Duration of Antimicrobial Therapy

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University Medical Center of Southern Nevada
August 15, 2017
It depends......

Thank you
Objectives

• Overview
• Generalized treatment concepts
• Disease specific
  • Pneumonia
  • Pyelonephritis
  • Intra-abdominal infection
• Summary
# 2008 Hospital Drug expenses

<table>
<thead>
<tr>
<th>Drug Expenses</th>
<th>2008 Expenditures ($ Thousands)</th>
<th>% change from 2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antineoplasticis</td>
<td>3,344,742</td>
<td>5.0</td>
</tr>
<tr>
<td>Hemostatic modifiers</td>
<td>3,459,980</td>
<td>6.6</td>
</tr>
<tr>
<td>Anti-infectives, systemic</td>
<td>3,188,596</td>
<td>7.3</td>
</tr>
<tr>
<td>Blood growth factors</td>
<td>2,196,040</td>
<td>-9.6</td>
</tr>
<tr>
<td>Hospital solutions</td>
<td>1,697,024</td>
<td>17.5</td>
</tr>
</tbody>
</table>

Unnecessary Use in Hospitals

- Prospective observational study conducted in adult inpatients over 2 weeks in August 2001
- 576 (30%) of 1941 total antimicrobial days of therapy (DOT) were deemed unnecessary

Most common Reasons for Unnecessary DOT

- DOT Longer than Necessary: 192
- Noninfectious or Nonbacterial Syndrome: 187
- Treatment of Colonization or Contamination: 94

Duration of Antimicrobial Therapy

“Among available strategies to reduce use, reductions in length of antimicrobial regimens are the safest and are likely to be the most palatable to practicing clinicians.”

Rice LB: Clin Infect Dis 2008; 46:491
General treatment duration Issues

• Duration depends on individual patient response
  • Quicker the response $\rightarrow$ shorter the duration
• Source control extremely important
  • Drain abscesses
  • Remove lines or urinary catheters
• Empirical treatment important
  • Need to get it correct up front so knowing local susceptibility patterns vital
PNEUMONIA
Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults


1McMaster University Medical School, Hamilton, Ontario, Canada; 2Northwestern University Feinberg School of Medicine, Chicago, Illinois; 3University of Texas Health Science Center and 4South Texas Veterans Health Care System, San Antonio; and 5Michael E. DeBakey Veterans

Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society


1Department of Internal Medicine, Division of Infectious Diseases, University of Nebraska Medical Center, Omaha; 2Division of Pulmonary and Critical Care Medicine, University of Connecticut...
CAP: Length of Therapy

• Minimum of 5 days

• Before discontinuation of therapy:
  • Afebrile for 48 – 72 hrs
  • ≤ 1 CAP-associated sign of clinical instability

• Longer duration usually indicated with Legionella, Chlamydyphila, MRSA

Mandell LA et al. CID 2007;44:S27-72
CAP: Criteria for Clinical Stability

• Temperature < 37.8°C
• Heart rate < 100 beats/min
• Respiratory rate < 24 breaths/min
• Systolic blood pressure > 90 mmHg
• Arterial O₂ sat > 90% or pO₂ > 60 mmHg RA
• Ability to maintain oral intake
• Normal mental status

Mandell LA et al. CID 2007;44:S27-72
Duration for CAP Clinical Trial

• Randomized, multicenter clinical trial to confirm IDSA duration recommendations
  • Intervention group
    • 5 days minimum
    • Stopped when temperature $\leq 37.8^\circ$ for 48h, and $\leq 1$ CAP stability sign
  • Control group
    • Duration determined by physician

Uranga A et al. JAMA Int Med 2016;176(9)1257:1265
# Results

<table>
<thead>
<tr>
<th>Table 3. Clinical Success Rates at Days 10 and 30 Among Different Severity Groups Defined by PSI Classa</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PSI Class</strong></td>
</tr>
<tr>
<td>Clinical Success at Day 10</td>
</tr>
<tr>
<td>PSI classes I-III</td>
</tr>
<tr>
<td>Intent to treat</td>
</tr>
<tr>
<td>Per protocol</td>
</tr>
<tr>
<td>PSI classes IV-V</td>
</tr>
<tr>
<td>Intent to treat</td>
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<tr>
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</tr>
<tr>
<td>Intent to treat</td>
</tr>
<tr>
<td>Per protocol</td>
</tr>
</tbody>
</table>
HAP/VAP guidelines

- 7 day course of antibiotics
  - Depending upon response of the patient
8 vs. 15d for VAP

- Randomized, double blind trial for VAP
- 51 ICUs
  - VAP confirmed by quantitative, BAL culture
- Randomized to either 8 days vs. 15 days of antibiotics
- Primary outcomes (at day 28 post BAL)
  - Death (any cause)
  - Microbiological reoccurrence

Chastre et al. JAMA 2003;290(19):2588-2598
Probability of survival

![Graph showing the probability of survival over days after bronchoscopy for two antibiotic regimens: 8-Day and 15-Day. The Log-Rank test shows a non-significant difference (P = .65). The table below lists the number of patients at risk at different time points for each regimen.](image)

<table>
<thead>
<tr>
<th>Antibiotic Regimen</th>
<th>No. at Risk</th>
<th>0</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>50</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>8-Day Antibiotic Regimen</td>
<td>197</td>
<td>187</td>
<td>172</td>
<td>158</td>
<td>151</td>
<td>148</td>
<td>147</td>
<td></td>
</tr>
<tr>
<td>15-Day Antibiotic Regimen</td>
<td>204</td>
<td>194</td>
<td>179</td>
<td>167</td>
<td>157</td>
<td>151</td>
<td>147</td>
<td></td>
</tr>
</tbody>
</table>

Chastre et al. JAMA 2003;290(19):2588-2598
## Results

<table>
<thead>
<tr>
<th></th>
<th>8 days (n=197)</th>
<th>15 days (n=204)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>18.8%</td>
<td>17.2%</td>
</tr>
<tr>
<td>Recurrent infection</td>
<td>28.9%</td>
<td>26.0%</td>
</tr>
<tr>
<td>Antibiotic free days</td>
<td>13.1 days</td>
<td>8.7 days</td>
</tr>
<tr>
<td>Antimicrobial resistance</td>
<td>42.1%</td>
<td>62.0%</td>
</tr>
<tr>
<td>Recurrence rate: Non-fermenting GNB</td>
<td>40.6%</td>
<td>25.4%</td>
</tr>
</tbody>
</table>

- No difference in outcomes with short course (8-day) treatment

Chastre et al. JAMA 2003;290(19):2588-2598
Aspiration Pneumonia

- Aspiration syndrome vs. chemical pneumonitis
  - Defined for patients intubated for > 48h
    - Temperature ≥ 38.5°C or ≤ 35.5°C
    - WBC ≥ 10,000/mm or ≤ 4,000/mm
    - New infiltrate
    - Purulent aspirate

- Randomized, prospective observational
- No differences in mortality, LOS or
- Empirical antibiotics – even with witnessed aspirations – not warranted unless clinical syndrome
  - Antibiotics stopped if appropriately obtained cultures negative

Lascarrour JB et al. Crit care Med 2017;45:1268-1275
Recommendations

- **CAP**
  - 5 days
  - Hospitalized patients may need to extend duration until \( \leq 1 \) CAP clinical stability marker

- **HAP/VAP**
  - Short course (7 days) appropriate for most
  - May need longer duration for non-fermenting gram negatives

- **Aspiration pneumonia**
  - Unless clinical signs/symptoms antibiotics not warranted
  - Antibiotics discontinued if cultures negative
INTRA-ABDOMINAL INFECTIONS
Uncomplicated Intra-abdominal

- Generally involve transmural inflammation of a portion of the GI tract or its appendages
  - No extension of the infection beyond the hollow viscus
  - Microorganisms cannot be cultured from peritoneal or other surrounding fluid
- If untreated, there is a substantial probability of these infections progressing to a complicated intra-abdominal infection

Complicated Intra-abdominal

- Growth of pathogenic microorganisms in a normally sterile region of the abdominal cavity
- Usually refers to secondary or tertiary peritonitis or an intra-abdominal abscess arising from a perforated viscus:
  - Appendix
  - Colon or small bowel
  - Stomach or duodenum
  - Gallbladder
  - Postoperative

Diagnosis and Management of Complicated Intra-abdominal Infection in Adults and Children: Guidelines by the Surgical Infection Society and the Infectious Diseases Society of America


Clinical Infectious Diseases 2010; 50:133–64

DOI 10.1186/s13017-017-0132-7

Management of intra-abdominal infections: recommendations by the WSES 2016 consensus conference

Massimo Sartelli, Fausto Catena, Fikri M. Abu-Zidan, Luca Ansaloni, Walter L. Biffl, Marja A. Boermeester
Guideline recommendations

• Uncomplicated intra-abdominal infections
  • Surgical interventions and antibiotics ≤ 24 h

• Complicated Intra-abdominal infection
  • 4 to 7 days UNLESS UNABLE to achieve adequate source control

• Bowel injuries due to penetrating, blunt or iatrogenic trauma
  • ≤ 24 hours if repaired within 12h

• Acute appendicitis without evidence of perforation, abscess or local peritonitis
  • ≤ 24 hours

Why Source Control?

• Risk factors for mortality in 108 bacteremic patients with intra-abdominal infections.
• Overall mortality was 27.8%
• Source control ≤ 24h: 74/101 patients (73.3%)
  • Mortality 9.5% adequate source control
  • Mortality 33.3% inadequate source control
• In the multivariate logistic regression analysis, inadequate source control was highly associated with mortality (P = 0.011)

Duration of Antimicrobial Therapy

• Prospective trial of 3 vs. > 5 days of antimicrobial therapy in 90 patients with low severity intra-abdominal infections
  • 50% with perforated appendicitis
SIS STOP-IT trial

• Randomized, open-label trial
  • Control: antibiotics until 2d post SIRS resolution (max 10d)
  • Experimental: antibiotics for 4 days
• Primary outcome: composite endpoint
  • Surgical site infection
  • Recurrent intra-abdominal infection
  • Death

Results

- 260 patients control vs. 257 experimental
- Similar baseline characteristics
  - Similar surgical interventions/source control
  - APACHE II score = 10

<table>
<thead>
<tr>
<th></th>
<th>Standard (N=260)</th>
<th>4 day (N=257)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical site infection; n(%)</td>
<td>23 (8.8)</td>
<td>17 (6.6)</td>
<td>0.43</td>
</tr>
<tr>
<td>Recurrent intra-abd infection; n(%)</td>
<td>36 (13.8)</td>
<td>40 (15.6)</td>
<td>0.67</td>
</tr>
<tr>
<td>Death; n(%)</td>
<td>2 (0.8)</td>
<td>3 (1.2)</td>
<td>0.99</td>
</tr>
<tr>
<td>Composite ; n(%)</td>
<td>58 (22.3)</td>
<td>56 (21.8)</td>
<td>0.92</td>
</tr>
</tbody>
</table>

Time to Primary Outcome

P = 0.96 by log-rank test

Recommendations

• Studies support guideline recommendations of shorter durations
  • Certain patients as few as 3 days
  • Most patients between 4 to 7 days

• Source control is still integral to the treatment of most patients with intra-abdominal infections
  • Duration of treatment without adequate source control not well defined
PYELONEPHRITIS
International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women: A 2010 Update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases

Kalpana Gupta, Thomas M. Hooton, Kurt G. Naber, Björn Wullt, Richard Colgan, Loren G. Miller, Gregory J. Moran, Lindsay E. Nicolle, Raul Raz, Anthony J. Schaeffer, and David E. Soper

1Department of Medicine, Veterans Affairs Boston Health Care System and Boston University School of Medicine, Boston, Massachusetts; 2Department of Medicine, University of Miami Miller School of Medicine, University of Miami, Miami Florida; 3Department of Family and Community Medicine, University
Guideline recommendations

• Pyelonephritis
  • 7 days with fluoroquinolone
    • Only if resistance rates < 10%
  • 14 days with TMP/SMX
  • 10-14 days with B-lactam

Guidelines published in 2011 – anything new?

Gupta K et al. Clinical Infectious Diseases 2011;52(5):e103-120

UMCSN outpatient resistance > 25%
Ciprofloxacin 7 vs. 14 days

- Randomized, prospective non-inferiority

<table>
<thead>
<tr>
<th></th>
<th>Ciprofloxacin for 7 days</th>
<th>Ciprofloxacin for 14 days</th>
<th>Difference (90% CI)</th>
<th>Non-inferiority test p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short-term efficacy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cure</td>
<td>73</td>
<td>83</td>
<td>-0.9% (-6.5 to 4.8)</td>
<td>0.004</td>
</tr>
<tr>
<td>Clinical failure or recurrent</td>
<td>2 (3%)</td>
<td>3 (4%)</td>
<td>..</td>
<td></td>
</tr>
<tr>
<td>symptomatic urinary tract</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>infections</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cumulative efficacy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cure</td>
<td>68 (93%)</td>
<td>78 (93%)</td>
<td>-0.3% (-7.4 to 7.2)</td>
<td>0.015</td>
</tr>
<tr>
<td>Clinical failure or recurrent</td>
<td>5 (7%)</td>
<td>6 (7%)</td>
<td>..</td>
<td></td>
</tr>
<tr>
<td>symptomatic urinary tract</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>infections</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Data are number (%), unless otherwise indicated.

Duration Re-evaluation

- Meta-analysis of RCT comparing ≤ 7 days to longer therapy
  - Not specific for which antibiotics included
- Primary outcome
  - Clinical failure at EOT longer treatment arm
- Secondary outcomes
  - Clinical failure at end of follow-up
  - Microbiological failure
  - All cause mortality
  - Resistance development

End of therapy

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Short</th>
<th>Total</th>
<th>Long</th>
<th>Total</th>
<th>Weight</th>
<th>RR M-H, Random, 95% CI</th>
<th>RR M-H, Random, 95% CI</th>
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</thead>
<tbody>
<tr>
<td>Peterson 2008</td>
<td>23</td>
<td>265</td>
<td>31</td>
<td>241</td>
<td>38.9%</td>
<td>0.67 [0.41–1.12]</td>
<td></td>
</tr>
<tr>
<td>Sandberg 2012</td>
<td>2</td>
<td>73</td>
<td>3</td>
<td>83</td>
<td>10.3%</td>
<td>0.76 [0.13–4.41]</td>
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</tr>
<tr>
<td>Talan 2000</td>
<td>4</td>
<td>113</td>
<td>19</td>
<td>111</td>
<td>21.5%</td>
<td>0.21 [0.07–0.59]</td>
<td></td>
</tr>
<tr>
<td>de Gier 1995</td>
<td>7</td>
<td>18</td>
<td>5</td>
<td>16</td>
<td>24.5%</td>
<td>1.24 [0.49–3.15]</td>
<td></td>
</tr>
<tr>
<td>Klausner 2007</td>
<td>1</td>
<td>80</td>
<td>5</td>
<td>76</td>
<td>4.8%</td>
<td>0.95 [0.06–14.92]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>549</strong></td>
<td><strong>527</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>59</strong></td>
<td><strong>63 [0.33–1.18]</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>37</td>
<td>59</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: (\chi^2=6.83, \text{df}=4 (P=0.15); I^2=41%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Test for overall effect: (Z=1.45 (P=0.15))</td>
<td></td>
<td></td>
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<td></td>
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</table>

End of Follow-up

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Short</th>
<th>Total</th>
<th>Long</th>
<th>Total</th>
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<td>Peterson 2008</td>
<td>23</td>
<td>265</td>
<td>21</td>
<td>241</td>
<td>32.8%</td>
<td>1.00 [0.57–1.75]</td>
<td></td>
</tr>
<tr>
<td>Sandberg 2012</td>
<td>5</td>
<td>73</td>
<td>6</td>
<td>84</td>
<td>8.3%</td>
<td>0.96 [0.31–3.01]</td>
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<tr>
<td>Talan 2000</td>
<td>10</td>
<td>106</td>
<td>24</td>
<td>106</td>
<td>35.8%</td>
<td>0.42 [0.21–0.83]</td>
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<tr>
<td>Jernelius 1988</td>
<td>3</td>
<td>32</td>
<td>1</td>
<td>29</td>
<td>1.6%</td>
<td>2.72 [0.30–24.70]</td>
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<tr>
<td>Klausner 2007</td>
<td>1</td>
<td>94</td>
<td>1</td>
<td>98</td>
<td>1.5%</td>
<td>1.04 [0.07–16.43]</td>
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</tr>
<tr>
<td>Mensa 1999</td>
<td>12</td>
<td>123</td>
<td>11</td>
<td>113</td>
<td>17.1%</td>
<td>1.00 [0.46–2.18]</td>
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<tr>
<td>Ode 1980</td>
<td>0</td>
<td>13</td>
<td>2</td>
<td>21</td>
<td>2.9%</td>
<td>0.31 [0.02–6.07]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>706</strong></td>
<td><strong>692</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>66</strong></td>
<td><strong>0.79 [0.56–1.12]</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>54</td>
<td>66</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: (\chi^2=6.06, \text{df}=6 (P=0.42); I^2=1%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: (Z=1.32 (P=0.19))</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Summary

• No differences in any outcomes
  • Clinical failure at EOT or EOF
  • Microbiological
  • Adverse events

Conclusion

• Shorter courses for the treatment of acute pyelonephritis appropriate
• If patient has urogenital abnormalities, longer durations may be warranted
B-lactams for pyelonephritis

- Retrospective, non-inferiority, multi-center cohort for cefazolin vs. ceftriaxone
  - Included for clinical signs/symptoms of pyelonephritis
  - Microbiological susceptibilities not required
- Primary outcome
  - If cefazolin non-inferior to ceftriaxone

### Time to Defervescence among Subjects Febrile at Baseline

![Graph showing the proportion of subjects still febrile over time with lines representing Ceftriaxone and Cefazolin.]

No different between groups.

### Antibiotic Use

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Cefazolin (N=92)</th>
<th>Ceftriaxone (N=92)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-Lactam</td>
<td>60 (65.2)</td>
<td>50 (54.3)</td>
<td>0.13</td>
</tr>
<tr>
<td>Fluoroquinolone</td>
<td>16 (17.4)</td>
<td>31 (33.7)</td>
<td>0.01</td>
</tr>
<tr>
<td>Sulfamethoxazole/trimethoprim</td>
<td>12 (13.0)</td>
<td>2 (2.2)</td>
<td>0.01</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>2 (2.2)</td>
<td>2 (2.2)</td>
<td>1</td>
</tr>
<tr>
<td>No antibiotics</td>
<td>2 (2.2)</td>
<td>7 (7.6)</td>
<td>0.12</td>
</tr>
<tr>
<td><strong>Duration of therapy (days), mean (SD)</strong></td>
<td><strong>8.4 (4.2)</strong></td>
<td><strong>7.2 (3.3)</strong></td>
<td><strong>0.02</strong></td>
</tr>
</tbody>
</table>

Summary

• Retrospective study
• No differences clinical response
  • 87.0% cefazolin vs. 85.9% ceftriaxone
• Cefazolin was non-inferior to ceftriaxone

Demonstrates

• Shorter courses even for B-lactam antibiotics may be appropriate
• Treatment outcomes were independent of susceptibilities

Recommendations

• Guidelines suggest 10-14 days
• Newer studies show shorter duration appropriate
  • ≤ 7 days
  • Does not appear to matter which antimicrobial
• Important to know local susceptibilities to ensure appropriate empirical therapy
  • Duration may have to be extended due to non-response if initial therapy not susceptible

Overall Summary

• Studies supporting shorter courses regardless of diagnosis

<table>
<thead>
<tr>
<th>Disease</th>
<th>Treatment days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Short</td>
</tr>
<tr>
<td>Community acquired pneumonia</td>
<td>3 – 5</td>
</tr>
<tr>
<td>VAP/HAP pneumonia</td>
<td>≤ 8</td>
</tr>
<tr>
<td>Aspiration pneumonia</td>
<td>3 – 7</td>
</tr>
<tr>
<td>Intra-abdominal infection</td>
<td>4</td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>5 – 7</td>
</tr>
</tbody>
</table>

• Duration should be individualized to patient response

Spellberg, B. JAMA Int Med 2016;176(9)1254:1255
Questions?

SUPPORT BACTERIA!
it’s the only culture some people have