Selective Decontamination of the Digestive Tract (SDD), a standard of care

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Definition
Selective decontamination of the digestive tract [SDD] is an antimicrobial prophylaxis regimen designed to prevent infections of the lower airways and blood in patients requiring treatment on the intensive care unit [ICU] [1].

The Philosophy of SDD is based on the concept of carriage
A major hazard for any intensive care patient is the development of infection.
SDD is a strategy aimed at preventing infection using prophylactic parenteral, enteral and topical antimicrobials. It is based upon two fundamental principles [2]:
1. The pathogenesis of infection is due to a limited range of potential pathogens.
2. The three types of pathogenetic pathway each require a different intervention.

Carriage exists when the same potential pathogen is isolated from at least two consecutive surveillance samples from throat and/or rectum in any concentration over a period of at least one week [2]. Colonisation, in this instance, is defined as the presence of micro-organisms in normally sterile sites. Normal carriage is the persistent presence of one or more of the six normal potential pathogens (Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Staphylococcus aureus, Escherichia coli and Candida albicans) and should be distinguished from abnormal carriage. Abnormal flora consists of nine abnormal potential pathogens, eight aerobic Gram-negative bacilli (AGNB) and methicillin-resistant Staphylococcus aureus [MRSA]. The eight AGNB are Klebsiella, Proteus, Morganella, Citrobacter, Enterobacter, Serratia, Actinobacter and Pseudomonas species.

Primary carriage is defined as the presence of both ‘normal’ and ‘abnormal’ potential pathogens in the admission flora surveillance samples. Secondary (super) carriage is defined as the persistent presence of ‘abnormal’ bacteria in throat and/or rectum acquired during treatment on the ICU but not present in the admission flora. The carriage concept defines three different types of infection [Table 1]. Normal carriage is usually primary whilst abnormal carriage can be both primary and secondary. Parenteral cefotaxime clears normal bacterial carriage; parenteral antimicrobials generally fail to clear normal yeast carriage and abnormal carriage. Enteral polyenes eradicate yeast carriage. Enteral polymyxin/tobramycin (paromomycin) clear abnormal AGNB and enteral vancomycin is indicated for MRSA eradication.
<table>
<thead>
<tr>
<th>Infection type</th>
<th>PPM</th>
<th>Timing</th>
<th>Frequency</th>
<th>Manoeuvre</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endogenous</td>
<td>6</td>
<td>‘normal’</td>
<td>&lt;1 week</td>
<td>55% Parenteral antimicrobials</td>
</tr>
<tr>
<td></td>
<td></td>
<td>‘abnormal’</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary endogenous</td>
<td>9</td>
<td>‘abnormal’</td>
<td>&gt;1 week</td>
<td>30% Hygiene and enteral antimicrobials</td>
</tr>
<tr>
<td>Exogenous</td>
<td>9</td>
<td>‘abnormal’</td>
<td>Anytime during ICU treatment</td>
<td>15% Hygiene and topical antimicrobials</td>
</tr>
</tbody>
</table>

1) **Primary endogenous infection** – generally develops within a week and is the most frequent type of infection, is responsible for approximately 55% of infections. This type of infection is caused by potential pathogens which are present in the patient’s admission (oropharynx or gut) flora.

2) **Secondary endogenous infection** – is caused by abnormal bacteria not present in the admission flora but acquired during treatment on the ICU. This type of infection generally occurs after one week in ICU and represents 30% of infections.

3) **Exogenous infection** is caused by abnormal potential pathogens never carried in the patient’s digestive tract. Exogenous infection may occur at any time, during ICU treatment, and accounts for 15% of infections [1]. Elimination of the primary endogenous route requires an initial course of parenteral antimicrobials which will eradicate carriage of normal flora and treat any established infection. Cefotaxime was originally chosen for two reasons: its spectrum of activity against normal flora and the majority of the AGNB [3], secondly, it is highly effective in eradicating oropharyngeal and gut carriage of normal flora due to high salivary and biliary concentrations [4]. Yeast carriage cannot be eradicated using parenteral antifungals. Enteral polyenes, including amphotericin B and nystatin, have been shown to achieve this [5].

Enteral antimicrobials polymyxin and tobramycin are administered to prevent secondary endogenous infection. The combination of enteral polymyxin [6] and tobramycin [7] was chosen because it covers all abnormal AGNB including *Pseudomonas* species. Additionally, it is a synergistic combination [8]. Only in the case of MRSA endemicity (i.e. 1 patient per month with an MRSA positive diagnostic sample) is enteral vancomycin added to polymyxin/tobramycin to eradicate and clear MRSA [9].

Standard hygiene measures and scrupulous attention to sterile technique is crucial in preventing the introduction of potential pathogens directly into sterile organs. Identical antimicrobials - polymyxin, tobramycin and vancomycin are indicated for topical use, e.g., in a paste on a tracheostomy site to control exogenous lower airway infections.

These three interventions were first combined by Stoutenbeek in 1984 [10]. Stoutenbeek expanded the prophylactic strategy to include surveillance cultures thus creating the full four component SDD prophylaxis.

**High grade carriage or gut bacterial overgrowth is harmful to the critically ill patient**

Carriage may be defined as either high grade (≥10^7 potential pathogens per mL or gram of digestive tract secretions) or low grade (<10^7 potential pathogens per mL or gram of digestive tract secretions) [2]. High grade carriage is also termed gut overgrowth [11].

1. Overgrowth also induces immunosuppression. AGNB carried in the gut are absorbed from the gut lumen into the Peyers patches where endotoxin stimulates macrophages to produce cytokines. Cytokinaemia results in a down regulation of macrophage activity in the gut, liver, abdomen and lungs [12].
2. Overgrowth associated with cytokinaemia is almost certainly a major factor in the inflammation of organs resulting in multiple organ failure [13].
3. Overgrowth can cause lower airway infections as potential pathogens carried in the oropharynx spill over into the lungs and bloodstream infections as potential pathogens carried in the gut migrate and translocate across the gut wall [14].
4. Finally, gut overgrowth guarantees increased spontaneous mutation, polyclonality of abnormal gut flora and subsequent antimicrobial resistance [15].

These four harmful consequences of gut overgrowth can be reduced by SDD [16-19] as it controls overgrowth, thereby reducing the faecal endotoxin pool [20].

**Mechanisms of action in controlling overgrowth**
The carriage classification is crucial in explaining the efficacy of SDD in order to select the correct antimicrobials [21]. The continuing success of SDD is based on the ability of the chosen antimicrobials to clear carriage, in particular high grade or gut overgrowth.

In order for the target potential pathogens to be completely eradicated, the concentrations of the selected antimicrobials in saliva, bile and faeces must be effective [22-30]. These concentrations are shown in Table 2 and are deemed to be of greater importance than sparing the colonisation resistance flora (the concept that indigenous anaerobic flora controls abnormal aerobic flora) [31,32].

<table>
<thead>
<tr>
<th>Antimicrobials selected for SDD</th>
<th>Concentrations [mg/L] in</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Saliva</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>6</td>
</tr>
<tr>
<td>Polymyxin E</td>
<td></td>
</tr>
<tr>
<td>Tobramycin</td>
<td></td>
</tr>
<tr>
<td>Amphotericin B or Nystatin</td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td></td>
</tr>
</tbody>
</table>

Practical guidelines on how to use SDD

All patients who need ventilation for more than two days are given parenteral cefotaxime in high doses for four days, to reduce morbidity and mortality due to ‘early’ primary endogenous infections caused by ‘normal’ potential pathogens such as *S. pneumoniae* and *S. aureus* (Table 3). Additionally, high doses of parenteral cefotaxime eradicate oropharyngeal and gut carriage of normal potential pathogens such as *S. aureus* and *E. coli*. The enteral antimicrobials are given throughout treatment on ICU to control morbidity and mortality associated with ‘late’ secondary endogenous infections. A paste or gel is applied into the lower cheeks to prevent or eradicate pre-existing oral carriage of ‘abnormal’ PPM, i.e., to decontaminate the oropharynx. A suspension is also administered via the nasogastric tube to decontaminate stomach and gut. Polymyxin and tobramycin are used to control ‘abnormal’ carriage of AGNB, in particular *Pseudomonas aeruginosa*. In the case of MRSA endemicity, enteral vancomycin is added to polymyxin/tobramycin. Tobramycin is replaced by paromomycin in the case of endemicity of AGNB producing ESBL resistant to tobramycin. If *Serratia* endemicity is present, both polymyxin and tobramycin are replaced by paromomycin. Enteral amphotericin B or nystatin is used to control yeast overgrowth. The third component of SDD is topical antimicrobials to control exogenous infections, e.g., paste to a tracheostomy. Finally, regular surveillance samples of throat and rectum are obtained to monitor efficacy and safety of SDD.
Table 3 Full four component-strategy of SDD

<table>
<thead>
<tr>
<th>Target PPM and antimicrobials</th>
<th>Total daily dose [ 4 x daily ]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;5 years</td>
</tr>
<tr>
<td>1. parenteral antimicrobials: ‘normal’ PPM</td>
<td>cefotaxime (mg)</td>
</tr>
<tr>
<td>2. enteral antimicrobials: ‘abnormal’ PPM</td>
<td></td>
</tr>
<tr>
<td>A. oropharynx</td>
<td></td>
</tr>
<tr>
<td>• AGNB : polymyxin E with tobramycin</td>
<td></td>
</tr>
<tr>
<td>• MRSA : vancomycin</td>
<td></td>
</tr>
<tr>
<td>• Yeasts : amphotericin B or nystatin</td>
<td></td>
</tr>
<tr>
<td>B. gut</td>
<td></td>
</tr>
<tr>
<td>• AGNB : polymyxin E (mg) with tobramycin (mg)</td>
<td>100</td>
</tr>
<tr>
<td>• MRSA : vancomycin (mg)</td>
<td>80</td>
</tr>
<tr>
<td>• Yeasts : amphotericin B (mg) or nystatin (units)</td>
<td>20-40/Kg</td>
</tr>
<tr>
<td></td>
<td>500</td>
</tr>
<tr>
<td></td>
<td>2 x 10⁶</td>
</tr>
<tr>
<td>3. topical antimicrobials: ‘abnormal’ PPM</td>
<td>2% and 4% paste or gel on tracheostoma, wound</td>
</tr>
<tr>
<td>4. surveillance cultures of throat and rectum on admission, Monday, Thursday</td>
<td>‘Abnormal’ PPM in overgrowth concentrations</td>
</tr>
</tbody>
</table>

PPM = potentially pathogenic micro-organism; AGNB = aerobic Gram-negative bacilli; MRSA = meticillin-resistant Staphylococcus aureus
Table 4: Efficacy of SDD (64 randomised controlled trials and 11 meta-analyses of only RCTs)

<table>
<thead>
<tr>
<th>Author</th>
<th>No RCTs</th>
<th>Sample Size</th>
<th>Lower airway infection OR [95%CI]</th>
<th>Bloodstream infection OR [95%CI]</th>
<th>Multiple Organ Dysfunction Syndrome OR [95%CI]</th>
<th>Mortality OR [95%CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vandenbroucke-Grauls [97]</td>
<td>6</td>
<td>491</td>
<td>0.12, 0.08 to 0.19</td>
<td>NR</td>
<td>0.92, 0.45 to 1.84</td>
<td>0.82, 0.22 to 2.45</td>
</tr>
<tr>
<td>D’Amico [98]</td>
<td>33</td>
<td>5727</td>
<td>0.35, 0.29 to 0.41</td>
<td>NR</td>
<td>0.80, 0.69 to 0.93</td>
<td>0.82, 0.22 to 2.45</td>
</tr>
<tr>
<td>Safdar [99]</td>
<td>4</td>
<td>259</td>
<td>NR</td>
<td>NR</td>
<td>0.82, 0.22 to 2.45</td>
<td>0.82, 0.22 to 2.45</td>
</tr>
<tr>
<td>Liberati [100]</td>
<td>36</td>
<td>6922</td>
<td>0.35, 0.29 to 0.41</td>
<td>NR</td>
<td>0.78, 0.68 to 0.96</td>
<td>0.78, 0.68 to 0.96</td>
</tr>
<tr>
<td>Silvestri [101]</td>
<td>42</td>
<td>6075</td>
<td>NR</td>
<td>0.89, 0.16 to 4.95</td>
<td>NR</td>
<td>0.74, 0.61 to 0.91</td>
</tr>
<tr>
<td>Silvestri [102]</td>
<td>51</td>
<td>8065</td>
<td>NR</td>
<td>0.63, 0.46 to 0.87</td>
<td>0.74, 0.61 to 0.91</td>
<td>0.74, 0.61 to 0.91</td>
</tr>
<tr>
<td>Silvestri [103]</td>
<td>54</td>
<td>9473</td>
<td>0.07, 0.04 to 0.13</td>
<td>0.36, 0.22 to 0.60</td>
<td>NR</td>
<td>0.71, 0.61 to 0.82</td>
</tr>
<tr>
<td>G-ve</td>
<td></td>
<td></td>
<td>0.52, 0.34 to 0.78</td>
<td>1.03, 0.75 to 1.41</td>
<td>NR</td>
<td>0.71, 0.61 to 0.82</td>
</tr>
<tr>
<td>G+ve</td>
<td></td>
<td></td>
<td>0.54, 0.42 to 0.69</td>
<td>NR</td>
<td>NR</td>
<td>0.71, 0.61 to 0.82</td>
</tr>
<tr>
<td>Silvestri [104]</td>
<td>21</td>
<td>4902</td>
<td>NR</td>
<td>NR</td>
<td>0.71, 0.61 to 0.82</td>
<td>0.71, 0.61 to 0.82</td>
</tr>
<tr>
<td>Liberati [105]</td>
<td>36</td>
<td>6914</td>
<td>0.28, 0.20 to 0.38</td>
<td>NR</td>
<td>0.75, 0.65 to 0.87</td>
<td>0.75, 0.65 to 0.87</td>
</tr>
<tr>
<td>Silvestri [106]</td>
<td>7</td>
<td>1270</td>
<td>NR</td>
<td>0.50, 0.34 to 0.74</td>
<td>0.82, 0.51 to 1.32</td>
<td>0.82, 0.51 to 1.32</td>
</tr>
<tr>
<td>Silvestri [107]</td>
<td>12</td>
<td>2252</td>
<td>0.54, 0.42 to 0.69</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

Or = odds ratio; CI = confidence interval; NR = not reported
Efficacy of the SDD regimen
There are 64 RCTs evaluating SDD [33-96] and eleven meta-analyses examining only RCTs assessing SDD efficacy [97-107] (Table 4). Six meta-analyses have the endpoint of lower airway infection [97,98,100,103,105,107] and all show a significant reduction of lower airway infections. The most recent meta-analysis also demonstrates that SDD, using parenteral and enteral antimicrobials, reduces the multiple organ dysfunction syndrome [106].

Mortality is an endpoint in eight meta-analyses [97-100,102,104-106], five with sample sizes between 4,902 and 8,065. A survival benefit is consistently shown [98, 100,102,104,105]. The mortality reduction was insignificant due to the small sample size in the remaining three meta-analyses (Table 4). The significant survival benefit is almost certainly due to the control of severe infections of both lower airways and blood. Bloodstream infections due to AGNB were significantly reduced (OR 0.36 CI 95% 0.22 -0.60) [102], fungaemia was also reduced (OR 0.89; CI 95% 0.16-4.95) but this did not achieve significance [101]. Although Gram positive blood stream infections increased this was not significant [OR 1.03; CI 95% 0.75-1.41] [103].

Safety profile of the SDD regimen
Concerns about resistance are legitimate for any antimicrobial prophylaxis [108,109] and the safety of SDD relies on resistance not emerging against the SDD antimicrobials [110]. A recent meta-analysis of the 64 SDD RCTs does not show any increase in resistance to the SDD antimicrobials but rather a significant reduction in resistance to them [111]. The main resistance problems in ICU come under four categories
1. AGNB: in particular *Klebsiella*, producing extended spectrum beta-lactamases (ESBL) and multi-resistant *Acinetobacter* and *Pseudomonas* species [112];
2. MRSA: [113];
3. Azole-resistant *Candida* species: an increasing problem since the introduction of fluconazole [114];
4. Vancomycin-resistant enterococci (VRE): particularly in North America [115].

Resistant AGNB
There are 3 RCTs with the endpoint of antimicrobial resistance amongst AGNB [43, 47 & 49]. In a Parisian hospital there was endemcity of an ESBL producing *Klebsiella*. The carriage and infection rates in the control group were 19.6% and 9%, respectively; enteral antimicrobials were added and the rates were reduced to 1% and 0% [43]. A Dutch study demonstrated that carriage of AGNB resistant to imipenem, cefazidime, ciprofloxacin, tobramycin and polymyxins occurred in 16% of SDD patients compared to 26% of control patients with a relative risk (RR) of 0.6 (95% CI 0.5 – 0.8) [47]. The most extensive RCT (6,000 patients) was also undertaken in The Netherlands. This study demonstrated that the percentage of patients carrying AGNB resistant to cefazidime was significantly less in those receiving enteral polymyxin/tobramycin compared to standard care [49] (Table 5).

<table>
<thead>
<tr>
<th>AGNB</th>
<th>SDD</th>
<th>Standard Care</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>E.coli</em></td>
<td>1.3</td>
<td>3.3</td>
</tr>
<tr>
<td><em>K.pneumoniae</em></td>
<td>0.4</td>
<td>2.2</td>
</tr>
<tr>
<td><em>E.cloaca</em></td>
<td>1.7</td>
<td>4.7</td>
</tr>
<tr>
<td><em>P.aeruginosa</em></td>
<td>0.7</td>
<td>2.6</td>
</tr>
</tbody>
</table>

Figures are percentages of patients

The gut resistance hypothesis may explain the findings of these three RCTs in that there is significantly less resistance when enteral antimicrobials are added. Parenteral antimicrobials alone do not reach lethal concentrations within the gut when excreted via bile resulting in faecal overgrowth of AGNB which in turn promotes resistant mutant strains. The addition of enteral antimicrobials clears high grade carriage or overgrowth including resistant mutants.

Approximately 30% of (ICU) patients will either import, acquire or develop *de novo* antimicrobial resistance [14,116]. The common denominator for these three mechanisms is the gut. ICU patients are prone to gut overgrowth due to impaired gut motility [11] and they have a high risk for *de novo* development [15].

The polymyxin/tobramycin combination creates a unique environment. This mixture is synergistic and results in high bactericidal levels in both saliva and faeces which maintains colonisation resistance [117,118]. These three properties combine to eradicate overgrowth and profoundly influence the balance of forces associated with resistance [119]. Practically all ESBL-producing AGNB are sensitive to the enteral combination of polymyxin/tobramycin [120]. Although rare, some ESBL-producing AGNB such as *Klebsiella* species may be resistant to tobramycin [121].
Tobramycin needs to be replaced by an aminoglycoside active against such species [122], e.g. neomycin [43] or paromomycin [123,124]. Parenteral antimicrobials that disregard the patients’ gut ecology or colonisation resistance may promote acquisition, carriage and subsequent overgrowth of ESBL-producing AGNB [125-127]. Therefore blind administration of SDD (i.e. without surveillance cultures) is deprecated and surveillance of faecal flora is required with modification of the enteral component of SDD as necessary.

There are four long-term studies (≥2 years) evaluating the impact of polymyxin/tobramycin on resistance amongst AGNB [128-131] (Table 6). The resistance data of these studies confirm the RCT findings. Rates of carriage and infection due to resistant AGNB in patients receiving parenteral and enteral antimicrobials are not increased but are actually lower compared with patients receiving solely parenteral antimicrobials.

MRSA
SDD was not designed to cover MRSA, as MRSA was not a significant problem in the early 1980’s. During 7 of the 64 SDD RCTs, MRSA was endemic in the study ICUs, resulting in a trend towards higher MRSA infection rates in those 7 RCTs [48, 52, 55, 59, 66, 90,91]. In order to combat endemic MRSA enteral vancomycin needs to be added to SDD [9].

Three studies using long term SDD with enteral vancomycin did not report any emergence of *Staphylococcus aureus* with intermediate sensitivity to vancomycin (VISA) or vancomycin-resistant enterococci (VRE) [132-134] (Table 7). Similarly, MRSA overgrowth is habitually present in the critically ill when MRSA is endemic and guarantees the presence of VISA strains following the parenteral use of vancomycin [135]. The addition of enteral vancomycin produces faecal vancomycin levels of up to 3,000µg/mL preventing or eradicating, if already present, the VISA mutants. A similar scenario applies to carriage and overgrowth of abnormal VRE and the intravenous administration of antimicrobials such as linezolid, resulting in the emergence of linezolid-resistant VRE mutants [136]. As far as we are aware, there are no studies that assessed the efficacy of enteral vancomycin in preventing and eradicating carriage and overgrowth of VRE [137,138].
Table 6 Long term studies of enteral polymyxin/tobramycin on AGNB resistance

<table>
<thead>
<tr>
<th>Author</th>
<th>Study</th>
<th>Patients</th>
<th>% patients with carriage [surv] and/or infection [diag] due to resistant AGNB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stoutenbeek [123]</td>
<td>Prosp observ</td>
<td>2½ years</td>
<td>Trauma</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>164</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leone [124]</td>
<td>Retrosp case-control</td>
<td>6 years</td>
<td>MV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>720</td>
</tr>
<tr>
<td>Sarginson [125]</td>
<td>Prosp observ</td>
<td>4 years</td>
<td>Children ≥4 days of ventil</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1241</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heininger [126]</td>
<td>Prosp observ</td>
<td>5 years</td>
<td>MV &gt;2 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1913</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Surv = Surveillance samples;  Diag = diagnostic samples

Table 7 Long term studies of enteral vancomycin on staphylococcal and enterococcal resistance

<table>
<thead>
<tr>
<th>Author</th>
<th>Study</th>
<th>Patients</th>
<th>% patients with carriage [surv] and/or infection [diag] due to VISA and/or VRE</th>
</tr>
</thead>
<tbody>
<tr>
<td>de la Cal [127]</td>
<td>Prosp observ</td>
<td>4 years</td>
<td>Med/Surg &gt;3 days of MV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>799</td>
</tr>
<tr>
<td>Cerda [128]</td>
<td>Prosp observ</td>
<td>4 years</td>
<td>Burns</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>375</td>
</tr>
<tr>
<td>Viviani [129]</td>
<td>Prosp observ</td>
<td>2 years</td>
<td>MV &gt;3 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>265</td>
</tr>
</tbody>
</table>

Surv = Surveillance samples;  Diag = diagnostic samples;  VISA = vancomycin-intermediate *Staphylococcus aureus*;  VRE = vancomycin-resistant enterococci
**Azole-resistant Candida species**
Surveillance cultures of throat and rectum are essential in detecting carriers of Candida species resistant to fluconazole. Knowledge of carriage of resistant strains allows the enteral administration of polyenes such as amphotericin B or nystatin, to eradicate the carrier state, preserving the value of fluconazole as a useful antifungal agent [139].

**VRE**
VRE was endemic in 2 locations in the 64 SDD RCTs [36, 60]. Carriage and infection rates of VRE were similar in both test and control groups. Six RCTs added enteral vancomycin to the classical SDD and screened for VRE [38, 56, 63, 64, 73, 83]. VRE was not isolated from any diagnostic or surveillance samples. Enteral vancomycin in high doses does not promote VRE; parenteral antimicrobials which disregard colonisation resistance are responsible for the promotion of VRE [137,138].

SDD was introduced into a paediatric intensive care unit in 1999 [130] and a database developed to record the relevant data on both carriage and infection [140]. The density of patients carrying and infected with resistant bacteria did not increase over the 5 years use of SDD (Figures 1 and 2).

The over-riding message from RCTs, meta-analyses and long-term studies is that the addition of enteral to parenteral antimicrobials does not promote resistance but contributes to its control [141].
Figure 1 Density of patients carrying resistant bacteria 1999-2004. No significant resistance patterns emerged over the five years.

Number of patients carrying resistant micro-organisms per month of 100 patients days

Figure 2 Density of patients with infections due to resistant micro-organisms 1999-2004

Number of patients with infections due to resistant micro-organisms per month of 100 patient days
Benchmarking SDD against other manoeuvres which reduce mortality on ICU

In recent years, five interventions have been shown to reduce ICU mortality in RCTs: Ventilation with low tidal volumes for acute lung injury and respiratory distress syndrome [142]; Recombinant human activated protein C for severe sepsis [143]; Intensive insulin therapy [144]; low doses of steroids in patients with septic shock [145] and SDD [47, 49, 64] (Table 8). Table 8 reports the levels of evidence obtained using the Grade system [146,147], which classifies the quality of evidence as high grade (grade A), moderate (grade B), low (grade C) or very low (grade D). RCTs may be downgraded due to limitations in implementation, inconsistency or imprecision of the results, indirectness of the evidence, and possible reporting bias [147]. An example of this is tight glucose control (A down to C): the success of the original Belgian RCT [144] in reducing mortality has not to date been reproduced [148-151]. Additionally, a recent tight glucose control meta-analysis produced negative and contradictory results [152].

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Relative Risk [95% CI]</th>
<th>Abs mort red [%] [95% CI]</th>
<th>Number needed to treat</th>
<th>Grade of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. low tidal volume [137]</td>
<td>0.78 [0.65 to 0.93]</td>
<td>8.8 [2.4 to 15.3]</td>
<td>11</td>
<td>1B</td>
</tr>
<tr>
<td>2. activated protein C [138]</td>
<td>0.80 [0.69 to 0.94]</td>
<td>6.1 [1.9 to 10.4]</td>
<td>16</td>
<td>2B</td>
</tr>
<tr>
<td>3. intensive insulin [139]</td>
<td>0.44 [0.36 to 0.81]</td>
<td>3.7 [1.3 to 6.1]</td>
<td>27</td>
<td>2C</td>
</tr>
<tr>
<td>4. steroids [140]</td>
<td>0.90 [0.74 to 1.09]</td>
<td>6.4 [-4.8 to 17.6]</td>
<td>16</td>
<td>2C</td>
</tr>
<tr>
<td>5. SDD [47,49,63]</td>
<td>0.65 [0.49 to 0.85]</td>
<td>8.1 [3.1 to 13.0]</td>
<td>12</td>
<td>1A</td>
</tr>
</tbody>
</table>

CI = confidence interval

The Grade system classifies recommendations as strong (grade 1) or weak (grade 2). The grade of strong or weak is considered of greater clinical importance than a difference in the A-D levels of quality of evidence. A strong recommendation in favour of an intervention reflects that the desirable effects of adherence to a recommendation (beneficial health outcomes, less burden on staff and patients and cost savings) will clearly outweigh the undesirable effects (harms, more burdens, greater costs).

SDD is the only evidence based manoeuvre with a Grade 1A recommendation

All RCTs and meta-analyses which assessed the full four component SDD protocol consistently demonstrated a significant survival benefit, providing the sample size was large enough. The mortality data show an intriguing observation that trial design determines the magnitude of the survival benefit [104]. The relative reduction in the odds ratio for mortality was 41% when all ICU patients receive the full SDD protocol [47], 29% when half the patients receive SDD (control and intervention patients in the same unit) [104] and 17% when one third of the population are treated with SDD [49,153]. In the trial of the unit-wide application of SDD [47], the SDD protocol virtually eliminated transmission of potential pathogens via the hands of carers and hence exogenous infection in decontaminated patients.

The survival benefit is diluted by mixing decontaminated and nondecontaminated patients in the same unit. This is the case in the RCT design, wherein the patients receiving and not receiving SDD are treated within the same unit [49,104]. Patients who are successfully decontaminated protect control patients from transmission, acquisition, carriage, and subsequent infection, whereas the patients receiving SDD remain at risk of acquiring potential pathogens and subsequent exogenous infections, resulting in a reduction in the true effect of SDD. The most recent multicentre RCT in 6,000 patients with a 17% relative reduction – albeit statistically significant – clearly underlines the issue of diluting the SDD effect by increasing the number of non-decontaminated patients treated in the same unit with patients receiving SDD [49,153].

Costs implication for using SDD

Although the cost effectiveness of SDD has not yet been formally calculated the daily costs of 6-12 euros per patient [49, 74,154] can hardly be an issue for an ICU intervention that reduces pneumonia, septicaemia and mortality by 72%, 37% and 29%, respectively (Table 4).

Conclusion
SDD is not yet a standard of care. The literature presented clearly demonstrates efficacy and the experience of 25 years shows that intelligent use of SDD is not associated with the emergence of resistant organisms. Why is it not more widely applied?

There is no doubt application of SDD is more demanding than simply prescribing an antibiotic and requires education of the entire critical care team. In the absence of evidence, the spectre of resistance is still raised, curiously by clinicians who are content to prescribe the parenteral antibiotics so prone to generating resistance. Antibiotic sensitivity testing has become the norm.

During the early years of SDD, when the drugs employed were still in patent, there was considerable commercial support. There were a lot of early adopters of SDD despite the relative paucity of evidence at that time. In short, it was fashionable. Paradoxically, now the evidence of efficacy and safety is stronger and the treatment is cheap, the commercial support has vanished and SDD has become far less fashionable. Could the practices of intensivists and microbiologists be influenced by pharmaceutical marketing? Clinicians should consider the wider use of SDD based on a dispassionate review of the extensive evidence. Sceptics may still wish to undertake further large scale RCTs, in which case the design will need to consider the contact networks between the intervention and control patients.

References


[111] Meta-analysis


