Management of Antibiotic-Resistant Pathogens

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I have no disclosures
Overview

• Introduction
  – Burden of antibiotic resistance (AR) – focus on inpatient settings
  – Critical antibiotics – current and under development
  – Diagnosis

• AR pathogens of epidemiologic significance
  – Gram-positive: *S. aureus, Enterococcus*
  – Gram-negative bacilli: ESBL, carbapenem resistance
  – Fungi: *Candida spp*
Learning Objectives

• Antimicrobial Resistance
  – How it develops
  – How it’s detected
  – How it spreads

• Specific and emerging antimicrobial resistance problems
  – Gram-positive: MRSA, VRE
  – Gram-negative: ESBL, carbapenemases, polymyxin resistance
  – Fungal: *Candida auris*

• Strategies to prevent AR infections
Disclaimers

- I am not a clinical microbiologist
- It took me 3 years to learn this stuff, so we won’t cover everything in an hour
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
Factors Contributing to Spread in Hospitals

- **Patient Factors:**
  - Severity of illness
  - Immunocompromising conditions
  - Medical technology and procedures (LDA, open wounds)

- **Infection Control:**
  - Increased introduction of resistant organisms from the community (and residential facilities)
  - Ineffective infection control & isolation practices (esp. compliance)

- **Antibiotic Overuse:**
  - Increased use of antimicrobial prophylaxis
  - Increased use of polymicrobial antimicrobial therapy
  - High antimicrobial use in intensive care units

Chart 1: Resistant Strains Spread Rapidly

Source: Centers for Disease Control and Prevention

This chart shows the increase in rates of resistance for three bacteria that are of concern to public health officials: methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and fluoroquinolone-resistant *Pseudomonas aeruginosa* (FQR). These data were collected from hospital intensive care units that participate in the National Nosocomial Infections Surveillance System, a component of the CDC.

IDSA. Bad Bugs No Drugs. 2004
**Antibiotic Resistance Timeline**

**Antibiotic Resistance Identified**
- penicillin-R *Staphylococcus* 1940
- tetracycline-R *Shigella* 1959
- methicillin-R *Staphylococcus* 1962
- penicillin-R *pneumococcus* 1965
- erythromycin-R *Streptococcus* 1968
- gentamicin-R *Enterococcus* 1979

**Antibiotic Introduced**
- 1943: penicillin
- 1950: tetracycline
- 1953: erythromycin
- 1960: methicillin
- 1967: gentamicin
- 1972: vancomycin

**Events**
- 1985: imipenem and ceftazidime
- 1987: ceftazidime-R *Enterobacteriaceae*
- 1988: vancomycin-R *Enterococcus*
- 1996: levofloxacin-R *pneumococcus*
- 1998: imipenem-R *Enterobacteriaceae*
- 2000: XDR tuberculosis
- 2001: linezolid-R *Staphylococcus*
- 2002: vancomycin-R *Staphylococcus*
- 2004/5: PDR-Acinetobacter and Pseudomonas
- 2009: ceftriaxone-R *Neisseria gonorrhoeae*
- 2010: PDR-Enterobacteriaceae
- 2009: ceftaroline-R *Staphylococcus*
- 2011: ceftaroline-R *Staphylococcus*
Why is this so fast?

• Most antibiotics are microbe-derived products
  – Penicillin: *Penicillium*
  – Cephalosporins: *Acremonium*
  – Carbapenems: *Streptomyces cattleya*
  – Vancomycin: *Amycolatopsis orientalis*
  – Also: tetracyclines, polymyxins, amphotericin B...

• Microbes have been fighting this war for billions of years
  – The genes for resistance are in the genetic pool
Principles of Antibiotic Resistance
(Levy SB. NEJM, 1998)

1. Given sufficient time and drug use, antibiotic resistance will emerge
2. Resistance is progressive, evolving from low levels through intermediate to high levels
3. Organisms resistant to one antibiotic are likely to become resistant to other antibiotics
4. Once resistance appears, it is likely to decline slowly, if at all
5. The use of antibiotics by any one person affects others in the extended as well as the immediate environment
How Antibiotic Resistance Happens

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.

Simply using antibiotics creates resistance. These drugs should only be used to treat infections.
Modern Care Continuum

- Patients may cycle between inpatient facilities, skilled nursing facilities, and home.
- AR pathogens can be acquired at any site and carried to the others.
- Inadequate infection control and poor antibiotic stewardship at any one site can create problems at the others.
CDC Four Core Activities to Fight Resistance

1. Prevent infections, prevent spread of resistance
2. Tracking
3. Improving antibiotic prescribing/stewardship
4. Developing new drugs and diagnostic tests
Antibiotic Pipeline

- Only 9 antibiotics approved since 2010
- Currently ~40 new antibiotics in development
  - Historically, about 1 in 5 will reach the market
- Barrier: limitations on sales
  - AR pathogens still uncommon
  - Brief courses
  - Antimicrobial stewardship
- Policy fixes: extension of patent protection, lower bar for FDA approval
Antibiotics Approved Since 2010

- 2010: Ceftaroline
- 2011: Telavancin
- 2012: Tedizolid, Dalbavancin, Oritavancin, Ceftolozane Tazobactam
- 2013: Ceftazidime/Avibactam
- 2014: Meropenem/Vaborbactam, Delafloxacin
Emerging AR Pathogens of Importance in US Inpatient Settings

• *Enterococcus*:  
  – Ampicillin, vancomycin

• *Staphylococcus aureus*:  
  – Oxacillin, clindamycin, vancomycin?

• Gram-negative enterics:  
  – ESBL, CRE

• *Pseudomonas, Stenotrophomonas, Acinetobacter*

• Fungi:  
  – *Candida krusei, C. auris*
ESKAPE Pathogens

*Enterococcus faecium* (VRE)

*Staphylococcus aureus* (MRSA)

*Klebsiella* and *Escherichia coli* producing ESBL

*Acinetobacter baumannii*

*Pseudomonas aeruginosa*

*Enterobacteriaceae*
Diagnosis of AR Pathogens

Culture
- “Gold standard”
- Requires sampling of site of infection prior to therapy
- Allows determination of antimicrobial susceptibility

PCR
- From blood, still requires an incubation step
- Rapid species identification
- Blood culture systems rapidly detect some resistance mechanisms (e.g., VRE, MRSA), but not 100%
- Direct detection of bacteria (e.g., from CSF or stool) can NOT provide resistance information
Mean Inhibitory Concentration (MIC)

- The MIC is a **phenotypic** test of a bacterial isolate’s growth when exposed to a particular antibiotic
- The lowest concentration of the antibiotic needed to prevent the bacteria from growing
  - Expressed in mcg/mL
- Requires interpretation!!
  - Cannot just pick the lowest MIC from the Micro report
MIC Determination – Broth Microdilution

Known quantity of bacteria placed into each tube

Lowest concentration of an antimicrobial that results in the inhibition of visible growth of a microorganism

Increasing antibiotic concentration

Many Labs Use Automated Testing

MIC Determination – Kirby-Bauer

1. Add test bacteria to small amount of melted agar.
2. Pour over surface of nutrient agar plate, let gel.
3. Add paper disks with known dose of antibiotic to surface.
4. Incubate: antibiotic will diffuse into medium as cells grow.
5. Examine plate: look for clear zones around disk where growth is inhibited.
6. Measure diameter of clear zones.
7. Diameter determines S/I/R
MIC Determination – E-test

- E-test strip impregnated with a known gradient of antibiotic
- Where the clearance zone intersects with the strip $\rightarrow$ MIC
MIC Interpretation

• For EVERY (relevant) combination of species and antibiotic, there is a breakpoint established by CLSI
• Requires understanding of pharmacology of antibiotic
• The breakpoint allows interpretation as susceptible or resistant
  – For example: MIC=1, breakpoint=4 → susceptible
• Not all breakpoints are appropriate.
  – *S. aureus* vancomycin breakpoint is <=2. However, outcomes are worse if MIC=2 than if MIC<=1.
Modes of Antibiotic Therapy

**Empiric**
- Infection suspected
- Pathogen not yet known (may never be found)
- Cover most common possibilities
- Broad, multiple agents, more toxicity

**Directed**
- Infection proven, pathogen identified, susceptibility known or predicted
- Almost always single-agent
- As narrow as possible
- Almost always less toxic
Gram-positive AR Pathogens
**Staphylococcus aureus**

- Community and nosocomial
- Infection types:
  - Skin and soft-tissue
  - Bone/joint
  - Nosocomial and postviral pneumonia
  - Wound infections
  - Bacteremia, CRBSI
  - Endocarditis/endovascular
  - Metastatic infection
**Staphylococcus aureus**

- Plain MSSA can be killed by most beta-lactams (nafcillin, oxacillin, cefazolin...)
  - MSSA may be just as invasive/virulent as MRSA
- Methicillin resistance is common
  - *meca* gene alters the beta-lactam target (can detect by PCR)
  - Treatment: usually vancomycin
  - Options (severe infxn): daptomycin, ceftaroline
  - Options (less severe): linezolid, clindamycin, doxycycline, TMP-SMX
Staphylococcus aureus • Clindamycin resistance – Clindamycin was an effective workaround for MRSA (not bacteremia), but regions are seeing variable rates of resistance • Vancomycin resistance (VISA and VRSA) – Extremely rare (handful of cases of VRSA ever) – However, “MIC creep” is a well-described phenomenon in hospitals with heavy vancomycin use – the most common MIC may rise from 0.5 → 1 → 1.5 → 2

Source: Centers for Disease Control and Prevention

This chart shows the increase in rates of resistance for three bacteria that are of concern to public health officials: methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant enterococci (VRE), and fluoroquinolone-resistant Pseudomonas aeruginosa (FQRP). These data were collected from hospital intensive care units that participate in the National Nosocomial Infections Surveillance System, a component of the CDC.
Healthcare- vs. Community-Acquired MRSA

- HA-MRSA emerged in the 1960s
  - Resistant to more antibiotics
  - Generally less virulent
- CA-MRSA (USA300 strain) emerged in the early 2000s
  - Highly virulent, propensity to cause SSTI
- CA-MRSA strains have moved into healthcare settings
  - Less distinction between the two
Staphylococcus aureus - Summary

• Causes a LOT of infections
  – Nosocomial and community-acquired
• Highly virulent
• We have options for dealing with MRSA
  – But usually more toxic and/or less effective than beta-lactams
  – The threat of MRSA → near-universal use of empiric vancomycin in severe acute infections
  – Can screen and isolate and decolonize patients
• VISA/VRSA are rare but can gradually be uncovered
Enterococcus faecium

- Infections:
  - UTI
  - CRBSI
  - Endocarditis
  - Wounds

- Less virulent than *S. aureus*, but difficult to treat

Antibiotic Resistance of *Enterococcus faecium* in United States

Vancomycin resistance ~75%

Center for Disease Dynamics, Economics & Policy (cddep.org)
Enterococcus faecium

- Generally, enterococci are susceptible to ampicillin but not cephalosporins
  - Tend to be hard to kill and synergistic approaches are used
- *E. faecium* is nearly universally resistant to ampicillin and usually resistant to vancomycin (VRE)
- Rarely encountered outside of healthcare settings
  - Major nosocomial AR pathogen
- High-risk populations (neonates, immunocompromised) can be screened with perirectal swabs
Treatment of VRE

- Vancomycin resistance encoded by genes \textit{vanA} or \textit{vanB}
  - Change in structure of target $\rightarrow$ complete resistance
- Daptomycin is often active
- Linezolid is almost always active
- Others: tigecycline, quinupristin-dalfopristin, telavancin
Gram-negative AR Pathogens
Gram-negative vs Gram-positive

- Both have a cell wall
- Gram-negatives have an outer membrane
- Able to regulate what comes in and out → much more complex
Gram-negative Rods – General Principles

• Genotype may not predict phenotype
• Lab phenotype may not predict clinical phenotype
• Different mechanisms interact (e.g., moderate expression of a beta-lactamase plus an efflux pump may act synergistically)
• Gram-negatives may share plasmid DNA promiscuously
Extended-Spectrum Beta-lactamases (ESBL)

- Large heterogeneous family of enzymes
- “Extended spectrum” generally means activity against penicillins, cephalosporins (including 4th-gen), and aztreonam
- Labs may use 3rd-gen cephalosporin resistance as proxy
- NOT active against carbapenems
- Inhibited by beta-lactamase inhibitors (e.g., tazobactam)
Epidemiology of ESBL

• Frequently found in:
  – *Klebsiella pneumoniae* and *oxytoca, E. coli*

• Less commonly: *Acinetobacter, Burkholderia, Citrobacter, Enterobacter, Morganella, Pseudomonas, Salmonella, Serratia, Shigella*

• **Plasmid**-based, mobile

• In general, one single type tends to predominate in a region or hospital
ESBL – Clinical Strategies

• Often resistant to other antibiotic classes as well (aminoglycosides and fluoroquinolones)
• Beta-lactam strategies
  – Carbapenems have given the best outcomes
  – Avoid cephalosporins (even if reported susceptible)
  – Pip-tazo has been associated with treatment failures. Fine for urine.
Carbapenem Resistance

- Carbapenems are the last-line beta-lactams
- The future of Gram-negative infections
- In Enterobacteriaceae (e.g., *E. coli, Klebsiella, Enterobacter*), carbapenem resistance is mediated by carbapenemases
  - CRE = Carbapenem-resistant Enterobacteriaceae
- *Pseudomonas* may have other mechanisms, such as altered porins and efflux pumps
Carbapenemases

- Major infection control concern
- Most are plasmid-mediated
- In general, active against all beta-lactams
- Generally not inhibited by BLIs
- Examples:
  - KPC = *Klebsiella pneumoniae* carbapenemase
  - NDM = New Delhi metallo-beta-lactamase
Treatment

- Often have resistance to other classes
- Other options
  - Tigecycline (bad for bloodstream infections and pneumonia)
  - Polymyxins: colistin, polymyxin B (extraordinarily toxic)
- Some suggest combination therapy when possible: a polymyxin plus tigecycline +/- carbapenem; polymyxin plus carbapenem or rifampin, etc.
- Newer antibiotics (ceftazidime-avibactam, meropenem-vaborbactam) may be effective and much less toxic.
Polymyxin Resistance

- Colistin and Polymyxin B: last-line antibiotics for resistant Gram-negative infections
  - Abandoned in the 1970s due to toxicity, revived in 2000s
- Resistance is mediated by mcr genes
  - Plasmid-mediated (transmissible)
- Emerged in food animals in China in 2014
  - Now spread across the globe
- Colistin is commonly used in agriculture, especially in China
Tracking the *mcr* genes

**About This Map**
- No isolates reported
- Human isolate
- Animal isolate
**Pseudomonas aeruginosa**

- Important cause of VAP (20 percent), CLABSI (18 percent), CAUTI, SSI
- Can accumulate multiple mechanisms of resistance
  - Often mediated at the outer membrane: porins and efflux pumps
- If *Pseudomonas* is suspected, consider double-coverage for **empiric** therapy: e.g., add tobramycin to cefepime to cover cefepime-resistant isolates
- Double-coverage is generally **not** recommended for **targeted** therapy
Acinetobacter baumanii

- Important nosocomial bacterial pathogen: VAP (8.4 percent), CLABSI, CAUTI, SSI
- Intrinsically resistant to many agents
- Definitions:
  - MDR: non-susceptible >= 1 agent in >= 3 categories (9 total)
  - XDR: non-susceptible to >= 1 agent all but <=2 categories
  - PDR: non-susceptible to all possibly active drugs
- Resistant infections treated with polymyxins + tigecycline or minocycline
Prevention of Resistant Gram-negative infections

• High-risk populations:
  – Trauma, diabetes, malignancy, organ transplantation
  – Mechanical ventilation, indwelling Foley, CVCs
  – Poor functional status, severe illness

• Strategies
  – Antibiotic stewardship
  – Contact precautions
  – During CRE outbreaks, screening for rectal colonization may be a good approach
Antifungal-Resistant *Candida*
Invasive Candidiasis

• Risk factors
  – Trauma, burns
  – Extremes of age
  – Venous catheter
  – TPN
  – Broad-spectrum antibiotic exposure
  – Renal failure
  – Abdominal surgery, GI tract perforations
  – Immunocompromise
Antifungal Agents

1. Triazoles
   – Fluconazole – fairly safe, effective against most *Candida*
   – Voriconazole – slightly broader-spectrum against *Candida*, lots of toxicities and challenging PK

2. Echinocandins (micafungin, caspofungin, anidulafungin)
   – Very broad coverage of virtually all *Candida*. Minimal toxicity.

3. Amphotericin B
   – Very broad coverage. Very toxic.
Antifungal Resistance

• *C. albicans* is usually fully susceptible
  – Historically the most common cause of infection, but non-*albicans* are becoming more common

• Examples
  – *C. krusei* is intrinsically resistant to fluconazole
  – *C. lusitaniae* is usually resistant to amphotericin B
  – *C. glabrata* is often resistant to azoles

• Echinocandin (micafungin, caspofungin) resistance is increasingly seen
**Candida auris**

- Emerging *Candida* species
  - 153 cases in 10 states
- Important concern for Infection Prevention
  - Prolonged patient colonization
  - Prolonged survival on surfaces
- Frequently misidentified by automated lab systems
Candida auris - Significance

- Infections have tended to be severe
- Antifungal resistance
  - Most are resistant to fluconazole/voriconazole
  - 30% are resistant to amphotericin B
  - 5 cases of echinocandin resistance. Can develop on therapy.
  - Specter of pan-resistant Candida
Candida auris

Centers for Disease Control and Prevention
Candida auris

Centers for Disease Control and Prevention
Infection Control for *Candida auris*

- CDC requests immediate reporting (candidaauris@cdc.gov)
- Single-patient room, contact precautions
- Screen index patient’s contacts for colonization
- Disinfection: disinfectants effective against C-diff spores
Dealing with Resistant Pathogens

**Community**
- Provide recommended vaccines
- Avoid unnecessary antibiotics
- Use appropriate drug to cover antibiotic resistant pathogens
- Provide appropriate dose and duration
- Use short course therapy if validated

**Hospital**
- Provide recommended vaccines
- Avoid unnecessary antibiotics
- Practice appropriate infection control
- Avoid prophylactic therapy unless supported by scientific evidence
- Use appropriate drug to cover antibiotic resistant pathogens
- Provide appropriate dose and duration
- Use short course therapy if validated
- Practice de-escalation
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References


