I think I need antibiotics for my col...

IT'S A VIRUS!
Antibiotic Resistant Bacteria

AKA Multi-Drug Resistant Organisms (MDRO)
Figure 1. Antibiotic timeline. This timeline indicates the approximate dates that the major antibiotic classes or important antibiotics of each class were introduced into clinical use. The dates that resistant organisms were identified are shown in the centre of the timeline. Abbreviations: AmpC, AmpC–producing Enterobacteriaceae; ESBL, extended-spectrum β-lactamase–producing Enterobacteriaceae; KPC, Klebsiella pneumoniae carbapenemase–producing Enterobacteriaceae; MRSA, methicillin-resistant Staphylococcus aureus; NDM-1, New Delhi metallo-β-lactamase-1–producing Enterobacteriaceae; PRSA, penicillin-resistant Staphylococcus aureus; VRE, vancomycin-resistant Enterococcus; VRSA, vancomycin-resistant Staphylococcus aureus.
FURTHER OBSERVATIONS ON PENICILLIN

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The work on penicillin briefly reported by Chain and others (1940) is here presented in greater detail, and its further development to the stage of human therapy is described.
• Case 1 41y/o policeman - suppuration of face scalp and orbits due to *S. aureus* and *S. pyogenes*. Develops pneumonia, osteomyelitis and skin abscesses. Receives 4.4 grams penicillin in 5 days until supply exhausted. Much improved with tx; dies later of overwhelming infection.

• Case 2 15y/o m s/p ORIF of femur with post-op *S. pyogenes* wound infection. (+) blood cultures; cured with 3.4 grams penicillin over 4 days

• Case 3 48 y/o laborer with staphylococcal carbuncle over lt. scapula. Cured with 7 day course of penicillin at dose of 100mg. Q 3 hrs.
Factors Contributing to Emergence of Resistance

- Microbial characteristics
- Environmental and human reservoirs
- Patterns of antimicrobial usage
- Societal and technologic changes
Microbial Characteristics

- Possession of intrinsic resistance
- Easily colonize and infect
- Survival in varying environmental conditions
- Fast generation time
- Propensity to easily exchange genetic material
Development of drug resistance

When a colony of bacteria is treated with an antibiotic, most of the microbes are killed. Sometimes, however, there is a microbe with a mutation that makes it resistant to the drug. When the colony grows back, all of its members will be descended from the drug-resistant survivor.
Reservoirs

- Provide opportunity for development of resistance by exchange of genetic material or persistence of the organism and its exposure to selective pressures
- Provide opportunity for organisms to persist and be transmitted
- Higher transmission leads to greater prevalence of resistance
Antimicrobial Usage

• 50-70% of patients receive antibiotics for acute bronchitis although of no proven benefit
• 50% of patients with colds receive antibiotics
• Reasons for this overuse include patient expectations, unique efficacy in treating previously deadly illnesses, fear of missing treatable infections, pharmaceutical marketing
I NEED YOU TO TAKE THESE PILLS BECAUSE THE PHARMACEUTICAL REP IS SMOKING HOT.
“Don’t forget to take a handful of our complimentary antibiotics on your way out.”
Societal Changes

- Increasing groups at risk including the very young, the very old, and immunocompromised
- Increase in day care attendance
- Increase in crowding, homelessness, poor nutrition and inadequate medical care conducive to transmission
- Erosion of public health infrastructure
- Changes in sexual activity
Technologic Changes

• Facilitation of travel and transportation of food
• Use of antibiotics in agriculture and aquaculture
• Use of OTC antibiotics in developing countries
• New technologies providing new vehicles for spread
• Introduction of new broad spectrum antibiotics
• Use of household disinfectants?
Future Trends

• In 1980’s pharmaceutical industry slowed R&D of antibiotics and turned attention to therapy of chronic illnesses

• 2007-2008 CMS begins to deny payment for preventable hospital-acquired infections - decubitus ulcers, UTI’s, MRSA

• Increasing morbidity, mortality, rates of hospitalization, expense
Possible Solutions

• Mandatory compliance with hand hygiene
• Active surveillance cultures for MRSA, VRE, CRE
• More prudent use of antibiotics in humans and animals
• Shortening duration of therapy and limiting long-term use
• New classes of antibiotics
• Rapid testing and approval
• Development of rapid diagnostic tests
• Better surveillance
• Vaccines
We’re talking *Staphylococcus aureus*

- Coagulase positive
- Among hardiest of non-spore forming human pathogens
- Skin serves as local barrier to invasion
- If skin barrier breached then invasion, abscess formation, release of toxins and possible dissemination
Colonization and Infection

- 30% of healthy adults colonized; 10% to 20% persistently colonized
- Colonized individuals at increased risk of subsequent infection
Transmission

- Colonized persons at increased risk of infection
- Nosocomial infection acquired following exposure to hands of healthcare workers after they have been transiently colonized from their own flora or contact with infected patient
- Outbreaks may occur from exposure to single long term carrier or environmental source (less common)
MRSA vs MSSA

- MRSA contains gene *mecA*
- *mecA* encodes an altered penicillin binding protein, PBP2a
- PBP2a has reduced affinity for beta lactam antibiotics, rendering MRSA resistant to penicillins and cephalosporins
MRSA, Why Bother?

- Patient outcome is worse in infection with MRSA compared to MSSA
- Infection with MRSA is more expensive to manage than MSSA
- Increases use of vancomycin, promoting spread of VRE
- Vancomycin resistance emerging in MRSA
Is MRSA Any Worse Than MSSA?

- Cosgrove et. al. compared mortality of MRSA vs. MSSA bacteremia
- Meta-analysis of 31 studies published studies from 1980-2000
- Significant increase in mortality with MRSA (pooled O.R. 1.93)
- Association persists when adjusted for comorbidities or severity of illness
Presence of MRSA Increases Costs in Surgical Site Infections

- Engemann et. al. compared uninfected controls to patients with SSI’s at Duke University between 1994 - 2000
- Presence of MRSA increased cost of hospitalization median of $40,000 compared to MSSA
- Also increased 90 day mortality, duration of hospital and ICU stay
Risk of Infection after Previous Infection or Colonization

- 209 patients at Brigham and Women’s hospital identified - newly placed in Contact Precautions for MRSA during 2 three month time periods
- Followed prospectively for 18 months
- 97(46%) considered colonized
- 112(54%) considered infected

Huang S, Platt R. CID 2003;36:281-285
Risk of Infection after Previous Infection or Colonization

- 60(29%) developed 90 subsequent infections during 18 months follow-up
- 19(9%) experienced >1 episode of subsequent infection
- 48(80%) of 60 had 67 infections at site different from initial site of isolation
- Bacteremia accounted for 22(33%) of the 67 infections
- 31(52%) of the infections manifested post-discharge

Huang S, Platt R. CID 2003;36:281-285
Control of HA-MRSA

- Contact precautions
- Decontamination of hands after gloves are removed
- Alcohol based hand rubs
- Masks for aerosol generating procedures
- HCW’s epidemiologically linked to transmission should receive decolonization therapy with intranasal mupirocin
Control of HA-MRSA

- Culturing of patients at high risk for MRSA shows patients often colonized in anterior nares, intact or broken skin, or GI tract before organism cultured for clinical purposes.

- Transmission from such patients not known to be colonized (and therefore not in isolation) 15X greater than those in isolation.
Control of HA-MRSA

- Surveillance cultures of high risk patients at time of admission and weekly during prolonged hospitalizations advocated in May 2003 SHEA guidelines (ICHE.24.May,2003.pp362-386)
Clostridium difficile Associated Diarrhea
Reservoirs

- Majority of disease causing organisms exogenously acquired
- During outbreaks, isolated from multiple inanimate sources and hands of HCW’s
- Outside hospital - soil, swimming pools, beaches, sea, river and tap water, animals, household pets etc.
Pathogenesis

• $10^{11}$ to $10^{12}$ bacteria per gram of feces
• Hundreds of distinct microorganisms
• Disruption prerequisite for \textit{C. difficle} disease
• Normal flora deplete carbon sources required for growth - especially monosaccharide component of mucin
Risk Factors

• Advanced age - Those >60 years old 20-100 X’s more likely to test positive for toxin than those aged 10-20 years

• Antibiotic administration, especially clindamycin, extended spectrum penicillins and cephalosporins, fluroquinolones

• Any antibiotic may be implicated

• Occasionally following methotrexate or paclitaxel
Trends Since 2000

• Increasing incidence
• Increasing virulence
• More community-acquired disease
• Increasing numbers of treatment failures
Fig. 1: Annual incidence (per 100 000 population) of Clostridium difficile-associated diarrhea (CDAD) in Sherbrooke, Que., 1991-2003

Pepin, J. et al. CMAJ 2004;171:466-472
**Table 3. Guidelines for Controlling *Clostridium difficile* Infection in Hospitals and Long-Term Care Facilities.***

Personnel should wash their hands frequently with soap.  
Clinicians should use vinyl gloves when they are caring for patients.  
Environmental surfaces should be cleaned with sporicidal agents.  
Symptomatic patients should be placed in private rooms, especially if they are incontinent of stool.  
The use of rectal thermometers should be avoided.  
Outbreaks may require restriction of the use of antibiotics.

*Data are from the Society for Hospital Epidemiology of America.⁴⁰*
Enhanced Infection Control Measures

- Require handwashing with soap and water (not alcohol based sanitizers)
- Use bleach (1:10 dilution) for cleaning rooms
- Routinely monitor for isolation compliance
- Contact isolation for entire LOS
- Consider targeted antibiotic restrictions
Carbapenem-resistant

*Enterobacteriaceae*
Klebsiella pneumoniae Carbapenemases (KPC)

- First identified in North Carolina in 1996
- Enzyme inactivates all β-lactams
- Plasmid encoded
- Spread predominately by clonal dissemination (ST 258)
- Most common CRE in United States
New Delhi Metallo-β-Lactamase (NDM-1)

- First identified from Indian patient managed in Sweden following transfer from New Delhi hospital 2008
- Following year identified in 29 patients in the UK and 143 from India
- Plasmid mediated - spread to multiple Enterobactericeae
- Identified in sewage and tap water in India and Vietnam
- Possess other resistance mechanisms rendering them resistant to all antibiotics except colisitin and sometimes tigecycline
- Rare in United States - most tracked back to India
NDM-1 Global Health Concerns

• Occurrence of gene in many unrelated species and presence in the environment (in India)
• Occurs in not only *Klebsiella*, but *E. coli*
• Huge reservoir - widespread in India
• Identified in *E. coli* ST 131 - responsible for dissemination of ESBL CTX-M-15 worldwide
• Identified in tap water and environmental sources from many unrelated bacteria in India
Figure 4. Global dissemination of *Klebsiella pneumoniae* carbapenemase–producing *K. pneumoniae* and New Delhi metallo-β-lactamase–1–producing Enterobacteriaceae. The earliest reported cases in each continent are shown. Arrows indicate the significant international movements of these organisms. Abbreviations: KPC, *Klebsiella pneumoniae* carbapenemase; NDM-1, New Delhi metallo-β-lactamase–1; UK, United Kingdom.
ORIGINAL ARTICLE

Attributable Mortality Rate for Carbapenem-Resistant
*Klebsiella pneumoniae* Bacteremia

Abraham Borer, MD; Lisa Saidel-Odes, MD; Klaris Riesenber, MD; Seada Eskira, RN, MPH; Nejama Peled, MSc; Ronit Nativ, RN, MPH; Francisc Schlaeffer, MD; Michael Sherf, MD
Methods

- 1000 bed tertiary referral hospital in Israel
- Matched retrospective historical cohort study
- Controls “very similar” to cases but no KPC bacteremia
  - 1:1 matching
<table>
<thead>
<tr>
<th>Variable</th>
<th>No. (%) of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case subjects ($n = 32$)</td>
<td></td>
</tr>
<tr>
<td>Crude mortality rate</td>
<td>23 (71.9)</td>
</tr>
<tr>
<td>Attributable mortality rate$^a$</td>
<td>16 (50)</td>
</tr>
<tr>
<td>Control subjects ($n = 32$)</td>
<td></td>
</tr>
<tr>
<td>Crude mortality rate</td>
<td>7 (21.9)</td>
</tr>
</tbody>
</table>

$^a$ 95% confidence interval, 15.3%–98.6%; the risk ratio was 3.3 (95% confidence interval, 2.9–28.5).
Results

- Highest ever reported mortality for bacteremia
- Largely elderly and very ill population
- No case patient received appropriate empiric antibiotic therapy
- KPC resistant to all tested antibiotics
  - Tigecycline not tested
  - 60% susceptible to gentamicin
  - 80% susceptible to colistin
Figure 4. Exposure network graph demonstrating the relationships of cases to long-term acute care hospitals (LTACHs), acute care hospitals, and nursing homes during the entire 12-month study period. Case patients and facilities to which case patients were linked are connected by arrows or by nondirectional lines. An arrow from a facility to a case patient indicates that the patient acquired *Klebsiella pneumoniae* carbapenemase (KPC)-producing *Enterobacteriaceae* at the facility. An arrow from a case patient to a facility indicates that the patient arrived at the facility already colonized or infected with KPC-producing *Enterobacteriaceae* (i.e., the patient brought KPC-producing *Enterobacteriaceae* to the facility and may have acted as a vector of transmission there). Nondirectional lines link cases and facilities if the facility where a case patient acquired KPC-producing *Enterobacteriaceae* could not be determined. Black arrows or lines link case patients and facilities when a patient had a KPC-producing bacterial isolate identified in a clinical culture. Red arrows or lines link case patients and facilities when a patient had a KPC-producing bacterial isolate identified only in a routine admission surveillance culture, not in a clinical culture; specimens for routine admission surveillance cultures were collected only at LTACHs.
Infection Prevention

- Hand Hygiene
- Contact Precautions
- Education
- Limit use of invasive devices
- Patient and staff cohorting
- Lab protocols for rapid notification
- Antibiotic stewardship
- Chlorhexadine bathing
- CRE Screening
  - Point prevalence
  - Screen epidemiologically linked patients
  - Active surveillance
What Can Be Done?

- Hand Hygiene (Standard Precautions)
- Environmental Disinfection
- Surveillance for infections
  - Data collected consistently and honestly
  - Data is actionable
- Prudent use of antibiotics (antibiotic stewardship)
  - At minimum order contains diagnosis, drug, duration, route
- Stringently follow best practices for central line insertion and maintenance
I TOLD YOU I WAS SICK,

B. P. ROBERTS

MAY 17, 1929

JUNE 18, 1979