Network of microbial and antibiotic interactions drive colonization and infection with multidrug-resistant organisms

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Introduction

• Single-species view of MDRO epidemiology does not reflect the complex reality
  – Multiple circulating MDRO species in healthcare facilities
  – Individuals are often colonized by more than one MDRO

• Interventions based on a single-species perspective can result in unintended consequences
  – Reducing cephalosporin use → decrease resistant *K. pneumoniae*
  – Carbapenems use instead → resistance in *P. aeruginosa*

• Interdependencies between antibiotic use and MDROs
Objectives

• How interactions among antibiotics and different MDRO species influence the dynamics of MDRO colonization and infection in LTCFs.

• 2010 to 2013 from 234 nursing home residents
  — Longitudinal surveillance data and diagnostic records
    • MDROs in the groin and perirectum

• Antibiotic administration or MDRO colonization increased risk of new MDRO acquisition or clinical infection

• Single-species stewardship paradigm → interventions that account for the downstream impacts of treatment decisions mediated by the ecology of MDROs in healthcare facilities
Methods: Study Population

– Targeted Infection Prevention (TIP) study

– 12 nursing homes 234 enrolled residents
  • Urinary catheter for longer than 72 h

– Longitudinal data
  • Indwelling device use, functional status, comorbidities, urine culture results, and antibiotic administration

– Microbiological samples
  • baseline, day 15, and monthly for up to a year.
  • Groin and perirectal area
  • MRSA, VRE, and Gram-negative bacteria resistant to ciprofloxacin or ceftazidime
Methods: Data management

- Bacteria of interest: detected microbiologically > 20 residents across visits during the study
  - VRE, MRSA, A. baumannii, E. coli, P. mirabilis, and P. aeruginosa.

- Duration of colonisation: Positive culture to Next visit

- Colonization status was treated as a time-dependent variable

- Prolonged effects of antibiotics on the acquisition of MDROs: 30 days past the end of antibiotic administration

- Statistical Analysis
  - Cox proportional hazard models to test effect of:
    - Presence of an earlier bacterial colonizer on acquiring secondary colonization;
    - Antibiotic exposure on MDRO colonization
    - Bacterial colonization on CAUTI urine culture results (MRSA, Enterococcus, E. coli, and P. mirabilis).
**Results**

**NH Residents Are Heavily Colonized with Antibiotic-Resistant Bacteria**

<table>
<thead>
<tr>
<th>Species</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VRE</td>
<td>71 (30.3)</td>
</tr>
<tr>
<td>MRSA</td>
<td>70 (29.9)</td>
</tr>
<tr>
<td>Resistant E.coli</td>
<td>71 (30.3)</td>
</tr>
<tr>
<td>Resistant Proteus mirabilis</td>
<td>62 (26.5)</td>
</tr>
<tr>
<td>Acinetobacter baumannii</td>
<td>28 (12.0)</td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>23 (9.8)</td>
</tr>
<tr>
<td>Colonized with one species</td>
<td>55 (23.5)</td>
</tr>
<tr>
<td>Colonized with 2 species</td>
<td>49 (20.9)</td>
</tr>
<tr>
<td>Colonized with &gt;2 species</td>
<td>46 (20)</td>
</tr>
<tr>
<td>At least one course of treatment with one of 50 different antibiotics</td>
<td>146 (62)</td>
</tr>
</tbody>
</table>
Results

- NH Residents Are Heavily Colonized with Antibiotic-Resistant Bacteria

Fig. 1. MDRO colonization patterns for 234 NH residents. The prevalence of most commonly observed multidrug-resistant organisms (MDROs) in the groin or perirectum of 234 nursing home residents who had a urinary catheter in place for >72 h is shown. Each column in the heatmap represents a catheterized resident, and each colored cell indicates colonization by the corresponding MDRO during their stay. The facility each resident resided in is color-coded on the top of the heatmap, with legend provided on the right (A–L). The total number of different species detected in each resident over time is summarized in the black barplot above.
Results

• Existing Bacterial Colonization Increases the Risk of Secondary Acquisition
  – Test whether **preexisting MDRO colonization predict new colonization with a different MDRO species**
    • Hazard ratio (HR) of acquiring a secondary organism in the presence of another organism
  – **P. mirabilis** colonization increased the risk of acquiring *A. baumannii*, MRSA, and VRE (unadjusted HR > 2 and P < 0.05 in all cases),
  – Preexisting colonization with *A. baumannii, E. coli*, and *P. aeruginosa* increased the risk of acquiring *P. mirabilis* (HR > 2 and P < 0.05 in all cases)
  – **Co-colonization is not simply a stochastic process, but is shaped by underlying microbial and host factors.**
Results

• Many-to-Many Relationships Between Antibiotic Exposure and MDRO Colonization
  – Multiple antibiotics associated with acquisition of a single MDRO
  – Single antibiotic associated with acquiring multiple MDRO species

• Microbial and Antibiotic Factors Jointly Influence Bacterial Colonization.
  – Except for MRSA, all MDRO colonization was found to be positively associated with at least one other MDRO and one antibiotic
    • VRE to glycopeptides, *E. coli* to penicillin, *P. mirabilis* to nitrofurans, and *P. aeruginosa* to carbapenems.
  – While several MDROs were associated with the acquisition of other MDROs, *P. mirabilis appeared to be the “hub” species*
Fig. 2. Risk network for MDRO colonization. Blue nodes represent MDRO colonization, and gray nodes represent antibiotic exposure. Each directed arrow indicates that the source node is predictive of the recipient node. Here antibiotic exposure is assumed to be risk factors for colonization, whereas bacterial colonization could either be the risk factor for subsequent colonization, or a result of antibiotic exposure and/or previous colonization. The magnitude of the hazard ratio is reflected in edge thickness and shown in numbers. All associations shown are statistically significant with $P < 0.05$. 
• Cocolonization Is Associated with Increased Risk of Having Specific Species in CAUTI Urine Culture

— 70 residents had a clinically diagnosed catheter-associated urinary tract infection (CAUTI)
  • *P. mirabilis* (n = 38), *Enterococcus* spp. (n = 22), *E. coli* (n = 20), and *Staphylococcus* spp. (n = 13) were the most commonly isolated bacteria in their urine.

— The presence of a specific co-colonizing species in the groin or perirectum increased the risk of infection
  • VRE + *E. coli* → increased risk of *Enterococcus* in urine,
  • *E. coli* or MRSA + *P. mirabilis* increased the risk of *E. coli* or MRSA
Results

Fig. 3. Risk network for catheter-associated urinary tract infection (CAUTI) events. CAUTI events were divided into four subsets based on the species found in the urine (Enterococcus, *P. mirabilis*, MRSA, and *E. coli*). Orange nodes represent species-specific CAUTI events, and blue nodes represent MDRO colonization. Figure includes only colonizing species that were also found in CAUTI urine. Directed arrows indicate the risk of a subsequent colonization in the presence of another MDRO colonization (\( **P < 0.05 \)), or the risk of having a species-specific CAUTI when colonized by an MDRO (\( *P < 0.1 \)). Red numbers indicate the hazard ratio of having a species-specific CAUTI in cocolonized residents; the hazard ratio of having such outcome in residents colonized by only one MDRO is not significant.
Discussion

• Strategies have to account for the complex set of interdependencies among MDROs and antibiotics

• *P. mirabilis* increased risk of acquiring other MDROs,
• Risk of acquiring *P. mirabilis* influenced by other colonizing MDROs
  – Produce both monospecies and polymicrobial biofilms, commonly with urease-producing species
  – *P. mirabilis* urease production is enhanced in the presence of urease nonproducers, including *Enterococcus, A. baumannii*, and *E. coli*
  – The colonization of bacterial pairs, including *E. coli/Enterococcus, P. mirabilis/E. coli*, and *P. mirabilis/MRSA*, synergistically increased risk of developing a CAUTI
Discussion

- *P. mirabilis* and *E. coli* promote one another’s growth:
  - Complementary metabolic pathways, with coinfection promoting the colonization and persistence of both species

- *P. mirabilis/E. coli* cocolonization increased the risk of subsequent movement into the urine and enhanced pathogenic potential
  - *Proteus species and Staphylococcus aureus* increase each other’s virulence in animals models,
  - *P. mirabilis* increased risk of CAUTI with other organisms, but no colonizing partners identified as increasing the risk of *P. mirabilis* CAUTI.
  - Consequence of *Proteus’* diverse interaction partners precluding the detection of specific interactions with our small number of CAUTI cases