Does Antimicrobial Stewardship and Specific *Clostridium difficile* Antimicrobial Prophylaxis Prevent CDI?

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BMBF 01KN1106
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Stop anti-infectives

- Excessive coverage
- Combination tx for *P. aeruginosa*
- ICU: Empiric tx
- Haem/SCT: Antifungal combination tx
- Toxicity
- Tx duration accomplished

Adjust dose

- Upon changing degree of renal failure
- According to Therapeutic drug monitoring

Focus treatment

- Replace vancomycin with flucloxacillin in MSSA

Diagnose

- Collect more blood cultures
- Pursue biopsy
Antimicrobial Stewardship could prevent too short courses of anti-CDI treatment

Early recurrence (relapse):
Fidaxomicin: 7.4%
Vancomycin: 19.3%

Late recurrence (relapse/reinfection):
Fidaxomicin: 6.6%
Vancomycin: 8.1%

Day of follow-up after completion of therapy for CDI:

Number of patients with recurrence of CDI:

- Fidaxomicin
- Vancomycin

Avoid Proton Pump Inhibitors (PPI)

Administration of proton pump inhibitors in critically ill medical patients is associated with increased risk of developing Clostridium difficile–associated diarrhea

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- PPI prevent gastrointestinal bleeding ICU patients
- PPI increase risk of CDI in non-ICU in-patients
- Retrospective, single-center analysis, 1999-2010
- N= 3,286 critically ill patients
- 91% received stress ulcer prophylaxis
  - 56% PPI
  - 6% H2 blockers
  - 10% sucralfate
  - 20% combinations

Avoid Proton Pump Inhibitors (PPI)

• 1% developed GI bleeding, independent of prophylaxis
• 3.3% developed CDI, associated with
• Independent risk factors for CDI by multivariate analysis
  ➢ Fluoroquinolones (odds ratio 1.9)
  ➢ 3rd generation cephalosporins (OR 1.8)
  ➢ PPI (OR 3.1)
• Risk adjusted PPI use should be investigated
  ➢ Mechanical ventilation
  ➢ Coagulopathy

Long-Term Care Facilities (LTCF)

- Setting: 160-bed LTCF attached to a hospital
- Initiation of an ID consulting service
- Comparison of systemic antimicrobial use & C. difficile tests before and after

Long-Term Care Facilities (LTCF)

• Total systemic antibiotic use decreased by 30%
  ➢ -32% reduction in oral
  ➢ -25% reduction in i.v.
  ➢ -64% for tetracyclines
  ➢ -61% for clindamycin
  ➢ -38% for sulfamethoxazole/trimethoprim
  ➢ -38% for fluoroquinolones
  ➢ -28% for β-lactam/β-lactamase inhibitor combinations

• The rate of positive *C. difficile* tests declined

Long-Term Care Facilities (LTCF)

- Positive *C. difficile* Tests – “Trend reversed”

Bedside CDI testing prevents empiric treatment

POC tests over last two years
N=275

Positive
N=22 (8%)

Negative
N=253 (92%)

Cornely O, data on file.
# Effect of Antimicrobial Stewardship on CDI Incidence – A Meta-Analysis


## Saturday, May 10, 14:18 Hall G

<table>
<thead>
<tr>
<th>Study of subgroup</th>
<th>log [Risk ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>Risk ratio IV, Random, 95% CI</th>
<th>Risk ratio IV, Random, 95% CI</th>
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</thead>
<tbody>
<tr>
<td>Elligson 2012</td>
<td>-0.37</td>
<td>0.393</td>
<td>5.0%</td>
<td>0.69 [0.32, 1.49]</td>
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<tr>
<td>Fowler 2007</td>
<td>-1.05</td>
<td>0.372</td>
<td>5.3%</td>
<td>0.35 [0.17, 0.73]</td>
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<tr>
<td>Frank 1997</td>
<td>0.029</td>
<td>0.522</td>
<td>3.6%</td>
<td>1.03 [0.37, 2.86]</td>
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<tr>
<td>Gulihar 2009</td>
<td>-1.65</td>
<td>0.522</td>
<td>3.6%</td>
<td>0.19 [0.07, 0.53]</td>
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<tr>
<td>Jones 1997</td>
<td>-0.4</td>
<td>0.205</td>
<td>8.1%</td>
<td>0.67 [0.45, 1.00]</td>
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<tr>
<td>Ludlam 1999</td>
<td>-0.721</td>
<td>0.177</td>
<td>8.7%</td>
<td>0.49 [0.34, 0.69]</td>
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</tr>
<tr>
<td>Malani 2013</td>
<td>-0.755</td>
<td>0.257</td>
<td>7.2%</td>
<td>0.47 [0.28, 0.78]</td>
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<tr>
<td>Miller 2009</td>
<td>-1.341</td>
<td>0.341</td>
<td>5.8%</td>
<td>0.26 [0.13, 0.51]</td>
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<tr>
<td>O’Connor 2004</td>
<td>-1.164</td>
<td>0.567</td>
<td>3.2%</td>
<td>0.31 [0.10, 0.95]</td>
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<tr>
<td>Price 2010</td>
<td>-0.661</td>
<td>0.082</td>
<td>10.1%</td>
<td>0.52 [0.44, 0.61]</td>
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<tr>
<td>Reinoso 2002</td>
<td>-3.372</td>
<td>1.438</td>
<td>0.7%</td>
<td>0.03 [0.00, 0.57]</td>
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<tr>
<td>Schön 2011</td>
<td>0.034</td>
<td>0.103</td>
<td>9.8%</td>
<td>1.03 [0.85, 1.27]</td>
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<td>Starks 2008</td>
<td>-0.984</td>
<td>0.309</td>
<td>6.3%</td>
<td>0.37 [0.20, 0.68]</td>
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<td>Stone 1998</td>
<td>-0.546</td>
<td>0.251</td>
<td>7.3%</td>
<td>0.58 [0.35, 0.95]</td>
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<tr>
<td>Talpaert 2011</td>
<td>-1.079</td>
<td>0.272</td>
<td>6.9%</td>
<td>0.34 [0.20, 0.58]</td>
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<tr>
<td>Thomas 2002</td>
<td>-0.78</td>
<td>0.19864</td>
<td>8.3%</td>
<td>0.46 [0.31, 0.68]</td>
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</tbody>
</table>

**Total (95% CI):** 100.0% 0.48 [0.38, 0.62]

**Heterogeneity:** $\tau^2 = 0.14; \chi^2 = 61.27, df = 15 \:(P<0.00001); I^2 = 76%$

**Test for overall effect:** $Z = 5.94 \:(P<0.00001)$
Many of Our Patients are at Risk of CDI

- >65 years\textsuperscript{1,2}
- Chronic underlying diseases\textsuperscript{3}
- Antibiotics use\textsuperscript{2,4}
- Immunosuppressants\textsuperscript{5}
  - AML\textsuperscript{7}
  - HSCT\textsuperscript{7}
- Surgical procedures\textsuperscript{6}
- Previous CDI episode\textsuperscript{2}

Specific Prophylaxis – Challenges

• Whose the target population?

▷ At Cologne University screening of all CDI cases for clinical trial inclusion since 2006

▷ No CDI clusters

▷ No two CDI patients on the same ward at the same time
Of note, 23/28 (82%) CDI episodes occurred within one month after allogeneic transplantation.
Specific Prophylaxis

- Safety and efficacy of fidaxomicin for prophylaxis against CDI
- Hematopoietic stem cell transplantation
- RCT, placebo-controlled, N=350
- Recruiting
Does prophylactic metronidazole – before patients receive other antibiotics – reduce the risk of CDI?

Retrospective cohort analysis

N= 12,026 high-risk patients (2008-2012)
Specific Prophylaxis with Metronidazole?

80% reduction (OR 0.2; 95% CI, 0.11–0.38) adjusted for age, sex, and comorbidities.

Probiotics for the Prevention of *Clostridium difficile*-Associated Diarrhea

A Systematic Review and Meta-analysis

Bradley C. Johnston, PhD; Stephanie S.Y. Ma, MD; Joshua Z. Goldenberg, BSc; Kristian Thorlund, PhD; Per O. Vandvik, MD, PhD; Mark Loeb, MD; and Gordon H. Guyatt, MD

• To assess efficacy & safety of probiotics for prevention of CDI
• 20 trials from 1989 - 2011
• N=3,818
• Moderate-quality evidence suggests that probiotic prophylaxis results in a large reduction in CDAD without increase in important adverse events

Prophylaxis of Recurrence – MoAbs

- MK-6072 and MK-3415A in CDI (MODIFY I)
  - RCT, placebo-controlled, N=1200
  - Recruiting

- MK-3415, MK-6072, and MK-3415A in CDI (MODIFY II)
  - RCT, placebo-controlled, N=1600
  - Recruiting

ClinicalTrials.gov
NCT01241552 & NCT01513239
Prophylaxis of Recurrence – Strategies

- Vaccines
- Non-toxigenic *C. difficile*
1. Diagnose CDI on the first day of diarrhoea

2. Treat along the ESCMID guidelines

3. Explain CDI to physicians, patients, relatives
   - e.g. ECDC fact sheets

4. ID consult when high risk of recurrence
   - e.g. continued antibacterial use
Outlook

• What might be used tomorrow
  ➢ New antibiotics are coming
  ➢ Other therapeutic principles
  ➢ Primary prophylaxis
    if we identify a population at high enough risk

• What can be used today
  ➢ Antimicrobial stewardship
  ➢ Prophylaxis of recurrence with FDX