in all ventilated patients (n=7), others reserved SDD for trauma patients, and in one unit just for liver patients. Of the 250 units approached, 205 contributed data to the case mix programme of the Intensive Care National Audit & Research Centre (ICNARC) and these were used to compare unit infection rates. Despite only three units using the i.v. component, acquired blood infections were fewer in these units.

First, it is briefly worth considering the survey response rates. 100% is an astounding response to a survey. Physician surveys are normally poorly responded to; a 50 – 70% response would normally be considered the best that could be expected, so why did this one succeed so well? There are a few tactics which may improve response rates. First, the clinical directors were the point of contact. Choosing a person with authority within a department, who is easily identifiable and likely to know the answers to the questions, circumvents problems associated with contact, confidence, and knowledge. Second-ly, the questionnaire was very simple with most questions requiring a tick rather than precise data or detailed comments, and thirdly, if the first post did not work, this was followed up with a reminder and then a phone call with the questionnaire filled in over the phone; there was no escape. It is also likely that as a small community responding to a well-known chief investigator, there was a willingness to contribute to the survey. Finally and perhaps as important as any other reason, the subject was considered important. SDD evokes strong opinions and raises very many questions.

There is no one standard form of SDD; different antibiotics may be applied in different ways and some regimens include parenteral antibiotic application and others do not. A typical regimen will include non-absorbable agents such as polymyxins B and E (colistin), tobramycin, and amphotericin applied as a paste to the oropharynx and in suspension via a nasogastric tube to the gastrointestinal tract. Cefotaxime is often used as the parenteral antibiotic of choice. A distinction is made between selective oropharyngeal decontamination (SOD) and SDD dependent on whether the antibiotics are applied beyond the oropharynx or not and a further distinction based on whether SDD include parenteral antibiotics or not.

Does SDD work? The answer would appear on the evidence available that it does. A Cochrane analysis in 2009, a multicentre cross-over trial of SDD, SOD, and standard care involving 5939 patients, and a very recent meta-analysis have all shown reductions in infection rates in critically ill patients and improved outcome. The recent meta-analysis from Price and colleagues suggest a mortality benefit from the use of both SDD and SOD with odds ratio of 0.73 (95% confidence interval 0.64 – 0.84) and 0.85 (0.74 – 0.97), respectively. In a specialty where results of interventions are rarely this effective, data such as these would normally set the standard in every unit, so why not in this case? The correspondence pages are where the clues to this may be found. The major doubt is over antibiotic resistance. The term counter-intuitive has been used to justify not using SDD and when the current literature is studied carefully, this begins to look a little more justified than the headline results might suggest. The emergence of resistant organisms is complex. In 1968, methicillin-resistant Staphylococcus aureus (MRSA) was being described as a British problem having been identified in Plymouth. In 1972, screening of patients in Philadelphia revealed zero cases of MRSA, but now in the USA, MRSA is endemic and increasing numbers of strains of vancomycin-resistant
resistant *S. aureus* (VRSA) are identified.\(^{16}\) Emergence and spread has been through cross-contamination, de novo mutations, and passage of plasmids between strains of *S. aureus* and even across bacterial species with evidence of the *in vivo* transfer of vancomycin resistance from *Enterococcus faecalis* to an MRSA strain to produce the Michigan VRSA.\(^{15}\) Antibiotic use has contributed to the emergence of resistance\(^{17}\) and a more recent decline in rates of MRSA has been attributed to good hygiene and antibiotic stewardship.\(^{18}\) *Staphylococcus aureus* is a relatively easy organism to study, it is readily cultured in the laboratory, its genome has been fully coded, and many of the resistance mechanisms identified. The same cannot be said of the organisms that make up the normal gut microbiome nor the pathogens likely to colonize the gut, many of which are very difficult to isolate and culture.\(^{19}\)

The gut receives organisms throughout life, although in the healthy adult human, the flora is remarkably stable. It is made up mainly of anaerobes and although pathogens are regularly ingested, even on a daily basis, the normal flora prevents the majority from causing illness. This balance can be disrupted and virulent pathogens may do this but so too do antibiotics.\(^{20}\)\(^{21}\)

The term selective decontamination of the digestive tract is a misnomer. There is very little selective about the antimicrobial activity of the regimens used. The application of enteral and parenteral antibiotics impacts on both abnormal flora and normal flora,\(^{19}\) and these are abolished in equal measure. The choice of antibiotic is important. The ridding of one species of bacteria may lead to the establishment of another including potential pathogens such as *Clostridium difficile*\(^{22}\) and resistant strains of organisms such as *Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Candida* spp., and *Acinetobacter* spp. The gut has been described as the epicentre of bacterial resistance,\(^{21}\) but the question remains does SDD cause resistance? The answer to this remains uncertain. In one recent study reporting a case series, the emergence of a colistin-resistant *K. pneumoniae* within a unit was attributed to the introduction of oral colistin as part of an SDD regimen.\(^{23}\)

The original multicentre cross-over comparison of SDD, SOD, and standard care reported in the *New England Journal of Medicine*\(^{4}\) has now been the subject of numerous subanalyses. In one such review of the data, it was observed that gram-negative bacteria (GNB) in the respiratory tract decreased at the onset of treatment, but as treatment continued, there was an increase in resistance rates, particularly to ceftazidime.\(^{26}\) In addition, antibiotic resistance increased in gut GNB after the cessation of SDD or SOD, leaving very real worries over the longer term impact of SDD on antimicrobial resistance. Indeed, yet another follow-up analysis on resistance acquisition published in the *Lancet Infectious Diseases*, the conclusion by de Smet and colleagues was: ‘Widespread use of SDD and SOD in intensive care units with low levels of antibiotic resistance is justified’.\(^{12}\) The recognition that centres with endemic resistance problems may not be suitable was alluded to. This was investigated in a third subanalysis of the original data. In this study, acquisition of colistin-resistant organisms was observed. The data suggest that within environments with low endemic level of resistant GNB, acquisition of colistin resistance is low and unaffected by topical colistin. However, when the data for centres with persistent endemic GNB colonization were separated out, acquisition of colistin resistance was about five-fold higher during the use of SDD and 15-fold higher during intestinal colonization with tobramycin-resistant GNB.\(^{25}\) Although the overall numbers were small, the importance of colistin as the last antibiotic option for some patients makes this finding very significant and with the constant evolution of bacteria and the worldwide spread of multi-resistant or even pan-resistant organisms concern has to be had over any sign of increased resistance to drugs such as colistin.\(^{26}\)

More recently, the impact of SDD on the reservoir of antibiotic resistance genes (i.e. the resistome) has been studied. Antibiotic resistance genes more than doubled in number during SDD use, mainly due to a 6.7-fold increase in aminoglycoside resistance genes.\(^{27}\) Only 12 patients were included and the clinical impact was not studied, but it does suggest the mechanisms of resistance are present and working. The problem is antibiotic resistance can take many years to establish and may depend on a number of factors, perhaps needing to come together at one time, but it would be very foolish of us to think we have considered them all. The evidence is really not good enough for us to assume the risks of resistance are small.

SDD does appear to improve outcome in critically ill patients, but could it be at a major cost in the long term? A colleague asked me during the preparation of this editorial whether I would want my relative to have SDD if they were on the ICU, because he would if it were his relative. I am not sure, today the answer might be yes, but might I regret the decision in 15 yr time with a different relative? The stakes are very high in this debate and the questions need to be tackled with openness and without prejudice. Strong emotions on either side of the debate may be motivating but risk failing to achieve coherent and considered analysis. Daneman and colleagues\(^{13}\) argue that in nearly 30 yr of SDD use without a strong signal of resistance developing, the arguments for perceived risk of long-term use of SDD cannot be justified, but even they fall short of stating there is no risk and call for a large multinational, non-cross-over, cluster randomized trial design, which would examine individual level, and, even more importantly, ICU level, changes in antimicrobial resistance rates over an extended period in recipients of SDD and controls in separate ICUs. This cannot be argued against.

**Declaration of interest**

The author is on advisory editorial boards of *BJA* and *Critical Care*, and Council member ICS.

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