Debate – Selective Decontamination of the Gut
Prof. Jan Kluytmans and Dr. Cliff McDonald
Broadcast live from the 2015 Infection Prevention Society conference

Debate
Selective Decontamination of the Gut

Debating Pros
Prof. Jan Kluytmans
Professor of Microbiology and Infection Control
St Elisabeth Hospital
The Netherlands

Debating Cons
Dr. Cliff McDonald
Senior Advisor for Science and Integrity
Division of Healthcare Quality Promotion
USA

SDD as antibiotic stewardship
Jan Kluytmans
University Medical Center, Utrecht
Amphia Hospital, Breda

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Stewardship

- Optimal treatment of patients while
  - limiting side effects
  - limiting antimicrobial resistance

What is SDD?

- Intravenous prophylaxis
  - cefotaxim
- Oropharyngeal decontamination
  - tobramycin and colistin
- Gastric and intestinal decontamination
  - tobramycin and colistin
- Avoiding the use of anti-anaerobic antibiotics
- Surveillance cultures twice weekly
- High level of hygiene

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Arguments for SDD

- Does it affect the outcome?
  - Mortality
  - Length of stay
- Does it prevent nosocomial infections?
- Does it affect the use of antibiotics?
- What is the effect on the development of resistance?

Meta-analysis: effect on ICU-mortality systemic and topical prophylaxis

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Effects of SDD on mortality  

<table>
<thead>
<tr>
<th></th>
<th>SDD</th>
<th>Controls</th>
<th>RR (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IC-mortality</td>
<td>14.8 %</td>
<td>22.9 %</td>
<td>0.65 (0.44 – 0.85)</td>
<td></td>
</tr>
<tr>
<td>Hospital-mortality</td>
<td>24.2 %</td>
<td>31.2 %</td>
<td>0.78 (0.63 – 0.96)</td>
<td></td>
</tr>
<tr>
<td>Duration ICU-stay (d)</td>
<td>11.6</td>
<td>13.4</td>
<td>&lt; 0.01</td>
<td></td>
</tr>
</tbody>
</table>

COMMENTARY

Selective digestive decontamination: for everyone, everywhere?  
THE LANCET • Vol 362 • September 21, 2003

So should SDD be applied routinely in all ICUs? To the question does SDD work, the answer now must definitely be yes—SDD reduces mortality. But, do the data apply to...
Decontamination of the Digestive Tract and Oropharynx in ICU Patients


Study design

- Cluster-randomized controlled multi-centre cross-over trial (ICUs in 13 hospitals)
  - 2 non-teaching; 7 teaching; 4 university
- Study periods: SDD, SOD and standard care
- Six months per study period
- 1 month wash in/wash out before and between study periods
- Order of study periods randomized per study centre

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Endpoints

- ICU-mortality (primary)
- Hospital-mortality (primary)
- Resistance (secondary)
- Duration of intubation (secondary)
- LOS ICU (secondary)
- Antibiotic use (secondary)
- Costs (secondary)

Patients

- Inclusion criteria:
  - Expected stay in ICU >72 hours
  - and/or expected duration of ventilation >48 hours
- Exclusion criteria:
  - Documented allergy for study medication
  - Pregnancy
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<table>
<thead>
<tr>
<th>End Point</th>
<th>Adjusted Odds Ratio or Hazard Ratio (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Standard Care</td>
</tr>
<tr>
<td>Death — no. (%)</td>
<td>1.00</td>
</tr>
<tr>
<td>During the first 28 days</td>
<td>1.00</td>
</tr>
<tr>
<td>In the ICU</td>
<td>1.00</td>
</tr>
<tr>
<td>In the hospital</td>
<td>1.00</td>
</tr>
<tr>
<td>Time to outcome for survivors at day 28 — days</td>
<td>1.00</td>
</tr>
<tr>
<td>Cessation of mechanical ventilation</td>
<td>Median</td>
</tr>
<tr>
<td>Discharge from ICU</td>
<td>Interquartile range</td>
</tr>
<tr>
<td>Discharge from hospital</td>
<td>Median</td>
</tr>
<tr>
<td></td>
<td>Interquartile range</td>
</tr>
</tbody>
</table>

Arguments

• Does it affect the outcome?
  – Mortality
  – Length of stay

• Does it prevent nosocomial infections?
• Does it affect the use of antibiotics?
• What is the effect on the development of resistance?

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Arguments

- Does it affect the outcome?
  - Mortality
  - Length of stay

- Does it prevent nosocomial infections?
- Does it affect the use of antibiotics?
- What is the effect on the development of resistance?

Lancet Infectious Diseases, March 21, 2011

Selective digestive tract decontamination and selective oropharyngeal decontamination and antibiotic resistance in patients in intensive-care units: an open-label, clustered group-randomised, crossover study

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ICU-acquired bacteremia and candidemia

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Standard care (n=183)</th>
<th>SDD (n=275)</th>
<th>SDD vs SOD (n=59)</th>
<th>Crude odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any microorganism, apart from</td>
<td>209 (13%)</td>
<td>315 (19%)</td>
<td>664 (27%)</td>
<td>SDD vs standard care</td>
</tr>
<tr>
<td>coagulase-negative staphylococci</td>
<td></td>
<td></td>
<td></td>
<td>SDD vs SOD</td>
</tr>
<tr>
<td><em>Candida spp and other yeasts</em></td>
<td>28 (1%)</td>
<td>20 (1%)</td>
<td>8 (4%)</td>
<td>SDD vs SOD</td>
</tr>
<tr>
<td>HRMO†</td>
<td>9 (1%)</td>
<td>20 (1%)</td>
<td>11 (6%)</td>
<td>SDD vs SOD</td>
</tr>
</tbody>
</table>

**Note:**
- SDD = selective decontamination
- SOD = standard care
- ARR = absolute risk reduction
- NNT = number needed to treat

HRMO = highly resistant microorganisms
*One case of *Candida parapsilosis* in the standard-care group.
*One patient in the control group had two episodes of bacteremia with HRMOs (one episode on day 6 with *Enterobacter cloacae* and *Escherichia coli* and one on day 29 with *Acinetobacter baumannii*).

**Table:** Patients with bacteremia and candidemia acquired in intensive care units.

Crude odds ratio (95% CI)

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Crude odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any microorganism, apart from</td>
<td>0.48 (0.38–0.60); ARR 6.4%; NNT 16</td>
</tr>
<tr>
<td>coagulase-negative staphylococci</td>
<td></td>
</tr>
<tr>
<td><em>Candida</em> spp and other yeasts*</td>
<td>0.33 (0.13–0.82); ARR 0.7%; NNT 152</td>
</tr>
<tr>
<td>HRMO†</td>
<td>0.41 (0.18–0.94); ARR 0.6%; NNT 170</td>
</tr>
</tbody>
</table>

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Arguments

• Does it affect the outcome?
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  – Length of stay

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Arguments

• Does it affect the outcome?
  – Mortality
  – Length of stay
• Does it prevent nosocomial infections?
• Does it affect the use of antibiotics?

• What is the effect on development of resistance?

Systemic antibiotic use (totals in DDD)

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>SDD group Total DDD use (A SDD vs Control)</th>
<th>SOD group Total DDD use (A SOD vs Control)</th>
<th>Standard care Total DDD use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillins</td>
<td>9,767 (+27.6%)</td>
<td>12,809 (+5.3%)</td>
<td>13,523</td>
</tr>
<tr>
<td>Carbapenems</td>
<td>724 (-45.7%)</td>
<td>995 (-25.4%)</td>
<td>1,334</td>
</tr>
<tr>
<td>Cefalosporins</td>
<td>8,473 (+86.6%)</td>
<td>3,935 (-13.3%)</td>
<td>4,541</td>
</tr>
<tr>
<td>Quinolones</td>
<td>2,637 (-31.4%)</td>
<td>3,291 (-14.4%)</td>
<td>3,846</td>
</tr>
<tr>
<td>Clindamycins</td>
<td>473 (-11.8%)</td>
<td>533 (+3.4%)</td>
<td>535</td>
</tr>
<tr>
<td>Other antibiotics</td>
<td>7,589 (-23.4%)</td>
<td>6,720 (-12.0%)</td>
<td>9,909</td>
</tr>
<tr>
<td>All Systemic antibiotics</td>
<td>29,883 (-12.0%)</td>
<td>30,299 (-10.1%)</td>
<td>33,688</td>
</tr>
</tbody>
</table>

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Effects on antibiotic use in ICU

Arguments

- Does it affect the outcome?
  - Mortality
  - Length of stay
- Does it prevent nosocomial infections?
- **Does it affect the use of antibiotics?**
- What is the effect on development of resistance?

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Conclusions

- SDD is an evidence based intervention
  - Reduced mortality
  - Reduced ICU acquired infection rates
  - Lower rates of resistance
  - Alters the use of systemic antibiotics
- Should be accompanied by
  - Careful monitoring of surveillance cultures
  - Good infection control

My own hospital uses SDD for >25 year
- 30 bed ICU
- No MRSA, VRE, CRE, C. diff etc.
- ESBL is often found on admission but disappears rapidly
- Extremely low rates of ICU-acquired bacteremia
- Long term use is not associated with increased resistance rates
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SDD in 2025?

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Just Do It...

Selective Decontamination of the Gut  
CON  
Selective Oral and Digestive Decontamination: Unveiling the Power of the Human Microbiome  

L. Clifford McDonald, MD  
Senior Advisor for Science and Integrity  
September, 29 2015

A Webber Training Teleclass  
www.webbertraining.com
No Financial Disclosures

The findings and conclusions in this presentation are those of the author and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

“To selectively decontaminate or not to selectively decontaminate, that is the question…

Whether 'tis nobler in the ICU to suffer The slings and arrows of outrageous fortune Or to take arms against a sea of troubles And by opposing, end them. “

--Hamlet’s 4th soliloquy, shamelessly abridged
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Outline to Address Selective Decontamination

- What is it?
- What is the evidence it improves which outcomes?
- What is the evidence it may be ecologically safe in the short term?
- What is the evidence it is likely to be ecologically unsafe in the long term?
- What are we learning about the microbiome and resistome that can build upon past successes?
- Why we need to develop tests and criteria to routinely measure and intervene on ‘Microbiome Disruption Indices’?

Selective Digestive Decontamination (SDD) and Selective Oral Decontamination (SOD)

- Protocolled administration of non-absorbable oral antibiotics and antifungals to ventilated ICU patients
- Usually administered with a short course of parenteral cephalosporin
- Widely practiced only in the Netherlands and other countries with low levels of baseline antibiotic resistance
- Favorable outcomes of infection and survival
- Variable effects on resistance--source of controversy
- Is this ecologically safe?
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Table 1. Description of selective decontamination of the digestive tract and selective oropharyngeal decontamination regimens

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Timing</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDD and SOD regimens</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5 g of a paste containing polymyxin E, tobramycin and amphotericin B each in 2% concentration applied in oropharynx</td>
<td>Four times daily until ICU discharge</td>
<td>Selective decontamination of the oropharynx</td>
</tr>
<tr>
<td>10 mL of a suspension containing 100 mg polymyxin E, 80 mg tobramycin and 500 mg amphotericin B via the nasogastric tube</td>
<td>Four times daily until ICU discharge</td>
<td>Selective decontamination of the gut from stomach to rectum</td>
</tr>
<tr>
<td>Cefotaxime 1 g i.v. during the first 4 days of study or other third-generation cephalospirades</td>
<td>Four times daily during the first 4 days</td>
<td>Preventive treatment of primary infections</td>
</tr>
<tr>
<td>Avoidance of (systemic) antibiotics that might impair the colonization resistance, that is, with antianerobic activity</td>
<td>During treatment with SDD, until ICU discharge</td>
<td>Avoidance of pericillin, carbapenem and so on</td>
</tr>
<tr>
<td>Oropharyngeal endotracheal, and rectal cultures</td>
<td>On admission and twice weekly</td>
<td>No addition of antibiotics for patients with colonization without clinical signs suggestive for infection</td>
</tr>
</tbody>
</table>

Table 2. Primary and Secondary End Points (a)

<table>
<thead>
<tr>
<th>End Point</th>
<th>Standard Care (N=1936)</th>
<th>Study Group</th>
<th>Standard Care (N=1936)</th>
<th>Study Group</th>
<th>Standard Care (N=1936)</th>
<th>Study Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death — in (N=1936)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>During the first 28 days</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>In the ICU</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>In the hospital</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Time to receive survivors at day 3 — day 29</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Censoring of mechanical ventilation</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Median (N=1936)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>1-17</td>
<td>1-19</td>
<td>1-15</td>
<td>1-19</td>
<td>1-15</td>
<td>1-19</td>
</tr>
<tr>
<td>Discharge (in ICU)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Median (N=1936)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>6-18</td>
<td>6-18</td>
<td>6-17</td>
<td>6-18</td>
<td>6-17</td>
<td>6-18</td>
</tr>
<tr>
<td>Median (N=1936)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>16-48</td>
<td>16-45</td>
<td>16-47</td>
<td>16-48</td>
<td>16-47</td>
<td>16-48</td>
</tr>
</tbody>
</table>

SDD and SOD in Crossover Study Among 13 Dutch ICUs (N=5,939)

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SDD and SOD in Crossover Study Among 13 Dutch ICUs (N=5,939)

Table 3. Cumulative Incidence of ICU-Acquired Bacteremia and Candidemia.1

<table>
<thead>
<tr>
<th>Type of Infection</th>
<th>Study Group</th>
<th>Crude Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Standard Care (N=1990)</td>
<td>SOD (N=2045)</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>22 (1.1)</td>
<td>9 (0.5)</td>
</tr>
<tr>
<td>Streptococcus pneumonia</td>
<td>3 (0.2)</td>
<td>1 (0.0)</td>
</tr>
<tr>
<td>GN/ GN species†</td>
<td>26 (1.8)</td>
<td>16 (0.8)</td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>87 (4.4)</td>
<td>39 (2.0)</td>
</tr>
<tr>
<td>Enterococci species</td>
<td>53 (2.8)</td>
<td>48 (2.3)</td>
</tr>
<tr>
<td>Candida species</td>
<td>36 (1.9)</td>
<td>16 (0.8)</td>
</tr>
<tr>
<td>Patients with at least one episode of bacteremia or candidemia — no. (%)</td>
<td>186 (9.3)</td>
<td>124 (6.5)</td>
</tr>
</tbody>
</table>

Figure 1. Detection of Gram-Negative Bacteria in Patients in the Intensive Care Unit Who Were Treated with Selective Digestive Tract Decontamination (SDD) or Selective Oropharyngeal Decontamination (SOD).
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SDD and SOD in Crossover Study Among 13 Dutch ICUs (N=5,939)

<table>
<thead>
<tr>
<th>Organism</th>
<th>Sensible Resistant</th>
<th>Ciprofloxacin Resistant</th>
<th>Cefazolin Resistant</th>
<th>Meropenem Resistant A</th>
<th>Meropenem Resistant B</th>
<th>meropenem Resistant C</th>
<th>percentage of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotal samples</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>6.5%</td>
<td></td>
<td>2.9%</td>
<td>3.1%</td>
<td>2.3%</td>
<td>2.9%</td>
<td>15%</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>4.9%</td>
<td></td>
<td>1.7%</td>
<td>2.7%</td>
<td>1.2%</td>
<td>1.4%</td>
<td>10%</td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td>1.9%</td>
<td></td>
<td>1.7%</td>
<td>2.1%</td>
<td>1.4%</td>
<td>1.3%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>4.2%</td>
<td></td>
<td>1.5%</td>
<td>2.5%</td>
<td>1.4%</td>
<td>2.3%</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

Respiratory tract samples:
| E. coli                   | 3.1%               |                         | 1.4%                | 2.1%                   | 1.5%                  | 1.7%                   | 0.2%                   |
| K. pneumoniae             | 2.9%               |                         | 0.9%                | 1.5%                   | 1.3%                  | 1.1%                   | 0.1%                   |
| E. faecalis               | 1.3%               |                         | 0.5%                | 0.8%                   | 0.9%                  | 1.1%                   | 0.0%                   |
| P. aeruginosa             | 2.1%               |                         | 1.6%                | 2.7%                   | 1.7%                  | 2.1%                   | 0.1%                   |

| P<0.05 for the comparison with SOD. |
| P<0.05 for the comparison with SDD. |


Persisting Survival Benefit of SDD and SOD at One Year (N=5,403)

**TABLE 3. STRATIFIED ANALYSIS FOR AGE WITH ADJUSTED ODD RATIOS FOR 1-YEAR MORTALITY FOR PATIENTS IN QUARTILES 1 AND 2, IN QUARTILLES 3 AND 4, AND FOR ALL PATIENTS**

<table>
<thead>
<tr>
<th></th>
<th>SC (Q 1, 2)</th>
<th>SC (Q 3, 4)</th>
<th>SOD (Q 1, 2)</th>
<th>SOD (Q 3, 4)</th>
<th>SDD (Q 1–4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>One-year survival vs. SC</td>
<td>Reference 81 (0.65–1.00)</td>
<td>0.81 (0.65–1.00)</td>
<td>1.00 (0.82–1.22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>aOR (95% CI) age, lower quartiles (Q 1, 2)</td>
<td>Reference 0.97 (0.79–1.18)</td>
<td>0.88 (0.72–1.07)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>aOR (95% CI) age, upper quartiles (Q 3, 4)</td>
<td>Reference 0.89 (0.77–1.02)</td>
<td>0.93 (0.81–1.07)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Oostink EA, Am J Resp Crn Care Med Vol 149 2013

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Percentage of patients colonized with gram-negative rods before, during, and after SDD

- Rectal
  - Ceftazidime R
  - Tobramycin R
  - Ciprofloxacin R
- Respiratory

Oostdijk EN. Am J Respir Crit Care Med Vol 181, pp 452-457, 2010

Effect of selective decontamination on antimicrobial resistance in intensive care units: a systematic review and meta-analysis


“We detected no relation between the use of SDD or SOD and the development of antimicrobial resistance in pathogens in patients in the ICU, suggesting that the perceived risk of long-term harm related to selective decontamination cannot be justified by available data. However, our study indicates that the effect of decontamination on ICU-level antimicrobial resistance rates is understudied. We recommend that future research includes a non-crossover, cluster randomised controlled trial to assess long-term ICU-level changes in resistance rates.”

Damaan N. Lancet Infect Dis 2013; 13: 328-41

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A 4 Year Ecological Study in 38 Intensive Care Units in the Netherlands

Crumbling Last Lines of Defense: Colistin-resistant *K. pneumoniae* in an Italian Hospital

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“...Must give us pause. There's the respect
That makes calamity of so long life. “

An Extended Outbreak of Colistin and Tobramycin Resistant Enterobacteriaceae Driven by SDD

<table>
<thead>
<tr>
<th>Isolate group</th>
<th>Disc diffusion (n = 89)</th>
<th>Vitek (n = 134)</th>
<th>Etest (n = 134)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S I R</td>
<td>S I R</td>
<td>S I R</td>
</tr>
<tr>
<td>Before SDD</td>
<td>12 0 0</td>
<td>28 0 0</td>
<td>28 0 0</td>
</tr>
<tr>
<td>After SDD</td>
<td>45 28 4</td>
<td>31 0 75</td>
<td>32 0 74</td>
</tr>
</tbody>
</table>

a Isolates are grouped according to whether they were identified before or after the introduction of SDD on the ICU in October 2002.
b S, susceptible; I, intermediate; R, resistant.

Habilly T. Antimicrobial Agents and Chemotherapy 2013; 57 (7): 3224-9

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An Extended Outbreak of Colistin and Tobramycin Resistant Enterobacteriaceae Driven by SDD

Introduction of SDD and Tobramycin Resistance Among Colistin-Resistant Enterobacteriaceae

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Short Communication
Rapid emergence of secondary resistance to gentamicin and colistin following selective digestive decontamination in patients with KPC-2-producing Klebsiella pneumoniae: a single-centre experience


1 Division of Infectious Diseases and Tropical Medicine, Department of Gastroenterology and Rheumatology, Leipzig University Hospital, Leipzig, 20, D-04103 Leipzig, Germany
2 Medical Diagnostic Centre, Leipzig University Hospital, Johannesallee 14, D-40591 Leipzig, Germany
3 Department of Gastroenterology and Infectious Care Medicine, Leipzig University Hospital, Leipzig, 20, D-04103 Leipzig, Germany
4 University Hospital, Leipzig University Hospital, Leipzig, 20, D-04103 Leipzig, Germany
5 Institute of Hygiene and Environmental Medicine, Charité – Universitätsmedizin Berlin, Hindenburg-Ufer 30, D-12200 Berlin, Germany
6 Department for Infectious Disease Epidemiology, Robert Koch Institute, Pandurstr 35, D-13353 Berlin, Germany
7 Institute for Medical Microbiology and Epidemiology of Infectious Diseases, Leipzig University Hospital, Leipzig, 20, D-04103 Leipzig, Germany

Impact of digestive and oropharyngeal decontamination on the intestinal microbiota in ICU patients

- Patients
  - 21 standard care
  - 19 SOD
  - 17 SDD
- Fluorescent in situ hybridization (FISH) using 16S sequences
  - 13 probes

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Table 3: Numbers and statistical analysis of the main intestinal microbiota groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Regimen:</th>
<th>Mean</th>
<th>95% CI</th>
<th>Mean</th>
<th>95% CI</th>
<th>Mean</th>
<th>95% CI</th>
</tr>
</thead>
</table>
| Probe          | SC (21)  | 4.6 × 10^6 | 2.2 × 10^6 | 6.0 × 10^6 | 3.6 × 10^6 | 4.5 × 10^6 | 3.4 × 10^6 | 2.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 10^6 | 0.1 × 0
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Metagenomic and resistome dynamics in one patient
- Neurotrauma, 30d ICU stay, 47d hospital stay
- SOD, SDD, cefotaxime IV x 4 days

16S HITChip and shotgun sequencing/assembly

Fosmid libraries

Quantitative PCR (qPCR) for aph(2")-Ib and the aadE-like gene in 12 ICU patients

Effects of SDD on the Gut Resistome

Figure 1. Patient history and gut microbiota composition. (a) The timeline indicates the major events throughout the patient's hospital stay and the times at which fecal samples were collected. Light green boxes indicate the antibiotics (C. erythromycin, P. flucloxacillin, V. parvum, C. ampicillin) that were administered to the patient. Further details are provided in the Methods section. Diagnostic culturing was performed for rectum, sputum, throat, urine.

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Effects of SDD on the Gut Resistome

Quantification of Antibiotic-resistant Fosmid Clones

“...cloned resistance genes were harboured by anaerobes from the phyla Firmicutes (Subdoligranulum, Clostridia), Bacteroidetes (Bacteroides uniformis) and Actinobacteria”

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Relative Abundance of the Aminoglycoside Resistance Genes aph(2")-lb and aadE-like in ICU Patients Receiving SDD

- While on SOD and SDD the resistome is, in at least some patients, expanding, not contracting
- This resistome is expanding in obligate anaerobes that form the core of the human microbiome
- The resistance genes that variably expand (like aph(2")-lb and aadE-like genes) may have heretofore unrecognized selective advantage for anaerobes
- The variable expansion of the resistome during SOD/SDD may be what drives the ‘blooming’ of resistance in aerobes after withdrawal of SOD/SDD

Profound Ecological Impact of SOD and SDD

Buelow E. J Antimicrob Chemother 2014; 69: 2215-2223

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Vancomycin-resistant *Enterococcus* domination of intestinal microbiota is enabled by antibiotic treatment in mice and precedes bloodstream invasion in humans

Carles Ubeda, Ying Taur, Robert R. Jeng, Michele J. Espindola, Tammy Son, Miriam R. Bank, Agnes Vale, Nicholas D. Sacci, Marcel R.M. van den Brink, Mini Kamboj, and Eric G. Palmer

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VRE Intestinal Domination Precedes Bacteremia in Human Cancer Patients

Intestinal Domination and the Risk of Bacteremia in Patients Undergoing Allogeneic Hematopoietic Stem Cell Transplantation

- N=94
- Intestinal domination: >30% of composition by single genus

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Decrease in Biodiversity among Hematopoietic Stem Cell Transplant Patients

![Graph showing decrease in biodiversity among hematopoietic stem cell transplant patients](image1)


Clinical Predictors of Intestinal Domination

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Enterococcus Domination</th>
<th>Streptococcus Domination</th>
<th>Proteobacteria Domination</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Age, years</td>
<td>1.00 (0.96-1.04)</td>
<td>0.700</td>
<td>0.99 (0.97-1.02)</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.94 (0.82-1.68)</td>
<td>6.11</td>
<td>1.07 (1.36-2.77)</td>
</tr>
<tr>
<td>Underlying diagnosis (leukemia vs other)</td>
<td>3.22 (1.60-6.48)</td>
<td>0.01</td>
<td>0.71 (1.32-5.13)</td>
</tr>
<tr>
<td>Prior antibiotics (14 days)</td>
<td>1.49 (1.77-2.94)</td>
<td>.237</td>
<td>1.03 (1.68-2.11)</td>
</tr>
<tr>
<td>Conditioning regimen (myeloablative or</td>
<td>1.01 (0.44-2.84)</td>
<td>.977</td>
<td>0.61 (1.25-1.75)</td>
</tr>
<tr>
<td>reduced intensity vs non-myeloablative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T-cell depleted graft</td>
<td>0.81 (0.80-1.61)</td>
<td>.561</td>
<td>0.91 (1.89-2.00)</td>
</tr>
<tr>
<td>Stem cell source (cord vs other)</td>
<td>1.22 (1.05-2.53)</td>
<td>.607</td>
<td>0.54 (1.19-1.34)</td>
</tr>
<tr>
<td>Fever^2</td>
<td>1.68 (1.78-3.74)</td>
<td>.182</td>
<td>0.90 (3.6-2.30)</td>
</tr>
<tr>
<td>Antibiotics^2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td>2.12 (1.87-10.21)</td>
<td>.222</td>
<td>0.95 (0.33-3.77)</td>
</tr>
<tr>
<td>Meropenem</td>
<td>3.38 (1.65-6.79)</td>
<td>.001</td>
<td>1.94 (1.01-4.09)</td>
</tr>
<tr>
<td>Fluoroquinolones^2</td>
<td>1.09 (0.49-2.24)</td>
<td>.032</td>
<td>1.19 (1.51-2.60)</td>
</tr>
<tr>
<td>Beta-lactam^2</td>
<td>1.64 (1.24-2.39)</td>
<td>.232</td>
<td>1.69 (2.6-5.64)</td>
</tr>
</tbody>
</table>


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Association of Preceding Intestinal Domination with Bacteremia

<table>
<thead>
<tr>
<th>Dominating Taxon</th>
<th>VRE Bacteremia HR (95% CI)</th>
<th>P</th>
<th>Gram-negative Bacteremia HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterococcus</td>
<td>0.36 (2.43–45.44)</td>
<td>.001</td>
<td>1.36 (25–5.08)</td>
<td>.600</td>
</tr>
<tr>
<td>Streptococcus</td>
<td>0.21 (1.00–1.75)</td>
<td>.184</td>
<td>0.62 (1.09–3.65)</td>
<td>.823</td>
</tr>
<tr>
<td>Proteobacteria</td>
<td>0.75 (0.11–6.14)</td>
<td>.637</td>
<td>5.46 (1.20–21.99)</td>
<td>.047</td>
</tr>
</tbody>
</table>


Transplant-related mortality is reduced in patients with a diverse microbiota following engraftment

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Comparison of Taxonomic and Functional Variations in the Human Gut Microbiome

[Graph showing variations in bacterial phylum and COG categories]

Tannhaugh PJ et al. Nature Vol 457/22 January 2009 Supplementary Info

CDC Developing Microbiome Disruption Indices (MDI)

- **Uses**
  - Monitor patients before, during, and after antibiotic therapy
    - Alert when disruption reaches critical level or if colonization or dominance is detected
    - Stage patient need for microbiome restoration
  - Characterize risk of specific antibiotics
    - Rating system to gauge relative risks of different agents
    - MDIs determined during approval process and included in package insert

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Antibiotic Resistance Threat from Microbiome Disruption

- What is the usual MDI seen with antimicrobial X?
- Antibiotic disruption
- Multidrug Resistant Organism*
- Further Antibiotic disruption
- Cross Transmission

Normal microbiome: Resistant to colonization
Disrupted microbiome: Susceptible to colonization
Colonization
Overgrowth and Dominance
What is the MDI that promotes dominance?
What is the cumulative MDI that leads to transmission?

*Examples include carbapenem-resistant enterobacteriaceae, vancomycin-resistant enterococci, extended-spectrum beta-lactamase producing enterobacteriaceae. May also include transfer of genetic transfer of resistance determinants

Developing Standards for Determining a Human Drug MDI

- Washington University Prevention Epicenter human volunteer study
  - 10 healthy volunteers
  - Stool sample collected at baseline
  - Antibiotic (amoxicillin/clavulanate) administration
  - 16S profiling before, after, and during resolution

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Understanding Candidate MDIs in Patients with Major Antibiotic Exposure Histories

- Cross-sectional pilot with Emory in long-term acute care hospital (LTACH) inpatients
  - Admission ‘screening’ for C. difficile infection, waste specimens
  - 16S ribosomal RNA encoding DNA amplification and sequencing
  - Association with antibiotic exposure histories and MDRO colonization
- Chicago Prevention Epicenter microbiome studies prior to and following CRE colonization
  - Begin to fill key need for natural history studies

Microbial Community Composition in Emory LTAC Patients

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Another MDI Metric: Loss of Diversity as Measured by the Shannon Diversity Index

De Man T, et al. Keystone Symposium on Molecular and Cellular Biology, Big Sky, MT, April, 2014

Here’s Your Gut Microbiome...

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...Here’s Your Gut Microbiome on Antibiotics

Other Potential MDIs: A Keystone Organism Genus that Prevents VRE Colonization in a Mouse Model

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**Barnesiella spp. Appear to Compete with VRE in Mice**

(A)

![Graph showing the competition between Barnesiella spp. and VRE in mice.](image1)

**Barnesiella spp. Appear to Protect Hematopoietic Stem Cell Patients from VRE Domination**

(A) Prior to VRE domination

(B) VRE dominated

(C) Barnesiella abundance


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Fecal Microbiota Transplant Engraftment

Provide Proof of Concept: Microbiome Restoration to Ameliorate MDRO Dominance or Colonization and Improve the Resistome

- Washington University Prevention Epicenter
  - Auto-transplant subset of human volunteers with FMT following antibiotic administration
    - Investigational New Drug number obtained from FDA
    - Enrollment beginning by end of summer
  - Assess how the intestinal resistome shrinks

- CDC has been in discussions with companies developing advanced probiotics that may ameliorate MDRO dominance or colonization

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Opportunities to Intervene
- Current status quo
- Reducing impact on microbiome
- Microbiome restoration
- Exploit microbiome protective mechanisms

Key:
- Normal microbiome
- Colonization
- Perturbed microbiome
- Clonal expansion
- Colonization and/or clonal expansion prevented

Strategic Public Health Priorities for Microbiome Research to Address AR
- Natural history or longitudinal studies in healthcare settings
  - Understanding the MDIs associated with MDRO colonization, dominance, and infection
- Larger cross-sectional studies
  - Understand major MDI fluxes around healthcare
  - Impact of AR determinants in food on the resistome
- Assess the health and presence of AR determinants in the collective U.S. microbiome
  - Nationally representative cross-sectional sampling to assess microbiome health and its association with exposures

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  - Washington University Prevention Epicenter
- Colleen Kraft, Emory
  - Director of Clinical Microbiology Laboratory
  - Co-director of FMT program
  - Investigator on several FMT translational projects
  - Member of DHQP MWG via CDC Interpersonal Agreement
- Mary Hayden, Vince Young, Robert Weinstein
  - Chicago-Rush Prevention Epicenter

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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