BUGS, DRUGS, AND SHRUGS

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ROOM WITH A VIEW
DOWN THE ROAD A SPELL
“There hath, by God's visitation, reigned a wonderful plague, the utter destruction, devastation, and depopulation of that whole territory, so as there is not left ... any that do claim or challenge any kind of interest therein. We, in our judgment, are persuaded and satisfied, that the appointed time is come in which Almighty God, in his great goodness and bounty towards us, and our people, hath thought fit and determined, that those large and goodly territories, deserted as it were by their natural inhabitants, should be possessed and enjoyed by such of our subjects.” – King James I
WHAT'S BUGGING US?

Tremendous Prevention of Morbidity and Mortality Vs. Unintended consequences and Diminishing Efficacy
WE’VE GOT ISSUES

1. Antibiotics have become overused
2. They are less effective than they have been
3. We’re having a hard time with alternatives
HOW'D WE GET HERE AND WHERE ARE WE GOING?

Look at prescription habits
Why we do what we do
How we can do it better
What the future holds
So Sayeth the CDC

In 2014, **266.1 million** courses of antibiotics were dispensed to outpatients in U.S. community pharmacies.

This equates to more than 5 prescriptions written each year for every 6 people in the United States.

At least 30% of antibiotics prescribed in the outpatient setting are unnecessary.

Total inappropriate antibiotic use approaches 50% of all outpatient antibiotic use.
HOW INAPPROPRIATE!

- Unnecessary use
- Selection
- Dosing
- Duration
DON’T KNOW MUCH GEOGRAPHY
LEAKY PENS

Dentists prescribed 24.5 million antibiotics, or about 10% of national total.

For perspective, about 25% of what PCPs and Pediatrics combined prescribed.

<table>
<thead>
<tr>
<th>Antibiotic Category</th>
<th>Number in Millions</th>
<th>Percentage</th>
<th>Per 1,000 People</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillins</td>
<td>17.07</td>
<td>69.6</td>
<td>53.9</td>
</tr>
<tr>
<td>Lincosamides</td>
<td>3.57</td>
<td>14.6</td>
<td>11.3</td>
</tr>
<tr>
<td>Macrolides</td>
<td>1.33</td>
<td>5.4</td>
<td>4.2</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>1.24</td>
<td>5.1</td>
<td>3.9</td>
</tr>
<tr>
<td>β-lactams, increased activity</td>
<td>0.56</td>
<td>2.3</td>
<td>1.8</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>0.47</td>
<td>1.9</td>
<td>1.5</td>
</tr>
<tr>
<td>Quinolones</td>
<td>0.21</td>
<td>0.8</td>
<td>0.6</td>
</tr>
<tr>
<td>Sulfonamides, sulfamethoxazole</td>
<td>0.05</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Other anti-infective agents</td>
<td>0.02</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Other</td>
<td>0.00</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Total</td>
<td>24.52</td>
<td>100.0</td>
<td>77.5</td>
</tr>
</tbody>
</table>
WHY DO WE WRITE?
38% of Polish adults had used antibiotics within the 12 months preceding their participation in the study.

90% of the antibiotics were prescribed by a physician.

3% of the respondents purchased an antibiotic without a prescription.

Mazinska et al PLoS One, 2017 Feb 17;12(2)
The prevailing reasons for taking antibiotics were the common cold, sore throat, cough and flu.

Approximately 40% of the respondents expected a prescription for an antibiotic against the flu.
A total of 419 parents participated. 9.8% knew the definition of antibiotic resistance. 21.2% knew when it was appropriate to use antibiotics. Respondents with higher education, employed, with a family member working in the health care sector knew about antibiotic
One third (32.7%) self-classified them as users of self-medication with antibiotics who did not use the physician as source of information on antibiotics.

One quarter (22.7%) would be willing to take an antibiotic without a prescription of a physician.

Participants recognized antibiotics must not
Almost two thirds of the patients included in this study expected to receive antibiotics after routine tooth extraction. 70% of this group indicated that they would request them if not prescribed. More than half of them had some college or at least a college degree. The reason given most often for wanting antibiotics (82%) was to prevent a possible infection.
RESISTANCE IS FUTILE
<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Overall data</th>
<th>Studies that reported previous use of ATBs as exclusion criterion (subgroup A)</th>
<th>Studies that did not report/employ previous use of ATBs as exclusion criterion (subgroup B)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%res&lt;sup&gt;b&lt;/sup&gt;</td>
<td>CI</td>
<td>%res&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>AMC</td>
<td>3.5</td>
<td>0.8–14.2</td>
<td>21/421</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>7.7</td>
<td>3.6–15.5</td>
<td>31/388</td>
</tr>
<tr>
<td>Penicillin G</td>
<td>12.3</td>
<td>3.6–34.6</td>
<td>100/458</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>13.1</td>
<td>5.6–27.5</td>
<td>123/919</td>
</tr>
<tr>
<td>Penicillin V</td>
<td>15.5</td>
<td>10.2–22.8</td>
<td>76/528</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>17.5</td>
<td>10.5–27.9</td>
<td>112/619</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>26.0</td>
<td>16.2–38.9</td>
<td>174/681</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>40.0</td>
<td>6.2–87.0</td>
<td>120/539</td>
</tr>
</tbody>
</table>

ATB, antibiotics; CI, confidence interval; AMC, amoxicillin/clavulanic acid.

<sup>a</sup> Subgroup A [20,21]; subgroup B [12,18,19,22,23].

<sup>b</sup> %res = percentage of resistant strains (pooled values).

<sup>c</sup> nRES/n, number of resistant strains/total number of strains.
THEY’RE OUT THERE...

29 healthy People given single 2g Dose of Amoxicillin

21% of individuals, Pen VK and Amox resistant viridans streptococci were isolated before dose

Prevotella spp. before antibiotic administration

Amoxicillin resistance 59%

Pen VK resistance 62%
One and Done

Single dose increased resistance **28%** for *Prevotella*
RESISTANCE: THE GIFT THAT KEEPS ON GIVING

The review included 24 studies.

In five studies of urinary tract bacteria (14,348 participants)

The pooled odds ratio (OR) for resistance was:

2.5 within 2 months of antibiotic treatment and

1.33 within 12 months

One prospective study reported changes in resistance over a long period:

12.2 at 1 week

6.1 at 1 month

3.6 at 2 months

2.2 at 6 months
Antimicrobial resistance is associated with increased morbidity and mortality.

Carbapenem-resistant *K. pneumoniae* is associated with an increased attributable mortality compared with sensitive *Klebsiella* (OR 4.69)

Methicillin-resistant *S. aureus* bacteremia, relative to methicillin-sensitive *S. aureus* bacteremia, has a significantly greater mortality risk as well (OR 1.93)

The cost of an antimicrobial-resistant infection is $18,588 to $29,069 per patient.

Excess duration of hospital stay of 6.4 to 12.7 days.

Attributable mortality of 6.5%.
RIGHTING THE SHIP
DECISIONS, DECISIONS

1. When are antibiotics indicated?
2. What is the right medication?
3. How long should we give it?
STEWARDSHIP

THE RIGHT DECISION

THE RIGHT DRUG

THE RIGHT DURATION
Acute dento-alveolar infections

As an **adjunct** to local treatment IFF

Patient is febrile

or

Evidence of systemic spread and local lymph node involvement.
Chronic dento-alveolar infections

Rarely require antibiotics unless:

Grossly spreading, or if there is an acute flare-up of infection or

Increased temperature or malaise is present.
Facial cellulitis with or without dysphagia requires immediate antibiotic treatment to prevent the spread of infection.
IMPACT OF WRITING

Impacted third Molars
Probably Reduce [compared to placebo] to some extent
Infection
Pain
Dry Socket
But no impact on Swelling or Fever

Cochrane Database Syst Rev. 2012 Nov 14;11
The etiology of dry socket is related to systemic factors localised infection and surgical trauma. Antibiotics are only recommended in the presence of spreading infection.

Studies have proven that approximately 38 healthy people would need to be treated with prophylactic antibiotics to prevent a single case of dry socket.

Cochran Database Syst Rev 2012; 11: CD003811
### Apical Periodontitis

- **Pulp necrosis and asymptomatic periapical periodontitis**
  - **Diagnosis:** Administration of antibiotic after endodontic treatment
  - **Outcome:** Administration of penicillin did not reduce pain

- **Necrotic pulp and symptomatic periapical periodontitis, acute apical abscess, or all of these**
  - **Intervention:** Administration of antibiotic after endodontic treatment
  - **Outcome:** Endodontic treatment was effective, with no demonstrable benefit from penicillin

- **Untreated symptomatic irreversible pulpitis**
  - **Intervention:** Administration of prophylactic antibiotic before treatment
  - **Outcome:** Administration of penicillin did not reduce pain

- **Necrotic pulp with symptomatic periapical periodontitis**
  - **Intervention:** Administration of antibiotic after endodontic treatment
  - **Outcome:** Administration of penicillin did not reduce pain

- **Necrotic pulp with asymptomatic periapical periodontitis**
  - **Intervention:** Administration of prophylactic antibiotic before treatment
  - **Outcome:** Administration of amoxicillin did not influence the incidence of endodontic flare-up
SHORT AND SWEETER

The role of postoperative antibiotics in orthognathic surgery, Lefort facial fractures and zygomatic fractures in 94 patients

Randomised, double-blind, placebo-controlled pilot clinical study.

1-day versus a prolonged regimen.

No difference in 1 day and 5-day treatments
LESS IS MORE

**Single implant placement**

360 patients randomized to either

A Single 2g dose

or

2g plus two additional days

No statistically significant differences were observed between the two regimens, although adverse events were reported only in the additional 2-day postoperative group.
Comparison of Azithromycin and Amoxicillin
Before Dental Implant Placement

Prophylactic regimen prior to placement
1 dose azithromycin 500 superior to 2g Amox
and reduced proinflammatory cytokines

AHA PROPHYLAXIS

Standards have not changed materially
Doses/exposure have been cut from

a few days in the 80s
to
two doses in the 90s
to
a single dose in the highest risk patients with the highest risk procedures
LAND, HO!
Since 1998 only 10 new antibiotics have been approved. The reason is simple: drug development is risky and expensive, and drugs to treat infections are not as profitable as those that treat chronic disease.

As of March 2015 there were only 28 antibiotics in Phase II/III clinical testing, compared with 504 oncology drugs.

RIGHT ON TARGET

Using genome-specific techniques to isolate unique or targets highly specific to bacteria. However, this has been “Spectacularly Unsuccessful.” Bacterial defense mechanisms quickly overwhelm and actually...
Bacteriophages can lyse bacterial cells. Mechanism is independent of antibiotic resistance. In a very short time, these replicate and amplify.
PRE AND POST PHAGE THERAPY

Enterococcus Faecalis

Not easily eliminated from root canals

Protected by Biofilm
WHY DIDN’T SOMEONE THINK OF THAT?

They Did!

But antibiotics are:
Cheaper
Easier to manufacture
And they work(ed)
Table 1. Phage therapy trials on bacterial biofilms using different model systems

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Model system</th>
<th>Phage treatment</th>
<th>Efficacy</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>P. aeruginosa</em></td>
<td>Catheters</td>
<td>Phage cocktail</td>
<td>99.9%</td>
<td>(97)</td>
</tr>
<tr>
<td><em>P. aeruginosa</em></td>
<td>Cystic fibrosis in lung airway cells</td>
<td>Single phage</td>
<td>75%</td>
<td>(98)</td>
</tr>
<tr>
<td><em>P. aeruginosa</em></td>
<td>Mouse wound model</td>
<td>Phage cocktail</td>
<td>Significant 2 log decrease</td>
<td>(99)</td>
</tr>
<tr>
<td><em>Proteus mirabilis</em></td>
<td>Catheters</td>
<td>3-phage cocktail</td>
<td>Complete prevention of blockage</td>
<td>(100)</td>
</tr>
<tr>
<td><em>S. epidermidis</em></td>
<td>Catheters</td>
<td>Single phage</td>
<td>–</td>
<td>(101)</td>
</tr>
<tr>
<td><em>S. aureus</em></td>
<td>Rabbit ear wound model</td>
<td>Single phage combined with debridement</td>
<td>Significant improvement in wound infection</td>
<td>(102)</td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>Urothelium</td>
<td>Single phage</td>
<td>45%</td>
<td>(103)</td>
</tr>
<tr>
<td><em>P. aeruginosa</em></td>
<td>In vitro biofilm from hospital isolates</td>
<td>Single phage</td>
<td>Highly efficient in prevention and dispersion of pre-formed biofilm</td>
<td>(104)</td>
</tr>
<tr>
<td><em>S. aureus and S. epidermidis</em></td>
<td>In vitro biofilm</td>
<td>Single phages and combined mixture of two phages</td>
<td>High efficiency in disrupting mono-species as well as dual-species biofilm.</td>
<td>(95)</td>
</tr>
<tr>
<td><em>P. fluorescens</em></td>
<td>In vitro biofilm grown on glass slides</td>
<td>Single phage</td>
<td>93% cell removal at early stage of biofilm formation and prevention of biofilm formation</td>
<td>(105)</td>
</tr>
<tr>
<td>MRSA and <em>P. aeruginosa</em></td>
<td>Implant-related infection</td>
<td>Single phage combined with antibiotics</td>
<td>MRSA: biofilm absent <em>P. aeruginosa</em>: no significant difference</td>
<td>(106)</td>
</tr>
<tr>
<td><em>S. aureus</em></td>
<td>In vitro biofilm</td>
<td>Single phage with antibiotic</td>
<td>Highly efficient as combined effect</td>
<td>(107)</td>
</tr>
<tr>
<td><em>P. aeruginosa</em></td>
<td>In vitro biofilm and extracted tooth model for root canal treatment</td>
<td>Single phages and combined mixture of two phages</td>
<td>Highly effective against <em>in vitro</em> biofilm.</td>
<td>(108)</td>
</tr>
<tr>
<td><em>E. faecalis</em></td>
<td>Human dental roots</td>
<td>Single phage</td>
<td>Substantial reduction in bacterial cell viability</td>
<td>(109)</td>
</tr>
</tbody>
</table>

The phage therapy here involves either use of single phages or phage cocktails or combination treatments where phages are used along with antibiotics or previous clinical treatments.
## BRING IT HOME

<table>
<thead>
<tr>
<th>Make</th>
<th>A concerted effort to learn and use best practices</th>
</tr>
</thead>
<tbody>
<tr>
<td>Educate</td>
<td>Our physician colleagues when possible</td>
</tr>
<tr>
<td>Educate</td>
<td>Our Patients and change expectations</td>
</tr>
</tbody>
</table>
Bruegel "The Triumph of..."
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