

# The Fall of the Antibiotic Era: Why Stewardship Matters

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# Disclosure

I, Spencer Durham, have no actual or potential conflict of interest in relation to this program.

# OBJECTIVES

- At the end of the presentation, the audience will be able to:
  - Define antimicrobial stewardship and list reasons why it is essential to perform
  - Recognize the general resistance patterns of pathogens that have developed since the advent of antimicrobials
  - Identify specific pathogens considered major threats
  - Utilize the SNAP approach to antimicrobial stewardship to work through real life cases

# What is Antimicrobial Stewardship?

- “Stewardship” – the activity or job of protecting and being responsible for something
- Antimicrobial stewardship involves taking responsibility for the management of antimicrobials with the goal of using them most appropriately

# Definition

- Per the Infectious Diseases Society of America (IDSA):
  - “Coordinated interventions designed to improve and measure the appropriate use of antimicrobials by promoting the selection of the optimal antimicrobial drug regimen, dose, duration of therapy, and route of administration.”
  - “Antimicrobial stewards seek to achieve optimal clinical outcomes related to antimicrobial use, minimize toxicity and other adverse events, reduce the costs of health care for infections, and limit the selection for antimicrobial resistant strains.”

# What is Antimicrobial Stewardship?

- Antimicrobial stewardship encompasses numerous strategies:
  - Limiting inappropriate use of all antibiotics
  - Utilizing narrow-spectrum antibiotics
  - IV to PO conversions
  - Decreasing actual or potential adverse effects
  - Renal dose adjustments
  - Cost effectiveness

# Why is Antimicrobial Stewardship Important?

- Multidrug-resistant organisms (MDROs) are increasing at an alarming rate
- 2 million illnesses and 23,000 deaths associated with antibiotic-resistant bacteria annually
- In May 2016, colistin-resistant *E.coli* was first reported in the U.S.
- Misuse of antimicrobial agents is the major contributing factor to disseminated resistance

# Why is Antimicrobial Stewardship Important?

- MDRO cost to the healthcare system
  - \$21-34 **billion** annually
- Additional 8 million days in the hospital
- At least 30% of antimicrobials prescribed in the outpatient and emergency settings are not needed
- 20-50% of antimicrobials prescribed in the acute care setting are unnecessary or inappropriate



# Benefits of Antimicrobial Stewardship

- Improved patient outcomes
- Decreased adverse events
  - Reduced incidence of *Clostridium difficile* infection (CDI)
- Improvement in the rates of antibiotic susceptibilities to targeted antibiotics
- Optimization of resource utilization across the continuum of care

From the  
“Golden Age of Antibiotics”  
to the  
“Fall of the Antibiotic Era”

# Introduction

- “The thoughtless person playing with penicillin treatment is morally responsible for the death of the man who succumbs to infection with the penicillin-resistant organism. I hope this evil can be averted.”

- Sir Alexander Fleming

- Penicillin first marketed for commercial use
  - Discovered in 1928, but first came to large-scale production in the early 1940s
- Revolutionized the treatment of infections
- Served to usher in the “Antibiotic Era”
  - Subsequent decades saw the discovery and marketing of many novel antibiotic agents

- Most *Staphylococcus aureus* isolates were sensitive to penicillin
- Within months, isolates began producing beta-lactamases
- By the late 1960s, >80% of community and hospital staphylococcal isolates were penicillin-resistant
- Today, near 100% of isolates produce beta-lactamases

- “Golden Age of Antibiotics”
- More than 20 new antibiotic classes are introduced to market
  - Cephalosporins
  - Erythromycin
  - Vancomycin
  - Doxycycline

# 1950s-1970s

- 1964
  - Maxwell Finland
    - Warned of the great dangers of antibiotic resistant bacteria
- 1965
  - Dissemination of penicillin-resistant pneumonia
- 1968
  - First case of methicillin-resistant *Staphylococcus aureus* (MRSA) reported in Boston

- More than 60 new antibiotics discovered
  - Many are not novel classes, but modifications of existing classes
    - Cephamycins
    - Minocycline
    - Imipenem/cilastatin
    - Ciprofloxacin
- 1988 – vancomycin-resistant *Enterococcus* (VRE) first reported



# 1990s-2000s

- Dramatic decrease in the number of companies developing new antimicrobials
  - Belief that most novel agents had already been discovered
  - Less financial incentive compared to drugs used for chronic ailments
- 1996 – Levofloxacin introduced to the market
  - Resistance began developing during the first year

- 2004-2005
  - *Pseudomonas* and *Acinetobacter* isolates are discovered to be resistant to all commercially available antibiotics
- 2008
  - New Delhi metallo-beta-lactamase (NDM-1) first discovered (carbapenemase)
  - Confers resistance to all beta-lactams

- 2012
  - Hospital outbreaks of carbapenem-resistant *Enterobacteriaceae* (CRE) reported from duodenoscopes that were not thoroughly cleaned
- 2016
  - Mobilized colistin resistance (*mcr-1*) gene discovered in US
- 2017
  - Patient dies from *Klebsiella pneumoniae* infection resistant to all 26 commercially available antibiotics in the US

- Centers for Disease Control issues the report “Antibiotic Resistant Threats in the United States”
- Classifies 18 drug-resistant pathogens in one of three categories:
  - Urgent
  - Serious
  - Concerning

# Urgent Threats

- 3 different pathogens
  - Potential to become widespread
  - Associated with serious risks
  - Require immediate public health attention
- *Clostridium difficile*
- Carbapenem-resistant *Enterobacteriaceae*
- *Neisseria gonorrhoeae*

# Serious Threats

- 12 different pathogens
  - Incidence of infection may be decreasing, or some therapeutic options may be available
  - Close public health monitoring is required to prevent them becoming “urgent threats”
- MRSA
- VRE
- Drug-resistant *Streptococcus pneumoniae*
- Drug-resistant Tuberculosis

# Serious Threats

- Drug-resistant *Shigella*
- Drug-resistant *Salmonella* (Typhi and non-typhoidal)
- Drug-resistant *Campylobacter*
- Multidrug-resistant *Acinetobacter*
- Multidrug-resistant *Pseudomonas aeruginosa*
- Extended-spectrum beta-lactamase (ESBL) producing organisms
- Fluconazole-resistant *Candida*

# Concerning Threats

- 3 different pathogens
  - Resistance is low and/or several treatment options available
  - Can cause severe illness
- Vancomycin-resistant *Staphylococcus aureus* (VRSA)
- Erythromycin-resistant group A *Streptococcus*
- Clindamycin-resistant group B *Streptococcus*



- World Health Organization (WHO) published its first ever list of “Priority Pathogens”
- 12 antimicrobial resistant organisms considered the greatest threat to human health
- Classified into 3 categories according to the urgency of need for new antimicrobials:
  - Critical
  - High
  - Medium

# Critical Priority

- 3 pathogens
- Carbapenem-resistant *Acinetobacter baumannii*
- Carbapenem-resistant *Pseudomonas aeruginosa*
- Carbapenem-resistant and ESBL-producing *Enterobacteriaceae*

# High Priority

- 6 pathogens
- MRSA and VRSA
- Vancomycin-resistant *Enterococcus faecium*
- Clarithromycin-resistant *Helicobacter pylori*
- Fluoroquinolone-resistant *Campylobacter*
- Fluoroquinolone-resistant *Salmonellae*
- Cephalosporin and fluoroquinolone-resistant *Neisseria gonorrhoeae*

# Medium Priority

- 3 pathogens
- Penicillin-non-susceptible *Streptococcus pneumoniae*
- Ampicillin-resistant *Haemophilus influenza*
- Fluoroquinolone-resistant *Shigella*

- IDSA issues a report called “Faces of Antimicrobial Resistance”
- Details 13 different specific cases of patients who have faced life-threatening antimicrobial resistance
- Goal of the publication is to highlight how antimicrobial resistance affects individual patients, families, and friends

# Faces of Antimicrobial Resistance

- Catherine Duff
- Diagnosed with severe diverticulitis, requiring surgery to remove one-third of her colon
- Subsequently, an abdominal abscess burst, requiring further surgery and subsequent sepsis due to MRSA
- Antibiotics used to treat sepsis caused a *Clostridium difficile* infection

# Faces of Antimicrobial Resistance

- Ms. Duff subsequently had a total of 8 different episodes of *C.diff.* over several years, each one becoming worse and taking longer to recover
- Experienced up to 30 diarrhea episodes in a day, became bedridden, and lost almost 70 pounds
- Eventually told she would not survive

# Faces of Antimicrobial Resistance

- Ms. Duff and her husband performed a fecal microbiota transplant (FMT) at home, resulting in rapid improvement
- A subsequent surgery resulted in another infection with resistant *C.diff*.
- Another FMT was performed via colonoscopy, with great success
- Ms. Duff subsequently started The Fecal Transplant Foundation



- The Joint Commission (TJC)
  - Standard MM.09.01.01 – effective January 1<sup>st</sup>, 2017
  - Applies to hospitals and critical access hospitals
  - “The hospital has an antimicrobial stewardship program based on current scientific literature.”
  - In effect, this standard requires hospitals to perform antimicrobial stewardship

How do you conduct stewardship?

# Antimicrobial Stewardship

- The perfect recipe for a bug to develop resistance to an antibiotic is to give a low concentration of the antibiotic over a prolonged period of time
  - In general, use upper end of dosing range
  - Do not prolong therapy longer than needed, but **MUST** counsel patients to finish their course of antibiotics!
- Try to use the most narrow-spectrum agent possible as quickly as possible

# Antimicrobial Stewardship

- SNAP approach to antimicrobial stewardship
- Safety, Need, Adequacy, Prudence
- Step-by-step process to assess antimicrobial therapy *when antibiotics have already been prescribed*
- If initially recommending an antibiotic, change to the NAPS approach

# Antimicrobial Stewardship

- “S” – Safety
- Ask “is it safe for this patient to be receiving this drug?”
- Assessment of allergies
- Assess for likelihood of potential adverse drug reactions

- “N” – Need
- Ask “Does this patient need antimicrobial therapy?”
  - Does the patient actually have an infection?
  - Is the infection likely to be:
    - Bacterial?
    - Viral?
    - Fungal?

# Antimicrobial Stewardship

- “A” – Adequacy
- Ask “Is the drug that has been prescribed treating, or likely to treat, the infection?”
  - Is the drug a guideline recommended therapy?
  - Does the drug provide appropriate coverage against the pathogens most likely causing the infection?
  - Will the drug reach the site of infection?

# Antimicrobial Stewardship

- “P” – Prudence
- Ask “Is this the most prudent drug to use for this infection?”
  - Is the drug the most-narrow spectrum agent that will adequately treat this infection?
- This often cannot be fully assessed unless culture and susceptibility results are available

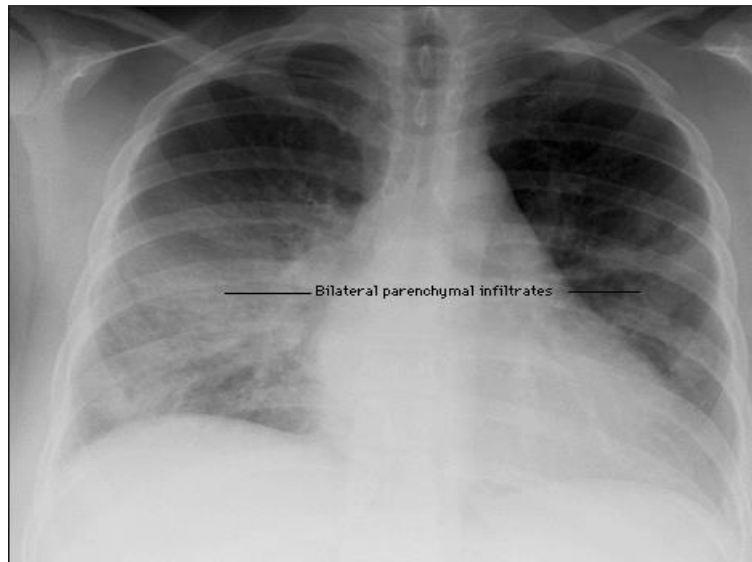


# Case 1

- HPI: D.B. is a 65 year old WM admitted to the hospital for evaluation of difficulty breathing, 3 day history of fever, productive cough, night sweats, and chills
- Allergies: NKDA
- PMH: DM, HTN, dyslipidemia
- Meds: Metformin, glypizide, atorvastatin, lisinopril, HCTZ
- PE: BP 130/82; HR 90; RR 28; Temp 103.5

# Case 1

- Chest x-ray: bilateral infiltrates



- The attending physician initiates therapy with ceftriaxone 1 gram IV daily and levofloxacin 500 mg IV daily

# Case 1

- Which of the following is the most appropriate recommendation for D.B. at this time?
  - A) Continue the currently prescribed therapy
  - B) Change to ceftriaxone 2 grams IV daily and levofloxacin 750 mg IV daily
  - C) Discontinue antibiotics; infection is likely viral
  - D) Change to levofloxacin 750 mg IV once daily

## Case 2

- J.S. is a 36 year old female who presents to her PCP for evaluation of a large, pus-filled boil on her back.
- Allergies: Sulfonamides (rash)
- PMH: PCOS
- Meds: metformin, multivitamin
- PE: BP 118/76; HR 70; RR 18; Temp 99

# Case 2

- She is prescribed Bactrim DS, 1 tablet PO BID for 14 days



## Case 2

- Do you agree with the initial choice of antimicrobial therapy?
- What is the most likely bacterial etiology?
- Are there any non-pharmacological therapies that should be recommended at this time?

# Case 3

- N.P. is an 85 year old AAF who is brought to the ED by her granddaughter because she is experiencing increased confusion from baseline
- Allergies: Penicillin (rash)
- PMH: Dementia, dyslipidemia, COPD, CHF
- Meds: Numerous
- PE: BP 132/76, P 80, RR 22, T 99.6°F

# Case 3

- A variety of tests were ordered, with the urinalysis showing multiple abnormalities
- A urine culture is ordered and sent to the lab
- She is admitted to the hospital and the attending physician orders levofloxacin 500 mg IV daily
- Do you agree with this choice of empiric therapy?



- Urine culture results:

- Klebsiella pneumoniae*

	SUSC	INTP
Amikacin.....	<=2	S
Ampicillin.....	>=8	R
Cefazolin.....	<=4	S
Cefepime.....	<=1	S
Ceftazidime.....	<=1	S
Ceftriaxone.....	<=1	S
Levofloxacin.....	<2	S
Imipenem.....	<=2	S
Gentamicin .....	<=2	S
Tobramycin.....	<=2	S
Nitrofurantoin.....	>=256	R
Piperacillin/tazobactam.....	<=4	S
Trimethoprim/sufamethoxazole....	<20	S

- Which of the following is the best recommendation for this patient?
  - A) Continue the current therapy
  - B) Change to cephalexin
  - C) Change to Bactrim
  - D) Change to IM ceftriaxone

# Case 4

- J.R. is a 62 year old WM, recent admit to your LTCF s/p stroke. He complains today of a dry cough x 3 days, rhinorrhea, and sore throat.
- Allergies: NKDA
- PMH: Stroke, HTN, DM
- Meds: Numerous
- PE: BP 140/86, P 74, RR 22, T 97.5°F

# Case 4

- Chest x-ray: negative
- Rapid strep: negative
- The attending physician orders cefdinir 300 mg PO BID for 7 days, plus azithromycin 500 mg PO on day 1, 250 mg PO on days 2-5

- What is the best recommendation for J.R. at this time?
  - A) Continue the current therapy
  - B) Change to levofloxacin
  - C) Change to Bactrim
  - D) Discontinue antibiotics

- Additional Resources:
- [www.idsociety.org](http://www.idsociety.org)
  - IDSA clinical practice guidelines
  - Antimicrobial Stewardship guidelines
- [www.cdc.org](http://www.cdc.org)
- [www.cms.org](http://www.cms.org)
- [www.jointcommission.org](http://www.jointcommission.org)

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QUESTIONS???