Decolonizing Approaches: Current State and Future Needs

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Drug Development Considerations for the Prevention of Healthcare-Associated Infections—Virtual Public Workshop

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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
Take-home messages

- Decolonization and pathogen reduction are already widely used for prevention in some forms of antimicrobial prophylaxis
- We can learn from unfolding failings of antimicrobial prophylaxis
- Future decolonization strategies should possess specific attributes
- Current and future products span various compositions and modes of action
- There is a central role for the human microbiome in colonization resistance that should be considered in all decolonization strategies
- A tolerable safety margin is impacted by local vs. systemic distribution and targeted vs. risk-based strategies
- It is important to tailor the intervention and its timing to the duration and timing of maximum risk of infection
Decolonization and pathogen reduction is already widespread in some forms of antimicrobial prophylaxis.

Antimicrobial prophylaxis involves localized or systemic administration to prevent infection through a range of mechanisms:

- Decolonization/pathogen reduction
- Prevention of invasion/translocation
- Prevention of pathogen attachment to establish infection
Antimicrobial prophylaxis that works through decolonization or pathogen reduction as examples of the effectiveness of approach
Evidence-based practice recommendations

- **US and International**
  - Pre-operative application of nasal mupirocin to prevent *S. aureus* infections following cardiac and orthopedic surgery.\(^1,2,3\)
    - ACS/SIS SSI Guidelines, 2016 Update: Decision about whether to implement screening and decolonization protocols should depend on baseline SSI and MRSA rates.\(^3\)
    - CDC Surgical Site Infection Guideline (2017) did not address issue\(^4\)
  - Pre-operative administration of non-absorbable antimicrobials, along with mechanical bowel preparation, to prevent surgical infection and anastomotic leaks following bowel surgery.\(^1,2,3,5\)
  - Prevention of secondary cases of meningococcal disease (oral rifampicin or other agents).\(^6\)

- **Netherlands**
  - From onset of ICU care, selective digestive decontamination (SDD) and selective oral decontamination (SOD) to prevent infections and reduce mortality\(^7\)

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Fig. 1 Components of SDD and SOD. SDD selective digestive tract decontamination, SOD selective oropharyngeal decontamination
Take-home message

In settings with low prevalence of antibiotic resistance, SDD is consistently associated with less antibiotic resistance and with improved patient outcome. In settings with moderate-to-high prevalence of antibiotic resistance, benefits of SDD on clinically relevant patient outcomes remain to be demonstrated.

Fig. 1 Components of SDD and SOD. SDD selective digestive tract decontamination, SOD selective oropharyngeal decontamination
Antimicrobial prophylaxis: learning from unfolding failings where decolonization plays a variable role

- **Systemic fluoroquinolones to prevent infections following transrectal prostate biopsy**
  - Some studies indicate improved prevention with administration beginning one day before procedure
  - Recent worldwide increases in breakthrough post-biopsy infections
  - Intestinal colonization with fluoroquinolone-resistant gram-negative pathogens increases risk of breakthrough infection

- **Systemic fluoroquinolones to prevent bloodstream infections in neutropenic patients**
  - Increasing reports of clusters of breakthrough infections
  - Intestinal domination by gram-negative pathogens (proteobacteria) is associated with bloodstream infection
  - Fluoroquinolone normally prevents intestinal domination by gram-negative pathogens (proteobacteria)
  - Intestinal colonization with fluoroquinolone-resistant gram-negative pathogens increases risk of breakthrough infection

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Intestinal domination by gram-negative pathogens (proteobacteria) is associated with bloodstream infection in hematopoietic cell transplant recipients

<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>9.35 (2.43–45.44)</td>
<td>.001</td>
<td>1.35 (.25–5.08)</td>
<td>.690</td>
</tr>
<tr>
<td>Streptococcus</td>
<td>0.21 (.00–1.75)</td>
<td>.184</td>
<td>0.82 (.09–3.65)</td>
<td>.823</td>
</tr>
<tr>
<td>Proteobacteria</td>
<td>0.75 (.01–6.14)</td>
<td>.837</td>
<td>5.46 (1.03–19.91)</td>
<td>.047</td>
</tr>
</tbody>
</table>

Intestinal domination: >30% of composition of gut microbiota by single genus

**Fluoroquinolone prophylaxis normally prevents intestinal domination by gram negative pathogens (proteobacteria) in hematopoietic cell transplant recipients**

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**Intestinal domination: >30% of composition of gut microbiota by single genus**

**Table 2. 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 (.98-1.04)</td>
<td>.790</td>
<td>0.99 (.97-1.03)</td>
</tr>
<tr>
<td>Female</td>
<td>0.84 (.42-1.64)</td>
<td>.611</td>
<td>1.07 (.50-2.27)</td>
</tr>
<tr>
<td>Underlying diagnosis (leukemia vs other)</td>
<td>3.22 (1.60-6.94)</td>
<td>.001</td>
<td>0.71 (.32-1.51)</td>
</tr>
<tr>
<td>Prior antibiotics (14 days)*</td>
<td>1.49 (1.77-2.94)</td>
<td>.237</td>
<td>1.03 (1.48-2.17)</td>
</tr>
<tr>
<td>Conditioning regimen (myeloablative or reduced intensity vs non-myeloablative)</td>
<td>1.01 (1.44-2.84)</td>
<td>.977</td>
<td>0.61 (1.25-1.75)</td>
</tr>
<tr>
<td>T-cell depleted graft</td>
<td>0.81 (.40-1.61)</td>
<td>.551</td>
<td>0.91 (.39-2.00)</td>
</tr>
<tr>
<td>Stem cell source (cord vs other)</td>
<td>1.22 (1.55-2.52)</td>
<td>.607</td>
<td>0.54 (1.19-1.34)</td>
</tr>
<tr>
<td>Fever*</td>
<td>1.68 (1.78-3.74)</td>
<td>.182</td>
<td>0.90 (1.36-2.39)</td>
</tr>
<tr>
<td>Antibiotics b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td>2.12 (.67-10.21)</td>
<td>.222</td>
<td>0.96 (.33-3.77)</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>3.38 (1.65-6.73)</td>
<td>.001</td>
<td>1.94 (1.81-4.30)</td>
</tr>
<tr>
<td>Fluoroquinolones c</td>
<td>1.09 (1.49-2.24)</td>
<td>.832</td>
<td>1.19 (1.51-2.60)</td>
</tr>
<tr>
<td>Beta-lactams b</td>
<td>1.64 (.74-3.99)</td>
<td>.232</td>
<td>1.69 (1.62-5.64)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio.
* Defined as administration of any antibacterial drug within 14 days prior to observation period.
* Analyzed as a time-varying predictor.
* Fluoroquinolones consist of ciprofloxacin and levofloxacin.
* Beta-lactams include cephalosporins, beta-lactam-beta-lactamase combinations, and carbapenems.

Colonization with fluoroquinolone-resistant gram-negative pathogens (Enterobacterales) increases risk for bloodstream infection in hematopoietic cell transplant recipients

Figure 2. Proportion of patients who developed fluoroquinolone-resistant Enterobacterales (FQRE) bloodstream infection (BSI), gram-negative BSI, gram-positive BSI, and any BSI, stratified by pretransplant FQRE colonization status. P-values represent comparisons between FQRE-colonized and noncolonized patients.
Intestinal domination by gram-negative pathogens is associated with subsequent bloodstream infection
- AND -
Fluoroquinolone prophylaxis normally reduces the risk of intestinal domination by gram-negative pathogens
- AND -
Colonization with fluoroquinolone-resistant gram-negative pathogens increases risk for breakthrough infection
- THEREFORE -
The protection from fluoroquinolone prophylaxis is mediated at least in part through pathogen reduction
- AND -
Fluoroquinolone resistance leads to breakthrough infections through breakthrough intestinal dominance
Rethinking the mechanisms of fluoroquinolone prophylaxis in neutropenia and improved approaches

Fluoroquinolones were developed for short term treatment of local infection through systemic administration and not specifically for decolonization or pathogen reduction:
1. High oral absorption
2. Excellent body site distribution and tissue penetration
3. Increasingly recognized toxicity
4. Although high fecal levels achieved (15-94 ug/g for levofloxacin),¹ resistance commonly leads to high MICs (> 32 ug/ml)²
5. Although initially thought to have little impact on anaerobic microbiota and gut microbiome,³ selection of resistance in anaerobes (e.g., C. difficile)⁴ and microbiome disruption increasingly recognized

Future decolonization strategies should possess specific attributes

- **Narrow spectrum and limited body site distribution**
  - To improve drug safety and reduce collateral damage to microbiome
  - Non-absorbable narrow-spectrum agent for enteral, topical, or other local application

- **Favorable pharmacokinetics**
  - To reduce emergence of resistance through local evolution
  - High levels achievable locally relative to minimum inhibitory (MIC) or even bactericidal concentration (MBC)

- **Unlikely to evoke cross resistance through markedly different mechanisms of action**
  - Antiseptics generally less likely to evoke cross resistance to antimicrobials, although co-selection still possible via genetic linkage or strain selection

- **Leveraging colonization resistance afforded by the microbiome**
  - Through microbiome sparing, protection, or restoration

- **Durability**
  - Phage or live biotherapeutics may extend duration of decolonization or colonization resistance through their replication
Current and future products span various compositions and modes of action

- **Small molecule antimicrobial**
  - Current use: Mupirocin, non-absorbable antibiotics used for gut decontamination

- **Bacteriocins, and local (monoclonal) antibodies**
  - Under development: Lysostaphin

- **Topical antiseptics—decontaminating agents**
  - Current use: Alcohol, chlorhexidine

- **Microbiome protectants**
  - Under development: Activated charcoal, beta-lactamase enzyme

- **Microbiome restoratives**
  - Current use (under enforcement discretion for rCDI): Fecal microbiota transplantation (FMT)
  - Under development: pathogen reduced or processed FMT or derivative, defined microbiota consortium

- **Phage**
  - Under development: single or in cocktail form
There is a central role for the human microbiome in colonization resistance that should be considered in all decolonization strategies.

**Table 2. Outcome Data in the Original Cohort and in the Propensity Score-Matched Cohort**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Original Cohort</th>
<th>Propensity Score Matching</th>
<th>Difference, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treated With FMT</td>
<td>Treated With Antibiotics</td>
<td>Treated With FMT</td>
</tr>
<tr>
<td><strong>Patients, n</strong></td>
<td>109</td>
<td>181</td>
<td>57</td>
</tr>
<tr>
<td><strong>Primary outcomes, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BSI</td>
<td>5 (5)</td>
<td>40 (22)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Polymicrobial*</td>
<td>1 (1)</td>
<td>11 (6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Bacterial</td>
<td>5 (5)</td>
<td>28 (15)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Fungal</td>
<td>0 (0)</td>
<td>12 (7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of hospitalization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD), d</td>
<td>13.3 (14.8)</td>
<td>29.7 (22.6)</td>
<td>13.4 (13.7)</td>
</tr>
<tr>
<td>Median (interquartile range), d</td>
<td>8 (2-20)</td>
<td>22 (14-39)</td>
<td>9 (2-21)</td>
</tr>
<tr>
<td>Overall survival at 90 d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alive after 90 d, n (%)</td>
<td>100 (92)</td>
<td>111 (61)</td>
<td>51 (89)</td>
</tr>
<tr>
<td>Total deaths within 90 d, n (%)</td>
<td>9 (8)</td>
<td>70 (39)</td>
<td>6 (11)</td>
</tr>
<tr>
<td>Deaths in days 0-30, n</td>
<td>5</td>
<td>53</td>
<td>3</td>
</tr>
<tr>
<td>Deaths in days 31-90, n</td>
<td>4</td>
<td>17</td>
<td>3</td>
</tr>
</tbody>
</table>

BSI = bloodstream infection; FMT = fecal microbiota transplantation.

* 12 of 45 patients developed a polymicrobial BSI (from multiple bacteria in 10 patients and from fungal and bacterial organisms in 2 patients.

There is a central role for the human microbiome in colonization resistance that should be considered in all decolonization strategies.

Either replicate essential components of these natural functions, or spare, protect, or restore the microbiome.

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A tolerable safety margin is impacted by local vs. systemic distribution and targeted vs. risk-based strategies

- **Local body site distribution**, for example an orally administered non-absorbed agent, limits end-organ exposure to potential toxicities
  - However, getting the locally-acting agent to its site of action may slow onset of action, for example oral ingestion requiring small-bowel transit to reach site of action in the large intestine

- **Targeted:**
  - Rapid screening for colonization with a specific pathogen
  - Generally smaller population exposure
  - Examples:
    - Pre-operative application of nasal mupirocin to prevent S. aureus infections following cardiac and orthopedic surgery
    - Targeted (known colonized) MRSA decolonization on discharge (CLEAR study)

- **Risk-based:**
  - Administration to all patients fitting a particular risk profile or patient care area
  - Generally larger population exposure
  - Examples:
    - SDD as recommended in the Netherlands for all ventilated ICU patients
    - Mupirocin and chlorhexidine decolonization as recommended for ICU patients and hospitalized adults with central venous catheters to prevent S. aureus bloodstream infection

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It is important to tailor the intervention and its timing to the duration and timing of maximum risk

- **Need to integrate screening (or risk stratification) with onset of action of the intervention**
  - If targeted application, need rapid turnaround screening methods\(^1,2\)

- **Speed of decolonization relative to onset of risk**
  - SDD/SOD, when extended to Europe, may have been hampered by removal of 3rd gen cephalosporin, if decolonization or pathogen reduction could not be achieved rapidly enough\(^3\)

- **Duration of decolonization relative to duration of risk**
  - Pre-partum decolonization (vs. intrapartum antibiotics) of Group B *Streptococcus* is not recommended as a prevention strategy for early onset infection of neonates because it cannot be achieved or maintained up to time of birth using available antibiotics\(^4,5\)

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\(^1\) Global guidelines for the prevention of surgical site infection. World Health Organization. Available at [http://apps.who.int/iris/bitstream/handle/10665/250680/9789241549882-eng.pdf?sequence=8](http://apps.who.int/iris/bitstream/handle/10665/250680/9789241549882-eng.pdf?sequence=8)


Take-home messages

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Thank you

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Supplementary Slides
Selective decontamination of the digestive tract (SDD) in critically ill patients

- The main goal of SDD is to prevent ICU-acquired infections (and thereby improve patient outcomes)
  - Patients with an expected ICU stay of at least 2 or 3 days, and receiving mechanical ventilation
  - Preferred moment to start SDD is immediately upon ICU admission
  - In most studies, SDD was continued until ICU discharge and in some until extubation
  - Later, as an alternative to SDD, selective oropharyngeal decontamination (SOD) was proposed, based on clinical studies suggesting a more important role of upper respiratory tract colonization in the pathogenesis of ventilator-associated pneumonia than intestinal carriage

- Until 2000, most studies were individually randomized trials
  - Recognition that individual randomization may reduce the generalizability of study results and is suboptimal if cross-transmission occurs, artificially reducing the effect size afforded by indirect protection in settings where SDD applied uniformly
  - To overcome this, investigators adopted cluster designs

- Complicating factor: requirement of informed consent
  - Practically precludes enrollment of all eligible patients and will delay the start of SDD in many that do consent
  - In three recent cluster-randomized studies, waivers for informed consent were granted in the Netherlands, Belgium, Spain, Portugal, Italy, Slovenia, and the UK
    - SDD was considered part of daily ICU practice in each country
    - True equipoise on the effects of SDD, leading to marked differences in practice between ICUs
    - SDD (and SOD) were considered safe and it was acknowledged that a cluster-randomized study would not be feasible without such a waiver
    - Waivers allowed an immediate start of SDD after ICU admission and enrollment of 6000 patients and more

### Overview of recent SDD studies using a cluster-randomized design

<table>
<thead>
<tr>
<th>Author</th>
<th>Study period</th>
<th>Design</th>
<th>Countries</th>
<th>Study Outcome(s)</th>
<th>Patient numbers</th>
<th>Effect size</th>
<th>Antibiotic resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jonge et al. (1)</td>
<td>1999-2001</td>
<td>CRCT, comparing SC to SDD</td>
<td>Netherlands</td>
<td>ICU and hospital mortality</td>
<td>SDD n=466, SC n=468</td>
<td>ICU mortality (SDD vs. SC): -69 (15%)/107 (23%) (P=0.002). Hospital mortality (SDD vs. SC): -113 (24%) vs 146 (31%) (P=0.02).</td>
<td>During SDD acquired carriage was lower for Pseudomonas aeruginosa resistant to ceftazidime, ciprofloxacin and imipenem, and for other Gram-negative bacteria resistant to other Gram-negative bacteria resistant to ciprofloxacin, imipenem and tobramycin.</td>
</tr>
<tr>
<td>Oostdijk et al. (2)</td>
<td>2004-2006</td>
<td>CRCT, comparing SC to SDD and SOD</td>
<td>Netherlands</td>
<td>Mortality at day 28</td>
<td>SOD n=2045, SDD n=1904, SC n=1990</td>
<td>Adjusted Odds ratio for mortality at day 28: SDD vs. SC: 0.83 (95% CI 0.72 to 0.97) vs. SOD vs. SC: 0.86 (95% CI 0.74 to 0.99).</td>
<td>Average prevalence of rectal carriage with Gram-negative bacteria resistant to gentamicin/tobramycin + ciprofloxacin or ceftazidime SDD 0.5% SOD 2.3% (P &lt;0.05 to SOD) SC 2.2% (P &lt;0.05 to SOD).</td>
</tr>
<tr>
<td>Oostdijk et al. (3)</td>
<td>2009-2013</td>
<td>CRCT, comparing SDD to SOD</td>
<td>Netherlands</td>
<td>Unit-wide prevalence of specific antibiotic-resistant microorganisms</td>
<td>SDD n=6.116, SC n=5.881</td>
<td>Proportions colonized with rectal with HRMO SOD vs. SDD: 12.7% (IQR 11.3-14.2) vs. 7.3% (IQR 6.1-8.4); P=0.008</td>
<td>Prevalence of rectal carriage of aminoglycoside-resistant gram-negative bacteria increased 7% per month (95%CI, 1%-13%) during SDD (P=.02) and 4% per month (95%CI, 0%-8%) during SOD (P=0.046; P=0.40 for difference).</td>
</tr>
<tr>
<td>Wittekamp et al. (4)</td>
<td>2013-2017</td>
<td>CRCT, comparing SC to SDD*, SOD and CHX</td>
<td>Spain, Italy, Portugal, Belgium, UK, Slovenia</td>
<td>ICU-acquired BSI with MDR-GNB</td>
<td>SDD n=2082, SOD n=2224, CHX n=2108, SC n=2251</td>
<td>Adjusted hazard ratios for ICU-acquired BSI with MDR-GNB SOD vs. SC: 0.70 (95% CI, 0.43-1.14) SOD vs. CHX: 0.89 (95% CI 0.55-1.45) CHX vs. SC: 1.13 (95% CI 0.68-1.88)</td>
<td>Adjusted Relative Risk for unit-wide rectal carriage with MDR-GNB SOD vs SC: 1.01 (95% CI 0.64-1.58) SOD vs CHX: 0.80 (95% CI 0.49-1.30) CHX vs SC: 0.80 (95% CI 0.50-1.27)</td>
</tr>
</tbody>
</table>

- Ongoing cluster, cross-over RCT (clinicaltrials.gov NCT02389036)
  - Currently recruiting 12,000-15,000 patients in Canada, UK, and Australia
  - Patients not already receiving intravenous therapeutic antibiotic: 4-day course of intravenous cephalosporin

References

Examples of antimicrobial prophylaxis with little role for decolonization and pathogen reduction: missed opportunities?

- Targeting only prevention of invasion/translocation or pathogen attachment
- Systemic surgical or endocarditis prophylaxis administered prior to procedure
  - Clean or clean-contaminated surgical procedures or dental work
  - Targeting a variety of gram-positive skin or oral aerobes
  - As currently practiced, little to no time to decolonize or pathogen reduce with drug achieving relatively low levels at sites of colonization—focus is on achieving high blood levels at time of procedure
- Systemic intrapartum prophylaxis for prevention of early-onset group B streptococcus (GBS) infection in neonates
  - Rectal GBS colonization in mother is pre-requisite for infection; heavy rectal colonization or GBS bacteriuria carries increased risk\(^1\)
  - Early attempts suggested pre-partum maintenance of decolonization was not possible\(^2\) Current guidance primarily targets administration based on screening at up to 5 weeks before delivery, risk-based administration if screening missed\(^1\)
  - Systemic prophylaxis administered in about half of all U.S. births, crossing the placental barrier and leading to significant population impact on early life microbiome development\(^3\)

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### Table 3. Organisms Involved in BSIs in the Original Study Cohort

<table>
<thead>
<tr>
<th></th>
<th>Total Patients, $n$</th>
<th>FMT Group, $n$</th>
<th>Antibiotic Group, $n$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacteria</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>XDR Acinetobacter baumannii</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>VR E faecium</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Klebsiella oxytoca</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>K pneumoniae</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>CRE K pneumoniae</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>ESBL K pneumoniae</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Staphylococcus species</td>
<td>7</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>S aureus</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>MR S aureus</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Proteus mirabilis</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>XDR P mirabilis</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Corynebacterium species</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>31</td>
<td>5</td>
<td>26</td>
</tr>
<tr>
<td><strong>Fungi</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candida albicans</td>
<td>9</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>C parapsilosis</td>
<td>4</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>C tropicalis</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>14</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>45*</td>
<td>5</td>
<td>40</td>
</tr>
</tbody>
</table>

BSI = bloodstream infection; CRE = carbapenem-resistant Enterobacteriaceae; ESBL = extended-spectrum β-lactamase-producing; FMT = fecal microbiota transplantation; MR = methicillin-resistant; VR = vancomycin-resistant; XDR = extensively drug-resistant. * 12 of 45 patients developed a polymicrobial BSI (from multiple bacteria in 10 patients and from fungal and bacterial organisms in 2 patients).