ANTIMICROBIAL STEWARDSHIP: COMBATTING RESISTANCE AND UNTREATABLE BUGS

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Objectives

- Describe historical background of antibiotics
- Review usage patterns of antibiotics
- Explain mechanisms of antibiotic resistance
- Outline unwanted consequences of antibiotic use
- Present consequences of antibiotic resistance
- Describe basic components of an antimicrobial stewardship program
- Discuss challenges to developing stewardship programs
- Introduce research in field of antibiotic development
Tuba City, Arizona

- 8,600 people (2010 census)
- Northern Arizona
- Hospital serves 6000 square miles
- 73 bed hospital – corporation (Tribal run/638)

Definitions

- Antibiotic = Antimicrobial
- ASP = Antimicrobial Stewardship Program
- EMR = Electronic Medical Record
- IDSA = Infectious Diseases Society of America
History of Antibiotics

Sir Alexander Fleming

“Wonder Drug”
Penicillin

- Discovered by Sir Alexander Fleming in 1928
- Introduced into clinical medicine by Sir Howard Florey, with assistance of Dr. Chain in 1941
- Earned the Nobel Prize for Medicine/Physiology in 1945
- World War II accelerated efforts to mass produce the antibiotic

Penicillin - World War II

- 1,633 billion units produced in 1944
- 7,952 billion units produced in 1945
- 85% of nation’s production went to armed forces
- Hundreds of thousands of war victims saved
Early Warnings of Resistance

- “There may be a danger, though, in under-dosage. It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them, and the same thing has occasionally happened in the body.”
  - Alexander Fleming, Nobel Lecture, December 11, 1945

Antibiotic Resistance

It was on a short-cut through the hospital kitchens that Albert was first approached by a member of the Antibiotic Resistance.
Was Fleming Correct?

- 3 years after Fleming’s warning, 38% of *S. aureus* in one London hospital were resistant to penicillin
- Now, about 90% of UK strains and nearly 100% of US strains are penicillin resistant
- In some communities, greater than 50% of strains are resistant to methicillin (i.e. MRSA)

What Is the Problem?

- Each year, at least 2 million people are infected with resistant bacteria
- At least 23,000 people die each year as a result
- Up to 50% of antibiotics are not prescribed appropriately
  - Appropriate medication, dose, duration
- 250,000 illnesses due to *C. diff* annually and 14,000 deaths

(Centers for Disease Control and Prevention – cdc.gov)
Resistant bacteria (i.e. staphylococci, enterococci, Klebsiella pneumoniae, and Pseudomonas) becoming common in healthcare institutions \( \rightarrow \) poor medical outcomes

**Spreading to communities**
- Long-term care facilities
- Sports teams
- Military recruits
- Day care centers

*(Huttner 2013)*

**Economic burden**
- Indirect costs
  - Prolonged morbidity
  - Reduced productivity
  - Social effects
Urgent Threats (CDC)

CLOSTRIDIUM DIFFICILE

- 250,000 infections per year
- 14,000 deaths
- $1,800,000,000 in excess medical costs per year

Urgent Threats (CDC)

CARBAPENEM-RESISTANT ENTEROBACTERIACEAE

- 9,000 drug-resistant infections per year
- 600 deaths
- 7,900 CRE cases
- 1,400 related deaths
- CRE have become resistant to all or nearly all available antibiotics

These images illustrate the significant public health threats posed by these microorganisms, highlighting the urgent need for action and intervention.
Urgent Threats (CDC)

- Multidrug-Resistant Acinetobacter
- Drug-Resistant Campylobacter
- Fluconazole-Resistant Candida
- Extended Spectrum Enterobacteriaceae (ESBL)
- Vancomycin-Resistant Enterococcus (VRE)
- Multidrug-Resistant Pseudomonas Aeruginosa
- Drug-Resistant Non-Typhoidal Salmonella
- Drug-Resistant Salmonella Serotype Typhi
- Drug-Resistant Shigella
- Methicillin-Resistant Staphylococcus Aureus (MRSA)
- Drug-Resistant Streptococcus Pneumoniae
- Drug-Resistant Tuberculosis

Serious Threats (CDC)
Rise of Superbugs

The Economist. March 31, 2011.

Superbugs

Nevada woman dies of superbug resistant to all available US antibiotics

www.statnews.com

The 70-year-old woman had broken her leg while traveling in India. The bacteria in her system was resistant to 26 different antibiotics.
Neisseria Gonorrhea
- Community acquired
- Penicillin
- Tetracycline
- Fluoroquinolones
- **Ceftriaxone**
  - Growing rates of resistance reported
  - British study – biggest predictor of resistant gonorrhea is exposure to antibiotics, not number of sexual partners (Fingerhuth, 2016)

What Causes Resistance?
- Selection pressure caused by antimicrobials
- Inappropriate prescription
- Poor hand hygiene
- Medical tourism
- Consumption of antimicrobials by food-producing animals worldwide
  - 80% of all antimicrobials are destined for animals (not humans)
Herman A. Most course of antibiotics for sinusitis are too long. NEJM. Physicians First Watch. March 27, 2018.

- IDSA recommends 5-7 day course (when indicated!)
- 70% of prescriptions were for 10+ days
- 20% of prescriptions were for Azithromycin
Overuse of Antibiotics


- **Most common dx:** acute respiratory tract infection (ARTI), bronchitis, otitis media, pharyngitis, tonsillitis, common cold, pneumonia
- **Suggested other potential harms:** asthma, obesity, immune system (HIV), mental health effects

Mechanisms of Resistance

- Intrinsic resistance
- Acquisition through de novo mutation
- Acquisition of resistance genes from other organisms
  - Conjugation
  - Transformation
  - Transduction
  - Transposons
4 Core Actions to Fight Infections (CDC)

1 - Preventing Infections, Preventing the Spread of Resistance
- Immunization
- Safe food preparation
- Hand washing
- Appropriate antibiotic usage

2 - Tracking
- Gather data on resistant infections, causes, and risk factors
- Develop strategies to prevent infections/resistance
3 – Improving Antibiotic Prescribing/Stewardship
- Commitment to use antibiotics appropriately and safely is known as antibiotic stewardship

4 – Developing New Drugs and Diagnostic Tests
- Resistance cannot be stopped, only slowed
- Needs new drugs and testing to keep up with this natural process
Barriers to Appropriate Antimicrobial Usage

- Healthcare worker assumption that patients expect antimicrobials
- Inappropriate duration of antimicrobial prescription
- Lack of research on appropriate duration of antimicrobials
- Lack of education
- Busy ER/clinics
- Laziness/Habit

Patient Satisfaction

- 2 studies in early 2000s found that patients/parents were more satisfied with physicians who explained why antibiotics were not indicated (Fiore D, Dec 2017)
- Recent British study showed higher patient satisfaction ratings with higher prescribing practices (Aswwhworth M, 2016)
Antimicrobial Stewardship Program (ASP) – Essential Participants

- Infectious Diseases (ID) Physician
- Clinical Pharmacist – ID trained
- Microbiology Laboratory
- Information Technology (IT)
- Hospital Administration
- Pharmacy and Therapeutics (P & T) Committee
- Infection Control and Hospital Epidemiology Staff

ASP Core Elements (CDC)

- Leadership Commitment
- Accountability
- Drug Expertise
- Action
- Tracking
- Reporting
- Education
Antimicrobial Stewardship Works

- “Effect of antibiotic stewardship on the incidence of infection and colonisation with antibiotic-resistant bacteria and Clostridium difficile infection: a systematic review and meta-analysis.”
  - Lancet Infectious Disease.
  - Bauer et al.

Antimicrobial Stewardship Works

- Meta-analysis 1960 to 2016
- 32 studies
- Looked at infection rates of drug resistant bacteria and C. diff. infections
- 51% reduction in drug resistant infections
- 32% reduction in C. diff. infections
  (Bauer et al)
Antimicrobial Stewardship Works

  - 100 bed community hospital
  - Post-prescriptive antimicrobial stewardship
  - Non-binding written recommendations made to prescribing physicians
  - 32% reduction in antimicrobial acquisition cost per admission

Methods – Broad (CDC)

- Antibiotic “time outs”
  - Should be 48 hours after antibiotics are started
  - Is there an infection?
  - Correct antibiotic, including dosage, route?
  - De-escalation?
  - Duration?
Methods – Broad (CDC)

- **Prior authorization**
  - Certain antibiotics restricted due to spectrum, activity, toxicities
  - Use is reviewed before antibiotic is implemented

Methods – Broad (CDC)

- **Prospective audit and feedback**
  - Conducted by staff other than the treating team
  - Need availability of expertise
Prospective Audit and Feedback

  - ID physician and ID-trained pharmacists not available
  - Multidisciplinary team targeting 6 antimicrobials with potential for misuse
  - Pharmacy-led interventions and antibiotic streamlining increased
  - Decreased antibiotic spending and C. diff infections

Pharmacy-Driven Methods

- Automatic changes from IV to oral antibiotic
- Dose adjustments (i.e. renal adjustment)
- Dose optimization (i.e. extended infusions of beta-lactams)
- Automatic alerts for multiple agents
- Automatic stop orders
- Drug interactions
- Antibiotic cycling – not recommended
IDSA Recommendations

- **Strong Recommendation, moderate quality evidence:**
  - Preauthorization and or Prospective Audit
  - ASPs should implement interventions designed to reduce use of antibiotics associated with *C. diff.* infection (CDI)
  - Reduce antibiotic therapy to shortest effective duration

- **Weak recommendation, low-quality evidence**
  - Didactic education useful
  - Use of Rapid Viral Testing for respiratory pathogens to reduce of inappropriate antibiotics
  - Antibiotic cycling
Other recommendations of interest:
- Rapid Diagnostic Testing – weak recommendation, moderate quality evidence
- Procalcitonin use – weak recommendation, moderate quality evidence

Biomarker widely used as a marker of sepsis

Study looked at use of procalcitonin algorithm to reduce antibiotic exposure in critically ill ICU patients
- No reduction in antibiotic exposure
- Possibly a different algorithm could produce different results
Other studies have supported use of procalcitonin in reducing antibiotic exposure in patients admitted with infection.

Challenges:
- Reduced availability of PCT testing in some facilities, especially smaller facilities
- PCT is a send-out lab in some facilities

Challenges to Implementing ASP:
- Lack of appropriate resources
- Lack of staff; staff turnover
- No centralized EMR
- Committee members may not have time allocated for ASP duties
- No Infectious Diseases physician
- No ID trained pharmacists
- Accountability
Positive Steps

- **High Risk antibiotic protocols**
  - Vancomycin indications, dosing, monitoring
    - Low rate of complications (i.e. Renal failure)
  - Zosyn infusion protocol
    - Long vs short infusion time

- **C. diff awareness/monitoring**
  - Infection rate lower than national rate

Positive Steps

- **Culture driven antimicrobial selection**
  - Evidence suggests that de-escalation leads to decreased ICU length of stay (LOS), hospital LOS, ventilator days, duration of therapy (*Zepke 2016*)
  - Push to have cultures obtained and utilized whenever possible
Some Solutions

- Regional ID Consultant
- Training for current pharmacists
- EMR !!
- Patient education
  - Handouts, posters
- Provider education
  - Hospital orientation
  - Ongoing, interactive
- Community Education
- Persistence!

Some Solutions

- Regional Network
  - Navajo Area
  - Quarterly meetings
  - Share ideas, challenges
  - Education
  - Support
Provider Education

Preserve the Power of Antibiotics

Antibiotic-resistant bacteria cause more than 2 million illnesses and at least 23,000 deaths each year in the United States. Antibiotic resistance occurs when germs no longer respond to the drugs designed to kill them. Inappropriate prescribing of antibiotics contributes to antibiotic resistance and is a threat to patient safety.

Healthcare Providers Can:
- Prescribe correctly
  - Avoid treating viral syndromes with antibiotics, even when patients ask for them.
  - Pay attention to dose and duration: The right antibiotic needs to be prescribed at the right dose for the right duration.
  - Be aware of antibiotic-resistance patterns in your area so that you can always choose the right antibiotic.
- Hospital and nursing home providers should reassess within 48 hours of starting the antibiotic, when the patient’s culture results come back. Adjust the prescription, if necessary. Stop the prescription, if indicated.
- Collaborate with each other and with patients
  - Talk to your patients about appropriate use of antibiotics.
  - Include microbiology cultures, when possible, when ordering antibiotics.
  - Work with pharmacists to ensure appropriate antibiotic use and prevent resistance and adverse events.
  - Use patient and provider resources offered by the Centers for Disease Control and Prevention.

Patient Education

You have just filled a prescription for an antibiotic...

Read this important information
- Take it exactly as your healthcare professional tells you
- Do not skip doses
- Do not share it with others
- Do not save it for later and talk to your pharmacist about safely discarding leftover medicines

Why is this checklist so important?
All medicines have good and bad side effects. Antibiotics can make future bacterial infections stronger and harder to treat. You can protect yourself and others by learning when antibiotics are and are not needed.

Take antibiotics the right way.
Patient Education

COMMON COLD TREATMENT

The common cold is caused by a virus, which affects the airway passages. You may have one or more of these symptoms:
- Runny or stuffy nose
- Sneezing
- Sore throat
- Cough
- Body aches
- Fever
- Headache
- Feeling tired

Treatment of the common cold includes:
- Drink plenty of liquids (water, tea with lemon and honey, clear soup or broth).
- Using extra pillows may help your cough when lying down.
- Get extra rest.
- Using a humidifier or boiling water on the stove to add moisture to the air.
- Wash hands often, cover mouth when sneezing or coughing, and avoid spreading the virus to others.

If your symptoms get worse after 10 days, see a doctor.

If you have any questions about cold medicines, please call our pharmacy and speak with one of our pharmacists.

Antibiotics will NOT help treat the common cold.

TCRHCC Revised 2/14


- Systematic review of reviews (14)
- Methods: audit and feedback, local opinion leaders, marketing, passive dissemination, patient-mediated, reminders, and multi-faceted
- Active methods (academic detailing, multi-faceted) led to greater effects
Changing Physician Behavior


- Lag time between clinical evidence and practice
- “Creatures of habit”, “resistant to change”
- Takes time to learn new practices
- May take even longer to “unlearn” old, outdated practices

Practice and System-level Interventions to Decrease Antibiotic Prescribing

- 1. Monthly e-mails to physicians
- 2. Electronic medical record “prompts” – require “justification note”.
- 3. Distribution of patient information

(Fiore D, 2017)
- Uncultured bacteria
- Teixobactin
- Inhibits cell all synthesis by binding Lipid II and Lipid III
- No mutants of *S. aureus* or *M. tuberculosis*

- The level of at least 3 drug resistance (Multidrug Resistance – MDR) has remained stable
- Clinical outcomes of patients with MDR is still debated
- Current (including ‘old’) antibiotics should suffice to treat infections
63 year-old female with diabetes, COPD, admitted with sepsis due to multi-lobar pneumonia
- **Rapid viral testing, Procalcitonin** not available
- Sputum and blood **cultures** obtained
- Started on **broad spectrum antibiotics**, IV fluids
- **Dose monitoring** with assistance of pharmacy

At 48 hours, **Time Out** is signaled by the EMR
- **Antimicrobial team** reviews the case, note that sputum and blood cultures positive for gram positive cocci in chains
- **Final culture results** shows *Strep pneumoniae* in sputum and blood, sensitive to penicillins and cephalosporins
- Broad spectrum antibiotics **discontinued**, treatment is narrowed based on **cultures**
- Monitored for clinical response
Summary

- Penicillin revolutionized the treatment of infections
- Multiple mechanisms for resistance
- We are in a battle!
- Antimicrobial stewardship has been mandated, and it works!
- Persistence is the key, especially in a small facility

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Questions?

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