Antibiotics: General Notions & Antimicrobial Stewardship

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Disclosures

- No conflict of interest
Objectives

After this intervention, the participants will be able to:

- Define the utility of antibiotics in medical practice using a case-based approach

- Recognize the value of antimicrobial stewardship to reduce the emergence of antibiotic resistance
Alexander Fleming

September 22, 1928

Penicillium notatum

Staphylococcus aureus

Published in 1929 in the British Journal of Experimental Pathology
Antibiotics

◆ Any of a variety of substances, usually obtained from microorganisms, that inhibit the growth of or destroy certain other microorganisms.

◆ First definition in 1942 excluded synthetic agents like sulfonamides.

WHAT IS AN ANTIBIOTIC OR AN ANTIBIOTIC SUBSTANCE? *

Selman A. Waksman

With the introduction, in 1941, of penicillin as an important chemotherapeutic agent, and with the isolation from cultures of different micro-organisms of a rapidly increasing number of new chemical substances found to possess similar antibacterial and other antimicrobial properties, it became apparent that a new name was required, which would include these and similar compounds.

A request for the submittal of such a name was addressed to the writer in July, 1941, by Dr. A. Flynn, editor of Biological Abstracts. After giving this matter considerable thought, the writer concluded that the terms antibiotic and antibiotic substance, which previously had been used in a rather loose sense, might well be restricted to a specific application. It was felt that the words

Classification of Antibiotics - I

- According to their antimicrobial activity, can be divided into:
  1. Bactericidal antibiotics
     1. Cell wall synthesis inhibition
     2. Cell wall alteration
  2. Bacteriostatic antibiotics
     1. Protein synthesis (except aminoglycosides)
     2. Nucleic acid synthesis (except quinolones and metronidazole)
     3. Anti-metabolites
Classification of Antibiotics - II

**GRAM NEGATIVE**
- 2nd and 3rd gen cephalosporins
- aminopenicillins
- quinolones
- aminoglycosides
- monobactams
- polymyxins

**BROAD SPECTRUM**
- pen & b-lactam inh
- 3rd/4th gen cephalosporins
- higher gen quinolones
- carbapenems
- tetracyclines
- TMP/SMX

**ATYPICAL ORGANISMS**
- tetracyclines
- higher generation quinolones
- macrolides

**ANAEROBES**
- metronidazole
- clindamycin
- 4th gen quinolones
- tetracyclines
- chloramphenicol

**GRAM POSITIVE**
- glycopeptides
- penicillin G
- 1st gen cephalosporins
- oxazolidones
- clindamycin
- daptomycin
Classification of Antibiotics - III

- Cell Wall Synthesis
  - D-cycloserine
  - Vancomycin
  - Bactracin
  - Penicillins
  - Cephalosporins
  - Cephamycins

- Cell Wall Integrity
  - β-lactamases

- DNA Synthesis
  - Metronidazole

- DNA Gyrase
  - Quinolones

- RNA Polymerase
  - Rifampicin

- Cell Wall

- DNA Replication

- Transcription

- Ribosomes
  - 50s
  - 50s
  - 50s
  - 30s
  - 30s
  - 30s

- Translation

- Cytoplasmic Membrane

- Protein Synthesis
  - (50S Inhibitors)
    - Erythromycin
    - Chloramphenicol
    - Cindamycin
    - Lincomycin

- Protein Synthesis
  - (30S Inhibitors)
    - Tetracyclines
    - Streptomycin
    - Spectinomycin
    - Kanamycin

- Phospholipid Membranes
  - Polymyxins
Vignette 1

- During a check-up for the employment yearly Health Certificate, a 26-year-old man from Puerto Rico was found with a positive VDRL test at 1:320 titers.

- 11 months ago, during the same screening, the patient had a negative VDRL test.

- Upon interview, he recalls an unprotected encounter with a sexual worker about 2 months, after which he had a penile ulcer. He did not seek for medical help because the ulcer was not painful and because it healed spontaneously.

- You request a FTA-ABS test, which is positive.

- The patient has no known drug allergies and is currently asymptomatic.
Vignette 1

What would be the best intervention for this patient?

- A. Oral ciprofloxacin 500 mg twice daily x 14 days
- B. Oral doxycycline 100 mg twice daily for 7 days
- C. One dose of intramuscular benzathine penicillin G 2.4 million units
- D. One dose of oral azithromycin 1g
CELL WALL SYNTHESIS AND INTEGRITY
Beta-lactams

- Beta-lactam antibiotics act at a target called (for some reason!) Penicillin-Binding Proteins (PBP).
- Penicillin-Binding Proteins causes peptidoglycan cross-linking.
- When bacteria is exposed to beta-lactam antibiotic, antibiotic binds to PBP, inhibiting cell wall synthesis and producing toxin release.
- Bacteria die. Hence, beta-lactams are bactericidal.
Cell wall synthesis inhibition: B-Lactam Antibiotics

- **Penicillins**
  - Natural penicillins (mostly GPC and anaerobes)
  - Amino penicillins (more GNB coverage)
  - Penicillinase – resistant penicillins (anti-Staph, methicillin-susceptible)
  - B-lactamase inhibitor and penicillin combination
    - Broad spectrum; Active against B-lactamase-producing organisms
  - NEW! - B-lactamase inhibitor and cephalosporin combination
    - Activity against ESBL-producing GNB and carbapenemase-producing *Klebsiella*

- **Cephalosporins** – less susceptible to penicillinases
  - 1\(^{st}\) Generation
  - 2\(^{nd}\) Generation
  - 3\(^{rd}\) Generation
  - 4\(^{th}\) Generation
  - 5\(^{th}\) Generation – anti-MRSA

- **Monobactams**
- **Carbapenems** – very broad spectrum
Adverse Reactions to Beta-Lactams

- Anaphylaxis
- Rash
- Diarrhea
- Platelet dysfunction
- Eosinophilia
- Neutropenia
- Elevated LFT’s
Allergic to PNC?

- The use of cephalosporins can be attempted in patients who had mild skin reactions with penicillin.

- Patients who had ANAPHYLAXIS to penicillin can have 10-30% cross-reaction with the use of cephalosporins.
  - The higher the generation of cephalosporin, the less is the risk of cross-reaction.
Vignette 2

- A 17-year-old male patient has been experiencing skin lesions in his face as shown for the past 6 months.

- He has tried several topical over-the-counter remedies (salicylic acid) without success.
Vignette 2

Which of the following treatments would be best to both improve the patient’s condition and to prevent the emergence of resistance:

– A. Continue topical salicylic acid alone
– B. Add erythromycin 2% gel BID
– C. Add systemic retinoid for 15-20 weeks
– D. Oral doxycycline 100 mg PO BID + topical benzoyl peroxide
Protein Synthesis Inhibition

- Aminoglycosides
- Tetracyclines
- Clindamycin
- Chloramphenicol
- Macrolides-Streptogramine-Lincosamide
- Ketolides
- Oxazolidones
Aminoglycosides

- Gentamicin
- Tobramycin
- Amikacin
- Streptomycin

Coverage:
- Infections Enteric GNB and *Pseudomonas*
- Synergism for GPC (≥ *Enterococcus*)
- Antimycobacterial (streptomycin, amikacin)
- Plague
- Tularemia
- Brucellosis
Adverse Events of Aminoglycosides

- Ototoxicity
- Neuromuscular blockade
- Nephrotoxicity
  - Age, dehydration, hepatic dysfunction
  - Drugs: Vanco, Ampho B, Foscarinet, IV Dyes
  - Frequency of dosing and duration of treatment
Tetracyclines

◆ Doxycycline
◆ Oxytetracycline
◆ Minocycline

◆ Broad Spectrum: GPC, GNB, anaerobes, atypical

◆ Uses
  – Actinomycosis
  – Bartonellosis
  – Bite Wounds
  – Sexually Transmitted Diseases
  – Leptospirosis
  – Lyme Disease
  – *Plasmodium falciparum*
  – Plague
  – Rickettsial Disease
  – Rat Bite Fever
  – Syphilis
  – Tularemia
  – Vincent’s Angina
  – Whipple’s Disease
  – Jaws, Pinta
  – Relapsing Fever
  – Psittacosis
Adverse Effects Tetracyclines

- GI Intolerance
- Stains and deforms teeth in children up to 8 years
- Hepatotoxicity
- Candidiasis (thrush and vaginitis)
- Photosensitivity
- Phlebitis with IV injection
- Aggravation of Myastenia Gravis
- Increased Intracranial Pressure
Clindamycin (Cleocin)

◆ Spectrum:
  – mostly GPC, including MRSA
  – Anti-anaerobic coverage
  – Certain anti-parasitic activity and antifungal activity:
    ◆ Cerebral Toxoplasmosis
    ◆ ☞ Primaquine for PCP
    ◆ ☞ Quinine for Babesiosis
Adverse Effects - Clindamycin

- ****Clostridium difficile colitis
- Allergic reactions
- Blood dyscrasias
- Esophageal ulceration
- Hepatotoxicity
- Neuromuscular blockade
- Fever
- Metallic taste
- Phlebitis at IV infusion sites
Macrolides

- Erythromycin
- Clarithromycin
- Azithromycin

Spectrum:
- some GPC
- some GNB
- coverage of atypical organisms
Adverse Effects of Macrolides

- Nausea, vomiting, abdominal pain
- Allergic reactions
- Cholestatic hepatitis
- Sensorineural hearing loss
- Prolongation of QT interval
Vignette 3

◆ A 23-year-old woman without systemic illnesses presents dysuria, change in urine odor, and an increased urinary frequency.

◆ She denies fever, low back pain or similar past episodes.

◆ U/A shows:
  – 48 WBC’s, many bacteria, positive nitrites, positive leukocyte esterase, but no casts.

◆ She is prescribed an antibiotic for uncomplicated urinary tract infection (cystitis).

◆ 2 days into treatment, she experiences a sudden-onset excruciating ankle pain while doing her daily 3-mile fitness run.
Vignette 3

- She is eventually diagnosed with an Achilles tendon rupture.

- What is the most likely etiology of the tendon rupture in this patient?
  - A) Trimethoprim/sulfamethoxazole
  - B) Nitrofurantoin
  - C) Ciprofloxacin
  - D) Ampicillin
NUCLEIC ACID INHIBITION
Nucleic acid inhibition

- DNA replication
  - 1. Quinolones:
    - a. Bind to DNA gyrase (mostly in gram negative)
    - B. Inhibit topoisomerase IV (mostly in gram positive)
    - Bactericidal
  - 2. Metronidazole:
    - Radicals derived from this antibiotic disrupt bacterial DNA
    - Bactericidal

- RNA synthesis: Prevent transcription at level of RNA synthesis
  - 1. Rifampin
  - 2. Rifabutin
  - 3. Rifapentin (Priftin)
# Fluoroquinolones

- **First Generation**
  - Nalidixic Acid

- **Second Generation**
  - Norfloxacin
  - Ciprofloxacin
  - Ofloxacin

- **Third Generation**
  - Levofloxacin
  - Gatifloxacin
  - Gemifloxacin

- **Fourth Generation**
  - Moxifloxacin
  - Trovafloxacin

<table>
<thead>
<tr>
<th>Generation</th>
<th>Activity</th>
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<tbody>
<tr>
<td>1st Generation</td>
<td>Gram-negative activity; urinary tract</td>
</tr>
<tr>
<td>2nd Generation</td>
<td>+ Gram-positive activity; systemic</td>
</tr>
<tr>
<td>3rd Generation</td>
<td>+ Gram-positive potency; <em>S. pneumoniae</em></td>
</tr>
<tr>
<td>4th Generation</td>
<td>+ Anaerobes</td>
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Clinical Uses of Fluoroquinolones

- Urinary Tract Infections
- Prostatitis
- Sexually Transmitted Diseases
- Gastroenteritis
- Intra-abdominal infections
- Respiratory Tract Infections
- Bone and joint infections
- Anthrax
- Typhoid and enteric fever
- Prosthetic joint infections
Adverse Effects of Fluoroquinolones

- **Gastrointestinal**
  - Nausea, vomiting, diarrhea

- **Central Nervous System**
  - Dizziness, insomnia, seizures

- **Cardiovascular**
  - \( QT_c \) prolongation

- **Hepatic**
  - Idiosyncratic hepatitis

- **Skin**
  - Photosensitivity

- **Musculoskeletal**
  - Cartilage erosions, tendinitis/tendon rupture
Metronidazole

◆ Spectrum:
  – Anti-anaerobic
  – Anti-parasitic

◆ Uses:
  – *Clostridium difficile* colitis
  – Amebiasis, Giardiasis
  – Vaginitis: *Trichomonas, Gardenella*
  – Anaerobic Coverage
Adverse Effects of Metronidazole

◆ + Alcohol => Disulfiram-like reaction
◆ Inhibits metabolism of warfarin
◆ Nausea, vomiting, metallic taste
◆ Pancreatitis
◆ Neurotoxicity: Seizures, peripheral neuropathy
◆ Teratogenicity
◆ Carcinogenicity
A 45-year-old man living with AIDS has experienced shortness of breath, cough, low grade fever during the past 2 weeks.

On physical examination, respiratory rate is 26 breaths/min and the lungs are clear to auscultation.

Influenza rapid test is negative.

ABG’s shows pO2 at 53 mmHg.

He is admitted and started on azithromycin, ceftriaxone, and trimethoprim/sulfamethoxazole, and prednisone.

6 days into treatment, he has shown clinical improvement, but creatinine levels have increased to 3.2 mg/dL (from a baseline of 1.2) and his K+ level is now 5.4 mEq/L
Vignette 4

What is the most likely cause of increased renal parameters in this patient?

- A) HIV
- B) Prednisone
- C) Azithromycin
- D) Ceftriaxone
- E) Trimethoprim/sulfamethoxazole
ANTIMETABOLITES
Antimetabolites

- Antibiotics that inhibit certain steps in metabolism include:

1. Sulfamides: inhibit folic acid synthesis
2. Trimethoprim: interferes with folic acid metabolism
   - Prevent conversion from dehydrofolate to tetrahydrofolate
3. Dapsone: inhibits folic acid synthesis
Trimethoprim/Sulfamethoxazole

- **Spectrum:**
  - Some GPC
  - Some GNB
  - Some antiparasitic

- **Uses:** *Pneumocystis*, alternative for *Listeria, Cyclospora* and *Isospora*, UTI, MRSA

- **Adverse reactions**
  - Rash, SJS, Toxic epidermal necrolysis
  - Pancytopenia
  - Increased creatinine/hyperkalemia
Lessons learned

◆ There is a broad variety of antibacterial agents with different mechanisms of actions and antimicrobial spectrum

◆ Knowledge of the adverse events of each class of antibiotics will help us anticipate and identify complications during the treatment course

◆ Antibiotics can be life-saving, but their inappropriate use can lead to antibiotic resistance.
Antibiotic use for specific conditions

- There are numerous indications and approved use of antibiotics for hundreds of conditions.
- Proper use of antibiotics is granted in the setting of probable or confirmed infections by likely susceptible organisms.
- Preventive and empiric use of antibiotic therapy is also contemplated in several settings.
Mechanisms of resistance

- Most, encoded in plasmids:
  - Transmissible
- Efflux pumps
- Antibiotic altering enzymes
- Antibiotic degrading enzymes
  - penicillinases

- Also, change in binding site

1. Lots of germs. A few are drug resistant.
2. Antibiotics kill bacteria causing the illness, as well as good bacteria protecting the body from infection.
3. The drug-resistant bacteria are now allowed to grow and take over.
4. Some bacteria give their drug-resistance to other bacteria, causing more problems.
Examples of How Antibiotic Resistance Spreads

- Animals get antibiotics and develop resistant bacteria in their guts.
- Drug-resistant bacteria can remain on meat from animals. When not handled or cooked properly, the bacteria can spread to humans.
- Fertilizer or water containing animal feces and drug-resistant bacteria is used on food crops.
- Drug-resistant bacteria in the animal feces can remain on crops and be eaten. These bacteria can remain in the human gut.
- George gets antibiotics and develops resistant bacteria in his gut.
- George stays at home and in the general community. Spreads resistant bacteria.
- George gets care at a hospital, nursing home or other inpatient care facility.
- Resistant germs spread directly to other patients or indirectly on unclean hands of healthcare providers.
- Resistant bacteria spread to other patients from surfaces within the healthcare facility.

Estimated minimum number of illnesses and deaths caused by antibiotic resistance*:

At least 2,049,442 illnesses, 23,000 deaths

*bacteria and fungus included in this report

Estimated minimum number of illnesses and death due to *Clostridium difficile* (C. difficile), a unique bacterial infection that, although not significantly resistant to the drugs used to treat it, is directly related to antibiotic use and resistance:

At least 250,000 illnesses, 14,000 deaths
Question

Which is expected to be the major cause of death by 2050?

- A. Cancer
- B. Trauma/Accidents
- C. Diabetes mellitus
- D. Resistant bacteria
Deaths attributable to AMR every year compared to other major causes of death

- Tetanus: 60,000
- Road traffic accidents: 1.2 million
- Measles: 130,000
- Diarrhoeal disease: 1.4 million
- Cholera: 100,000 - 120,000
- Cancer: 8.2 million
- Diabetes: 1.5 million

AMR now: 700,000 (low estimate)

AMR in 2050: 10 million
WORLDWIDE MORTALITY FORECAST FOR ANTIMICROBIAL RESISTANCE 2050
Burden of resistance

- Antibiotic-resistant bacteria could lead to the use of:
  - combination therapy
  - alternative agents which could promote more adverse events
  - more expensive options
  - antibiotics which could be less effective => higher mortality
People at high risk

CANCER CHEMOTHERAPY
People receiving chemotherapy are often at risk for developing an infection when their white blood cell count is low. For these patients, any infection can quickly become serious and effective antibiotics are critical for protecting the patient from severe complications or death.

COMPLEX SURGERY
Patients who receive cardiac bypass, joint replacements, and other complex surgeries are at risk of a surgical site infection (SSI). These infections can make recovery from surgery more difficult because they can cause additional illness, stress, cost, and even death. For some, but not all surgeries, antibiotics are given before surgery to help prevent infections.

RHEUMATOID ARTHRITIS
Inflammatory arthritis affects the immune system, which controls how well the body fights off infections. People with certain types of arthritis have a higher risk of getting infections. Also, many medications given to treat inflammatory arthritis can weaken the immune system. Effective antibiotics help ensure that arthritis patients can continue to receive treatment.

DIALYSIS FOR END-STAGE RENAL DISEASE
Patients who undergo dialysis treatment have an increased risk for getting a bloodstream infection. In fact, bloodstream infections are the second leading cause of death in dialysis patients. Infections also complicate heart disease, the leading cause of death in dialysis patients. Infection risk is higher in these patients because they have weakened immune systems and often require catheters or needles to enter their bloodstream. Effective antibiotics help ensure that dialysis patients can continue to receive life-saving treatment.

ORGAN AND BONE MARROW TRANSPLANTS
Transplant recipients are more vulnerable to infections. Because a patient undergoes complex surgery and receives medicine to weaken the immune system for a year or more, the risk of infection is high. It is estimated that 1% of organs transplanted in the United States each year carry a disease that comes from the donor—either an infection or cancer. Effective antibiotics help ensure that organ transplants remain possible.

Question

What is the most important factor contributing to antimicrobial resistance?
Antibiotics contribute to resistance!

- The use of antibiotics is the single most important factor leading to antibiotic resistance around the world.
- Antibiotics are among the most commonly prescribed drugs used in human medicine.
  - up to 50% of all the antibiotics prescribed for people are not needed or are not optimally effective as prescribed.
- Antibiotics are also commonly used in animals to prevent, control, and treat disease, and to promote the growth of food-producing animals.

“Obama acknowledged drug-resistance”

Obama publishes US strategy to tackle rise in Antibiotic Resistant Bacteria - is it enough?
“The evolution of antibiotic resistance is now occurring at an alarming rate and is outpacing the development of new countermeasures capable of thwarting infections in humans.”

- President Barack Obama, 2015
NATIONAL STRATEGY
FOR COMBATING ANTIBIOTIC-RESISTANT BACTERIA

Vision: The United States will work domestically and internationally to prevent, detect, and control illness and death related to infections caused by antibiotic-resistant bacteria by implementing measures to mitigate the emergence and spread of antibiotic resistance and ensuring the continued availability of therapeutics for the treatment of bacterial infections.

September 2014
Preventing Antibiotic Resistance

1. Preventing Infections, Preventing the Spread of Resistance
   Avoiding infections in the first place reduces the amount of antibiotics that have to be used and reduces the likelihood that resistance will develop during therapy. There are many ways that drug-resistant infections can be prevented: immunization, safe food preparation, handwashing, and using antibiotics as directed and only when necessary. In addition, preventing infections also prevents the spread of resistant bacteria.

2. Tracking
   CDC gathers data on antibiotic-resistant infections, causes of infections and whether there are particular reasons (risk factors) that caused some people to get a resistant infection. With that information, experts can develop specific strategies to prevent those infections and prevent the resistant bacteria from spreading.

3. Improving Antibiotic Prescribing/Stewardship
   Perhaps the single most important action needed to greatly slow down the development and spread of antibiotic-resistant infections is to change the way antibiotics are used. Up to half of antibiotic use in humans and much of antibiotic use in animals is unnecessary and inappropriate and makes everyone less safe. Stopping even some of the inappropriate and unnecessary use of antibiotics in people and animals would help greatly in slowing down the spread of resistant bacteria. This commitment to always use antibiotics appropriately and safely—only when they are needed to treat disease, and to choose the right antibiotics and to administer them in the right way in every case—is known as antibiotic stewardship.

4. Developing New Drugs and Diagnostic Tests
   Because antibiotic resistance occurs as part of a natural process in which bacteria evolve, it can be slowed but not stopped. Therefore, we will always need new antibiotics to keep up with resistant bacteria as well as new diagnostic tests to track the development of resistance.

Preventing Antibiotic Resistance

◆ Promoting proper handwashing

◆ Vaccination
  – *S. pneumonia*

◆ Adhering to Treatment Guidelines
  – *Mycobacterium tuberculosis*

◆ Promotion of Safer Sex
  – *Neisseria gonorrhoeae*

2. TRACKING RESISTANCE PATTERNS

CDC gathers data on antibiotic-resistant infections, causes of infections, and whether there are particular reasons (risk factors) that caused some people to get a resistant infection. With that information, experts develop specific strategies to prevent those infections and prevent the resistant bacteria from spreading.

FOUR CORE ACTIONS
PREVENTING INFECTIONS, PREVENTING SPREAD.
TRACKING RESISTANCE PATTERNS.
IMPROVING USE OF ANTIBIOTICS.
DEVELOPING NEW ANTIBIOTICS AND DIAGNOSTIC TESTS.

CDC’s Antibiotic Resistance and Antibiotic-Resistant Infections Tracking Platform

<table>
<thead>
<tr>
<th>Tracking Networks</th>
<th>Data Collected</th>
<th>Resistant Bacteria/Fungus</th>
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<tbody>
<tr>
<td><strong>EIP</strong> Emerging Infections Program</td>
<td>A network of public health-academic-hospital collaborations in 10 states. It provides access to bacterial and fungal samples for testing and detailed clinical case data. The three main programs within EIP collect different types of resistance data:</td>
<td><strong>ABCs:</strong> Staphylococcus pneumoniae Groups A and B Streptococcus Methicillin-resistant Staphylococcus aureus <strong>HAIC:</strong> C. difficile Candida (a fungus) Carbapenem-R Enterobacteriaceae MDR Acinetobacter FoodNet (see NARMS list)</td>
</tr>
<tr>
<td><strong>ABCs:</strong> Active Bacterial Core surveillance</td>
<td>ABCs provides clinical information and resistance data for bacteria that cause infections predominantly in the community. The HAIC provides clinical information and resistance data for bacteria and fungi that cause infections at the intersection of healthcare and the general community. FoodNet supplies clinical and epidemiologic data on some human isolates in the National Antimicrobial Resistance Monitoring System (NARMS).</td>
<td></td>
</tr>
<tr>
<td><strong>HAIC:</strong> Healthcare-Associated Infections-Community Interface</td>
<td><strong>NARMS</strong> National Antimicrobial Resistance Monitoring System</td>
<td><strong>Salmonella</strong> Campylobacter Shigella</td>
</tr>
<tr>
<td><strong>FoodNet:</strong> Foodborne Diseases Active Surveillance Network</td>
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<tr>
<td>NHSN</td>
<td>A system that collects and provides data on infections and drug-resistance in healthcare settings. Since NHSN collects data directly from healthcare facilities, it can provide facility-level information on healthcare-associated infections and antibiotic resistance (and in the future, on antibiotic use).</td>
<td><em>Staphylococcus aureus</em></td>
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<tr>
<td></td>
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<td><em>Enterococcus</em></td>
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<td></td>
<td></td>
<td><em>Enterobacteriaceae</em></td>
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<td><em>Acinetobacter</em></td>
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<td></td>
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<td><em>Pseudomonas aeruginosa</em></td>
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<td></td>
<td></td>
<td><em>Candida</em> (a fungus)</td>
</tr>
<tr>
<td>GISP</td>
<td>A program to track antibiotic resistance data for gonococcal isolates. Isolates are collected from sexually transmitted disease clinics in approximately 28 cities.</td>
<td><em>Neisseria gonorrhoeae</em></td>
</tr>
<tr>
<td>NTSS</td>
<td>National Electronic Disease Surveillance System (NEDSS)-based reporting of tuberculosis cases including resistance data. Public health departments from 50 states and the US territories contribute data.</td>
<td><em>Mycobacterium tuberculosis</em></td>
</tr>
</tbody>
</table>
What can be done to diminish antimicrobial resistance?

- A. Nothing
- B. Wait until the CDC and the White House take further actions
- C. Stop using antibiotics
- D. Use antibiotics wisely
Antimicrobial stewardship
Declining Antibacterial Approvals (1983-2010)¹⁻³

Antibiotic shortage

“Analyzing data from the University of Utah Drug Information Service database, a national database of drug shortages, the researchers found that 148 antibiotics experienced shortages during the study period, with an upward trend starting in 2007.”

“Thirty-two antibiotics (22 percent) experienced multiple shortages, with a median duration of more than six months. At the end of the study period in December 2013, 26 antibiotics were still in short supply or not available.”
Antibiomicarial stewardship

- Multidisciplinary intervention that involves:
  - Selection of appropriate agents
  - Correct dosing
  - Adequate route and duration
  - Marriage between infection control and antimicrobial management
  - Effective de-escalation (when feasible)
De-escalation

- Only possible when:
  - Appropriate broad spectrum antibiotic therapy is initiated
  - Adequate cultures are obtained
  - Effective laboratory resources are available
  - Rapid flow of information occurs
ATS/IDSA Guidelines: Initial Management Strategies for Patients With Suspected HAP, VAP, or HCAP

HAP, VAP, or HCAP suspected

Obtain lower respiratory tract (LRT) sample for culture (quantitative or semiquantitative) and microscopy

Unless there is both a low clinical suspicion for pneumonia and negative microscopy of LRT sample, begin empiric antimicrobial therapy using algorithm and local microbiologic data

Days 2 and 3—Check cultures and assess clinical response: temperature, white blood cells, chest x-ray, oxygenation, purulent sputum, hemodynamic changes, and organ function

Clinical improvement at 48 to 72 Hours

Cultures –
Search for other pathogens, complications, other diagnoses, or other sites of infection

Cultures +
Adjust antibiotic therapy; search for other pathogens, complications, other diagnoses, or other sites of infection

Cultures –
Consider stopping antibiotics

Cultures +
Do-escalate antibiotics, if possible. Treat selected patients for 7 to 8 days and reassess

ATS=American Thoracic Society; IDSA=Infectious Diseases Society of America; HAP=hospital-acquired pneumonia; VAP=ventilator-associated pneumonia; HCAP=healthcare-associated pneumonia

The provision of this information is not meant to imply or otherwise suggest that ZYVOX® (linezolid) should be used to treat each of these infections or microorganisms. Pfizer recommends that ZYVOX be used only in accordance with its approved indications.

How to implement an Antimicrobial Stewardship Program?

**EIGHT KEY STEPS**
for implementing an Antimicrobial Stewardship Program (ASP)

1. Assess the motivations
2. Ensure accountability and leadership
3. Set up structure and organization
4. Define priorities and how to measure progress and success
5. Identify effective interventions for your setting
6. Identify key measurements for improvement
7. Educate and Train
8. Communicate

1. **Assess the motivations**
   - Analyse your situation and what problems you want to address. There are many international guidelines available (see page 38), but you will need to adapt them to your local situation.
   - Define where you are and where you want to go, with quantitative figures. One of the ways of obtaining these data is to measure the quantity and quality of antibiotic use (see Chapter 6).
   - What can be implemented will depend on local needs/issues, geography, available skills/expertise and other resources.
   - For example, easier or less costly approaches can include:
     - Simple clinical algorithms
     - Prescribing guidance for treatment, surgical prophylaxis
     - Intravenous (IV) to oral conversion
     - Provision of microbiological support
     - Restricting availability of certain antibiotics (formulary restriction)
     - Automatic therapeutic substitution
     - IV antimicrobial batching
     - Promoting education.
     - [Coff et al., 2012]

2. **Ensure accountability and leadership**

To ensure a successful Antimicrobial Stewardship Program:

- The program should be supported by the senior hospital management, who are accountable for the outcomes.
- A team of people and resources should be allocated by the head of the organization to implement and evaluate the program.
- The ASP team members must possess power, expertise, credibility and leadership. These individuals need to convince managers and healthcare staff of the added value of the program.

A key component of a stewardship program is leadership and culture of antibiotic use. This can be set out as a driver diagram (see pages 14 and 16 for more details).
Antibiotic Stewardship Team Interaction

Multidisciplinary involvement and core team members for a larger hospital. Smaller hospitals need the same core members, but may not have some of the groups listed.

*ASP=antibiotic stewardship program.

Figure reprinted from Diagnostic Microbiology and Infectious Disease, Vol 61, Owens RC Jr, Antimicrobial stewardship: concept and strategies in the 21st century, pp 110-128, copyright 2008 with permission from Elsevier.

IDSA Guidelines. CID 2007; 44:159-77.
## Antimicrobial Stewardship Program

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Antimicrobial stewardship programs (ASP)

CDC Recommends All Nursing Homes Implement Core Elements to Improve Antibiotic Use

Urged to implement at least one core element immediately

Press Release

For Immediate Release: Tuesday, September 15, 2015
Contact: Media Relations
(404) 639-3286

New recommendations from the Centers for Disease Control and Prevention (CDC) advise all nursing homes to improve antibiotic prescribing practices and reduce their inappropriate use to protect residents from the consequences of antibiotic-resistant infections, such as *C. difficile*.

- “The Centers for Medicare & Medicaid Services (CMS) recently proposed a rule that would require long-term care facilities to incorporate an antibiotic stewardship program, including antibiotic use protocols and antibiotic monitoring, into their infection prevention and control program.”
Improving diagnostic tests

- Procalcitonin as a biomarker in the diagnosis and management of sepsis\(^1,2\)
- PCR for diagnosis of Tb vs mycobacterial culture
- Rapid diagnostic test for *Strep* throat\(^3\)
- RT PCR for the detection of health-care associated bloodstream infections in critical care\(^4\)
- Depressed monocytic activity as a marker of sepsis\(^5\)
- Lactate levels as a marker of hypoperfusion

\(^3\)Lean WL. *Pediatrics*. 2014 Oct;134(4):771-81
Educating patients

- Antibiotics are required only for bacterial infections
- Antibiotics should only be taken by a specific patient when prescribed for that patient
- Patients should be instructed to take the antibiotics as indicated for the complete course
Conclusions

- Antibiotics can be life-saving, but their inappropriate use can lead to antibiotic resistance.
- Antibiotic resistance has a high impact on morbidity, mortality and costs.
- An interdisciplinary approach can diminish antibiotic resistance.
A 49-year-old woman with bronchial asthma is admitted with shortness of breath, sputum production, fever (39 degrees), and leukocytosis (22,000 WBC’s).

Her Chest X-ray was as follows:
Vignette 1

- She underwent a bronchoscopy and was started on ceftriaxone, vancomycin and azithromycin.
- Two days later, she has no fever, sputum production has decreased and WBC are now at 9,000 cells.
- Culture from bronchoscopy reveals a *Streptococcus pneumonia* with the following susceptibility:
  - ampicillin \( S \)
  - erythromycin \( R \)
  - cefazolin \( S \)
  - cefotaxime \( S \)
  - vancomycin \( S \)
Vignette 1

What is the most appropriate action now?

- A. Continue current therapy
- B. Discontinue cetriaxone
- C. Discontinue azithromycin and vancomycin
- D. Switch from vancomycin to linezolid
Vignette 1: Learning Point

- De-escalate if the patient has improved in 48-72 hours and results from appropriate cultures are available
Conclusions

- An interdisciplinary approach, such as an antibiotic stewardship team, can diminish antibiotic resistance
“For better or worse, life would not be the same without microbes”...