Management of Antibiotic Resistant Pathogens

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Conflicts of Interest

- None

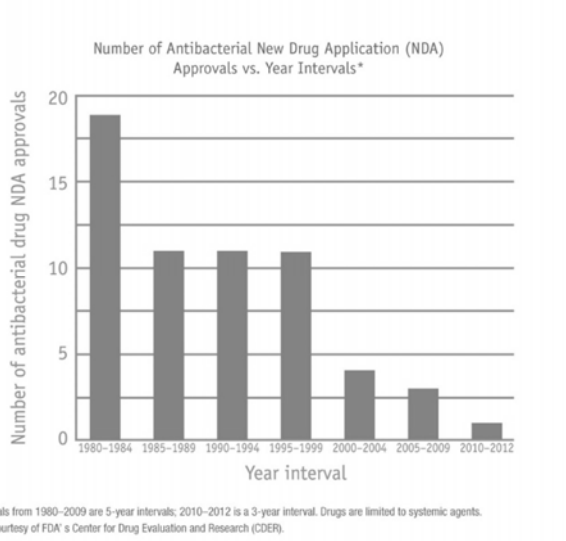
Goals of Lecture

- Current anti-infectives
  - » Antibiotic development
- Antimicrobial Resistance
  - » Factors impacting development and spread of resistance
  - » Mechanisms of Action
  - » Mechanisms of Resistance
  - » Methods for Testing Resistance
- Practical classification of microbes for choosing an antibiotic
  - » Diagnosis
  - » Choosing an appropriate antibiotic therapy
- Methods for Testing Resistance
- Summary of Dealing with Resistant Pathogens

TRENDS IN ANTIMICROBIAL DEVELOPMENT

- Fewer companies producing antibiotics and few antibiotics introduced

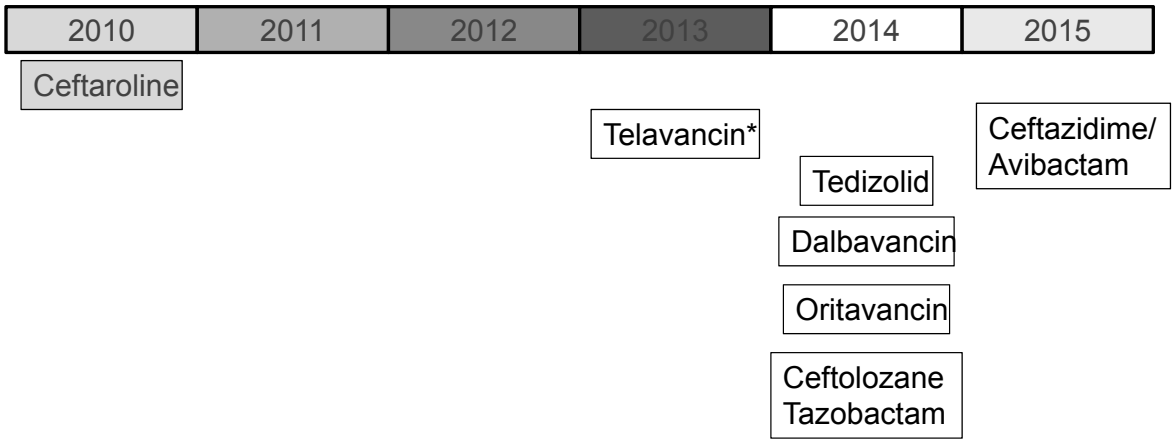
The number of new antibiotics developed and approved has steadily decreased in the past three decades, leaving fewer options to treat resistant bacteria.



TRENDS IN ANTIMICROBIAL DEVELOPMENT

- Broader spectrum
- Reduced dosing frequency
- Novel mechanisms of action and coverage
- Modifications based on understanding structure-function relation
- **Newly introduced agents focused on coverage of resistant *S. aureus* and *Enterococcus*, HIV, and fungi (especially uncommon *Candida* spp. and zygomycetes)**

Antibiotics Approved Since 2010



IDSA
Infectious Diseases Society of America

- American Academy of Pediatrics
- American Gastroenterology Association
- Trust for America's Health
- Society for Healthcare Epidemiology of America
- Pediatric Infectious Disease Society
- Michigan Antibiotic Resistance Reduction Coalition
- National Foundation for Infectious Diseases
- European Society of Clinical Microbiology and Infectious Diseases

Bad Bugs Need Drugs

10x'20

Ten new **ANTIBIOTICS** by 2020

Support the development of 10 new systemic antibacterial drugs through the discovery of new drug classes as well as exploring possible new drugs from existing classes of antibiotics.

Support the concurrent advancement of improved diagnostic tests specific to multidrug-resistant infections

CID (2010) 50: 8, pp 1081-1083.

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

THE WHITE HOUSE

Goals

Goal 1: Slow the Development of Resistant Bacteria and Prevent the Spread of Resistant Infections

Goal 2: Strengthen National One-Health Surveillance Efforts to Combat Resistance

Goal 3: Advance Development and Use of Rapid and Innovative Diagnostic Tests for Identification and Characterization of Resistant Bacteria

Goal 4: Accelerate Basic and Applied Research and Development for New Antibiotics, Other Therapeutics and Vaccines

Goal 5: Improve International Collaboration and Capacities for Antibiotic Resistance Prevention, Surveillance, Control and Antibiotic Research and Development

Key Terms

- Antibiotic = A drug that kills or inhibits the growth of microorganisms
- Resistant = Somewhat arbitrary designation that implies that an antimicrobial will not inhibit bacterial growth at clinically achievable concentrations
- Susceptible = Somewhat arbitrary designation that implies that an antimicrobial will inhibit bacterial growth at clinically achievable concentrations

Key Terms

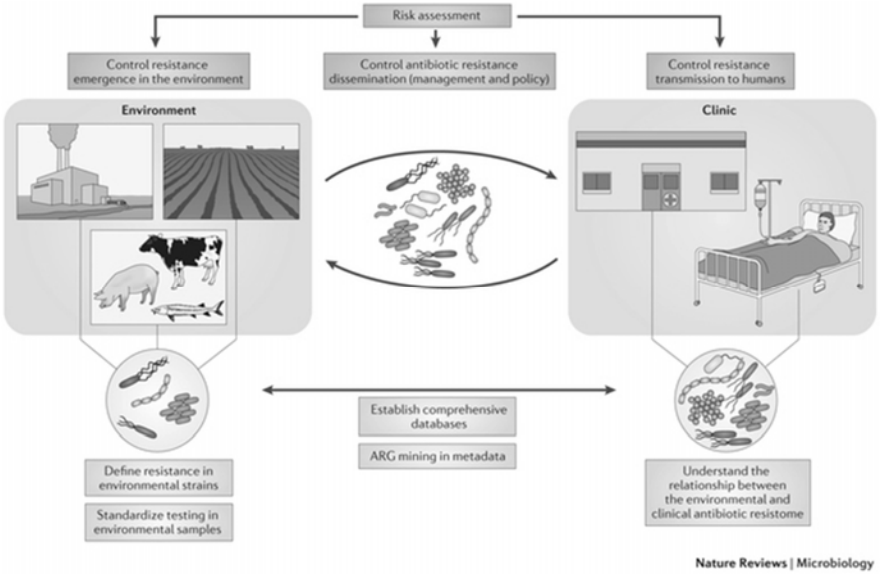
- MIC = Minimal inhibitory concentration. Lowest concentration of antimicrobial that inhibits growth of bacteria. Commonly used in clinical lab
- MBC = Minimal bactericidal concentration. Concentration of an antimicrobial that kills bacteria. Used clinically only in special circumstances
- Breakpoint = The MIC that is used to designate between susceptible and resistant. Arbitrarily set by a committee

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

Selective Pressures: Antimicrobial Use and Resistance



The figure summarizes the current goals (purple boxes) in trying to minimize the emergence and spread of antibiotic resistance genes (ARGs) and antibiotic resistant bacteria (ARB) in the environment and their transmission into the clinic. The current needs and limitations that must be resolved to achieve these goals are also shown (yellow boxes).

Berendonk (2015) Nature Micro.

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OPEN ACCESS PEER-REVIEWED

RESEARCH ARTICLE

Livestock-Associated Methicillin and Multidrug Resistant *Staphylococcus aureus* Is Present among Industrial, Not Antibiotic-Free Livestock Operation Workers in North Carolina

Jessica L. Rinsky, Maya Nadimpalli, Steve Wing, Devon Hall, Dothula Baron, Lance B. Price, Jesper Larsen, Marc Stegger, Jill Stewart, Christopher D. Heaney

Published: July 2, 2013 • D

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

ELSEVIER

Human recreational exposure to antibiotic resistant bacteria in coastal bathing waters

Anne F.C. Leonard, Lihong Zhang, Andrew J. Balfour, Ruth Garside, William H. Gaze *

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RESEARCH ARTICLE

Prevalence of Veterinary Antibiotics and Antibiotic-Resistant *Escherichia coli* in the Surface Water of a Livestock Production Region in Northern China

Xuelian Zhang, Yanxia Li, Bei Liu, Jing Wang, Chenghong Feng, Min Gao, Lina Wang

Published: November 5, 2014 • DOI: 10.1371/journal.pone.0111026

Antibiotic Use Leads to Antibiotic Resistance

- Resistant bacteria or their genetic determinates are selected when colonizing or infecting bacteria are exposed to antibiotics
- Resistant bacteria can then be transmitted between patients
- Highest risk patients:
  - » Immunocompromised
  - » Hospitalized
  - » Invasive devices (central venous catheters)

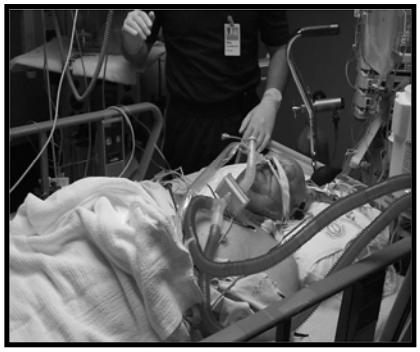
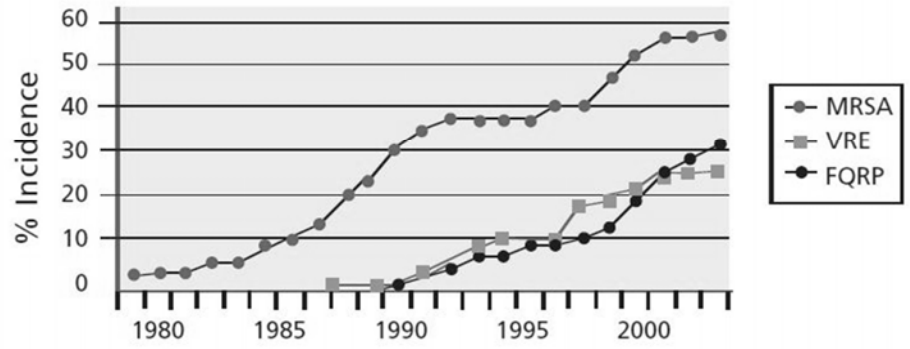


Chart 1: Resistant Strains Spread Rapidly



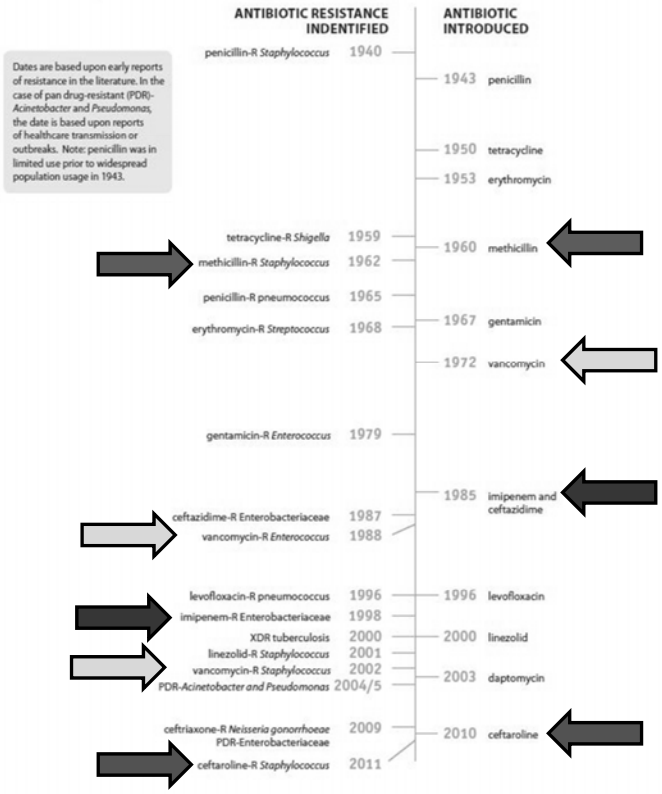
Source: Centers for Disease Control and Prevention

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* (FQRP). These data were collected from hospital intensive care units that participate in the National Nosocomial Infections Surveillance System, a component of the CDC.

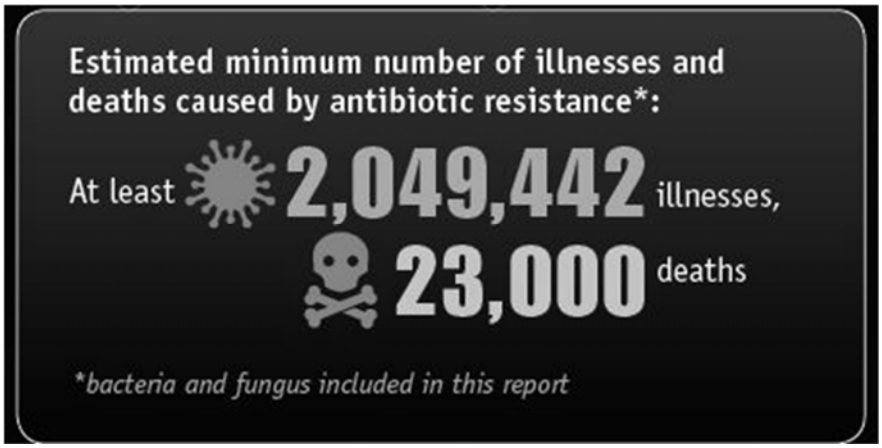
IDSA. Bad Bugs No Drugs. 2004

Developing Resistance

Timeline of Key Antibiotic Resistance Events



MDRO Organisms Are a Growing Threat



EMERGING RESISTANT PATHOGENS: COMMUNITY

- HIV:
  - » Multiple antivirals
- *Pneumococcus*:
  - » Multiple drugs (including penicillins/cephalosporins, macrolides)
- *Staphyloccus aureus*:
  - » Multiple drugs (including oxacillin)
- Gram negative enterics:
  - » Cephalosporins, carbapenems
- Group A streptococcus:
  - » Macolides, tetracyclines
- *Neisseria gonorrhoeae*:
  - » Penicillin, tetracycline, quinolones
- *Salmonella typhimurium*:
  - » Multidrug (amp-, TMP-SMX, +/-quinolones)
- *Mycobacterium tuberculosis*:
  - » MDR (INH, rifampin), XDR (INH, rifampin, others)

ANTIBIOTIC RESISTANCE: FACTORS CONTRIBUTING TO SPREAD IN COMMUNITIES

- Increase in “high-risk” (immunodeficient) population
- Prolonged survival of persons with chronic diseases
- Congregate facilities (e.g., jails, day care centers)
- Lack of rapid, accurate diagnostic tests to distinguish between viral and bacterial infections
- Increased use of antibiotics in animals & agriculture

Source: Segal-Maurer S. ID Clin NA 1996;10:939-957.

ANTIBIOTIC RESISTANCE: FACTORS CONTRIBUTING TO SPREAD IN COMMUNITIES

Reasons for Antibiotic Overuse : Conclusions from 8 Focus Groups

Patient Concerns
- Want clear explanation
- Green nasal discharge
- Need to return to work

Physician Concerns
- Patient expects antibiotic
- Diagnostic uncertainty
- Time pressure

Antibiotic Prescription

Barden L.S. Clin Pediatr 1998;37:665

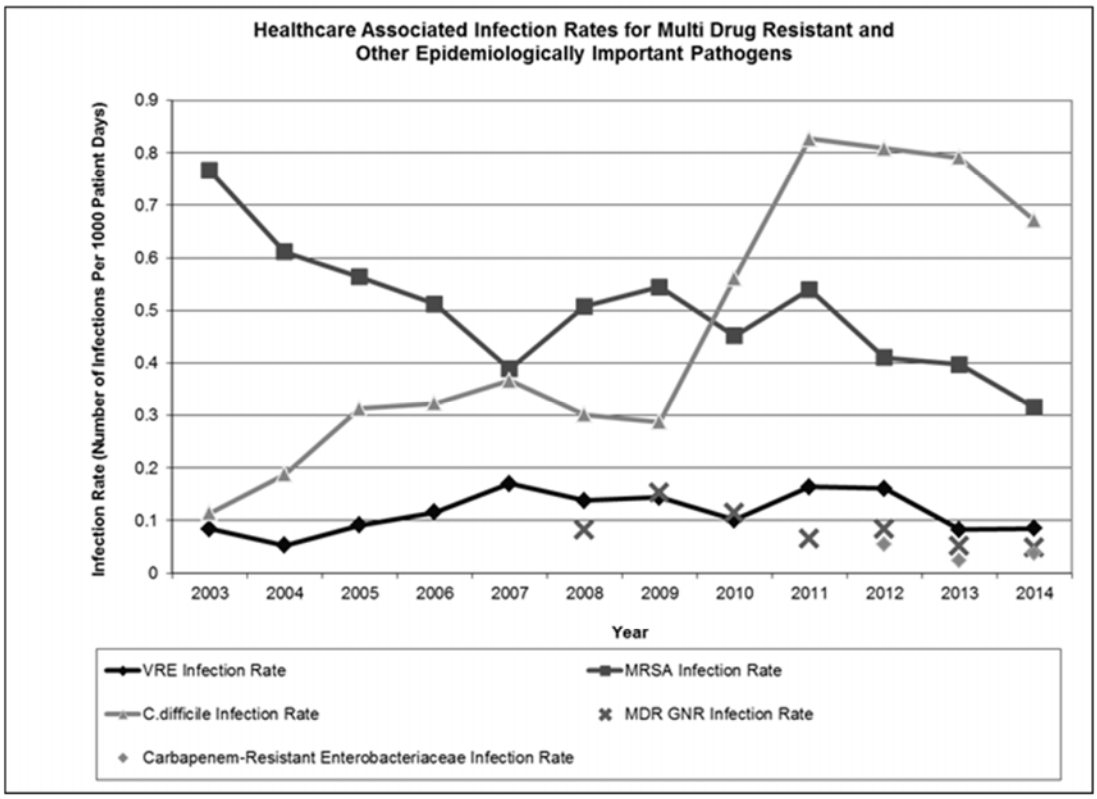
EMERGING RESISTANT PATHOGENS: HEALTH CARE FACILITIES

- *Staphylococcus aureus*:
  - » Oxacillin, vancomycin, linezolid
- *Enterococcus:*
  - » Penicillin, aminoglycosides, vancomycin, linezolid, dalfopristin-quinupristin
- *Enterobacteriaceae:*
  - » ESBL producers, carbapenems
- P. aeruginosa, *Acinetobacter* spp:
  - » β-lactams including carbapenems
- *Candida spp*.:
  - » Fluconazole
- *Mycobacterium tuberculosis*:
  - » MDR (INH, rifampin); XDR (multiple)

ANTIBIOTIC RESISTANCE IN HOSPITALS: FACTORS CONTRIBUTING TO SPREAD IN HOSPITALS

- Greater severity of illness of hospitalized patients
- More severely immunocompromised patients
- Newer devices and procedures in use
- Increased introduction of resistant organisms from the community
- Ineffective infection control & isolation practices (esp. compliance)
- Increased use of antimicrobial prophylaxis
- Increased use of polymicrobial antimicrobial therapy
- High antimicrobial use in intensive care units

Source: Shlaes D, et al. Clin Infect Dis 1997;25:684-99.



ESKAPE Pathogens

*E**nterococcus faecium* (VRE)

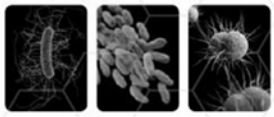
*S**taphylococcus aureus* (MRSA)

*K**lebsiella* and *Escherichia coli* producing ESBL

*A**cinetobacter baumannii*

*P**seudomonas aeruginosa*

*E**nterobacteriaceace*

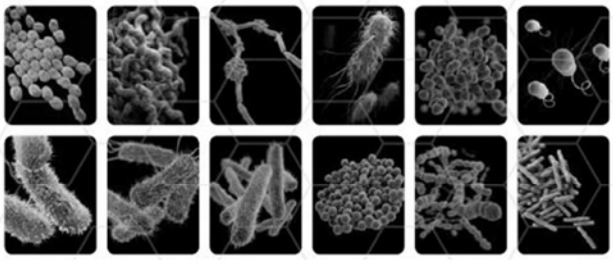


THREAT LEVEL **URGENT**

These bacteria are immediate public health threats that require urgent and aggressive action.

MICROORGANISMS WITH A THREAT LEVEL OF URGENT

Clostridium difficile
Carbapenem-resistant **Enterobacteriaceae**
Drug-resistant ***Neisseria gonorrhoeae***

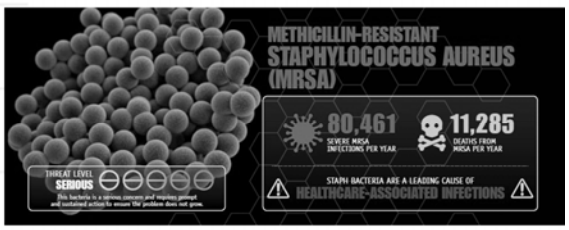


THREAT LEVEL **SERIOUS**

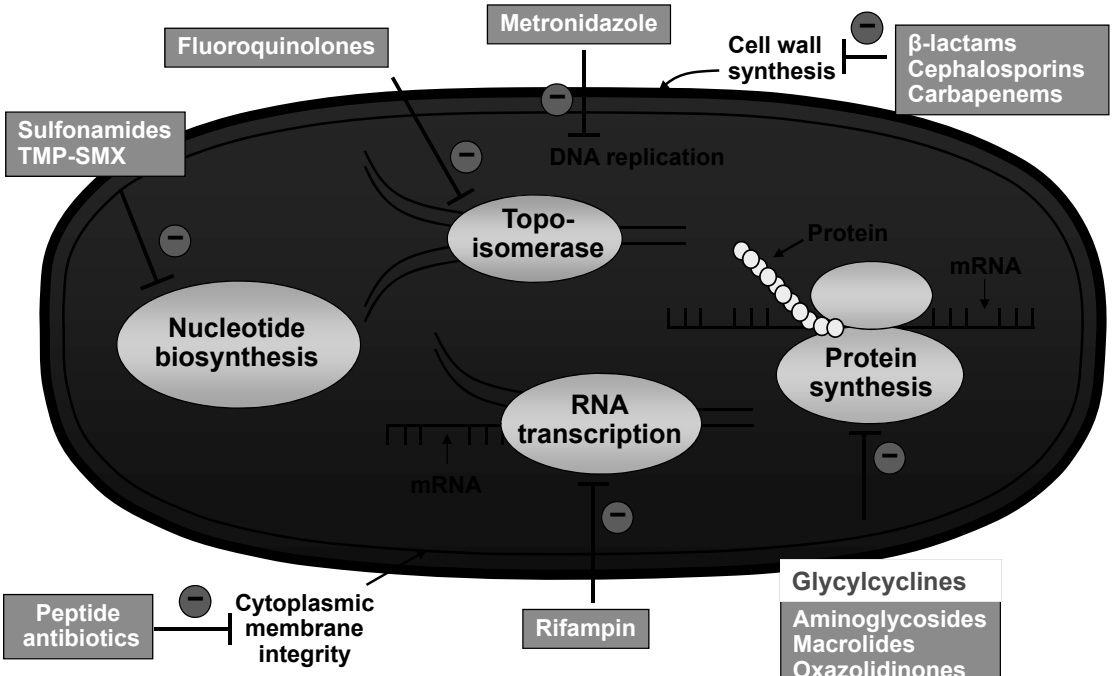
These bacteria are a serious concern and require prompt and sustained action to ensure the problem does not grow.

MICROORGANISMS WITH A THREAT LEVEL OF SERIOUS

Multidrug-resistant ***Acinetobacter***
Drug-resistant ***Campylobacter***
Fluconazole-resistant ***Candida*** (a fungus)
Extended spectrum β-lactamase producing **Enterobacteriaceae (ESBLs)**
Vancomycin-resistant ***Enterococcus*** **(VRE)**
Multidrug-resistant ***Pseudomonas aeruginosa***
Drug-resistant **non-typhoidal *Salmonella***
Drug-resistant ***Salmonella* Typhi**
Drug-resistant ***Shigella***
Methicillin-resistant ***Staphylococcus aureus*** **(MRSA)**
Drug-resistant ***Streptococcus pneumoniae***
Drug-resistant **tuberculosis**



Mechanisms of Action of Antibiotics



TMP-SMX = trimethoprim-sulfamethoxazole.

Adapted from: Chopra I. *Curr Opin Pharmacol*. 2001;1:464-469.

ANTIBACTERIALS: MECHANISMS

- Interference with cell wall synthesis (bactericidal)
  - » Penicillins: Oxacillin, ampicillin, piperacillin
  - » Cephalosporins: 1^{o}, 2^{o}, 3^{o}, 4^{o}, 5^{o} cephalosporins
  - » Carbapenems: Imipenem, meropenem, ertapenem, doripenem
  - » Monobactams: Aztreonam
  - » Glycopeptides: Vancomycin, Dalbavancin, Oritavancin, Telavancin

ANTIBACTERIALS: MECHANISMS

- Inhibition of DNA gyrase (bactericidal)
  - » Quinolones: Ciprofloxacin, levofloxacin, moxifloxacin

ANTIBACTERIALS: MECHANISMS

- Interference with ribosomal function
  - » Aminoglycosides (bactericidal): Gentamicin, tobramycin, amikacin
  - » Tetracyclines: Tetracycline, minocycline, doxycycline
  - » Glycylcyclines: Tigecycline
  - » Macrolides: Erythromycin, azithromycin, clarithromycin
  - » Chloramphenicol
  - » Lincosamines: Clindamycin
  - » Oxzalidinone: Linezolid
  - » Streptogramin: Dalfopristin-quinupristin

ANTIBACTERIALS: MECHANISMS

- Antimetabolites
  - » Sulfonamides
  - » Trimethoprim-sulfamethoxazole
- Inhibition of DNA-directed RNA polymerase
  - » Rifampin, rifapentine, rifabuten
- Degradation of DNA
  - » Metronidazole
- Cyclic lipopeptide (effects calcium transport)
  - » Daptomycin

Mechanisms of Resistance

Antibiotic Degrading Enzymes

- Sulfonation, phosphorylation, or esterifictation
  - » Especially a problem for aminoglycosides
- β-lactamases
  - » Simple, extended spectrum β-lactamases (ESBL), cephalosporinases, carbapenemases
  - » Confer resistance to some, many, or all beta-lactam antibiotics
  - » May be encoded on chromosome or plasmid
  - » More potent in gram-negative bacteria

Mechanisms of Resistance

Antibiotic Degrading Enzymes

- Extended spectrum β-lactamases
  - » Can hydrolyse extended spectrum cephalosporins, penicillins, and aztreonam
  - » Most often associated with *E. coli* and *Klebsiella pneumoniae* but spreading to other bacteria
  - » Usually plasmid mediated
  - » Multiple resistance genes (often Aminoglycoside, ciprofloxacin and trimethoprim-sulfamethoxazole) encoded on same plasmid

- Class A Carbapenemase
  - » Most common in *Klebsiella pneumoniae* (KPC)
  - » Also seen in *E. coli, Enterobacter, Citrobacter, Salmonella, Serratia, Pseudomonas* and *Proteus spp.*
  - » Very often with multiple other drug resistance mechanisms, resistance profile similar to ESBL but also carbapenem resistant
  - » Spreading across species to other gram-negatives and enterobacteriaceae

Mechanisms of Resistance

Decreased Permeability

- Affects many antibiotics including carbapenems

Efflux Pumps

- Tetracyclines
- Macrolides

Mechanisms of Resistance

Target Alteration

- DNA gyrase
  - Fluoroquinolones
- Penicillin-binding protein
  - Methacillin/penicillin
- Gram positive cell wall
  - Vancomycin
- Ribosome
  - Tetracyclines
  - Macrolides

Principles of Antibiotic Therapy

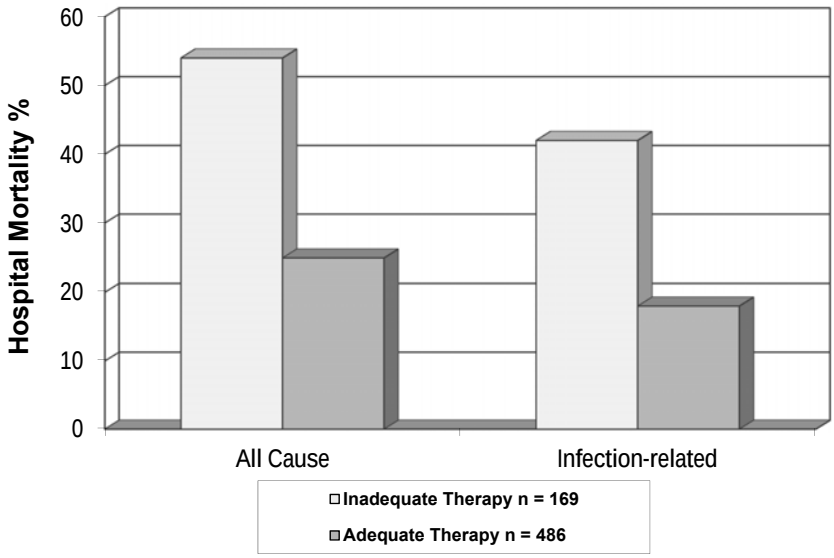
Empiric Therapy (85%)

- Infection not well defined ("best guess")
- Broad spectrum
- Multiple drugs
- Evidence usually only 2 randomized controlled trials
- More adverse reactions
- More expensive

Directed Therapy (15%)

- Infection well defined
- Narrow spectrum
- One, seldom two drugs
- Evidence usually stronger
- Less adverse reactions
- Less expensive

IMPACT OF ANTIMICROBIALS



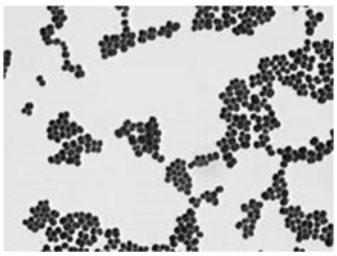
Kollef *Chest* 115:462, 1999

DIAGNOSIS

- Gram stain
  - » Often provide clues to etiology (may allow presumptive diagnosis in some cases)
- Gram Stain
  - » Gram Positive
  - » Gram Negative
  - » Non-staining
- Shape
  - » Cocci
  - » Rods

GRAM POSITIVE ORGANISMS

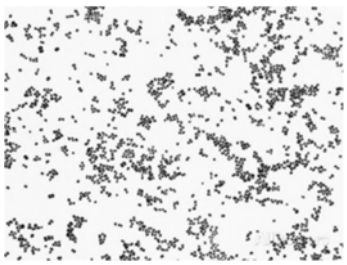
- Gram positive cocci
  - » *Staphylococcus aureus*
  - » Coagulase negative staphylococcus
  - » *Pneumococcus* sp.
  - » *Streptococcus* sp.
  - » *Enterococcus* sp.



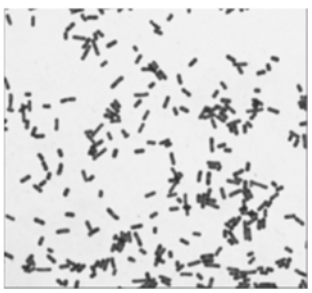
- Gram positive rods
  - » *Bacillus* sp. (aerobes)
  - » *Clostridial* sp. (anaerobes)

GRAM NEGATIVE ORGANISMS

- Gram negative cocci
  - » *Neisseria meningitidis*
  - » *Neisseria gonorrhoeae*

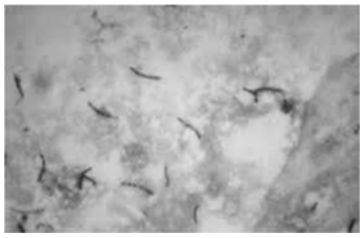


- Gram negative rods (non-enteric)
  - » *Pseudomonas aeruginosa*
  - » *Stenotrophomonas maltophilia*
  - » *Acinetobacter* sp.
  - » *E. coli*
  - » *Klebsiella* sp.
  - » *Enterobacter* sp.
  - » *Proteus* sp.
  - » *Serratia* sp.



NON-STAINING PATHOGENS

- Not stained by Gram's method
  - » *Legionella* sp.
  - » *Chlamydia*
  - » *Rickettsia*
  - » Mycobacteria
    - *M. tuberculosis*
    - Non-tuberculous mycobacteria



Ziehl-Neelsen Stain of TB

DIAGNOSIS

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

Evidence for Efficacy

- *In vitro* activity (discussed later)
- Clinical trials
  - » Gold standard = randomized clinical trial
  - » Should be comparative (best available alternative)
  - » Should use appropriate population
  - » Small number precludes discovery of rare adverse reactions

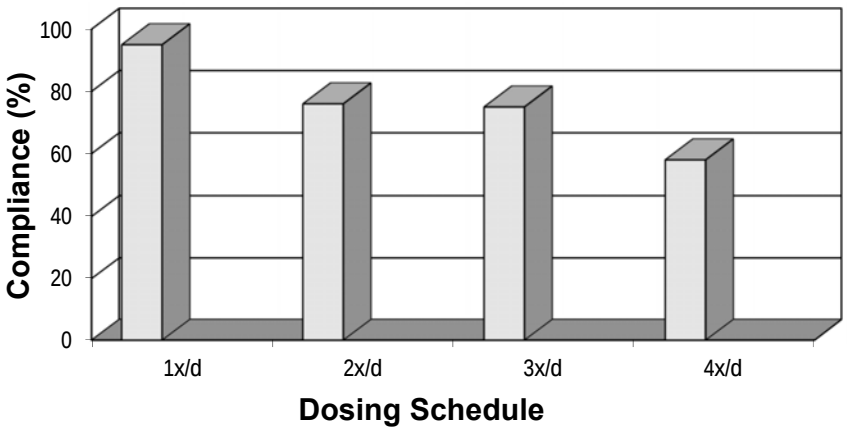
Patient Safety

- Drug interactions
- Age
- Pregnancy, breast feeding
- Toxicity (idiosyncratic reactions)
- Dose adjustment for renal dysfunction
- Dose adjustment for hepatic dysfunction
- Ability to absorb an oral antibiotic

Adherence/compliance

- Frequency of administration
- Duration of therapy
- Multiple drug therapy
- Adverse effects
- Reduction of symptoms
- Taste
- Cost

COMPLIANCE RELATED TO DOSING



Cockburn J BMJ 1987

Antibiotics with Gram (+) Activity

S. aureus	MRSA	VRE	*E. faecalis*
Nafcillin/Oxacacillin			Ampicillin
Amp/Sulb, Pip/Tazo			Amp/Sulb, Pip/Tazo
Cephalosporins	Ceftaroline (only)		
Carbapenems			
Fluoroquinolones			
Vancomycin	Vancomycin		Vancomycin
Clindamycin	Clindamycin +/-		
Quin/Dalf	Quin/Dalf	Quin/Dalf	
Linezolid	Linezolid	Linezolid	Linezolid
Daptomycin	Daptomycin	Daptomycin	Daptomycin
Telavancin	Telavancin		
TMP-SMX	TMP-SMX		

Antibiotics with Gram (-) Activity

E. coli	*K. pneumoniae*	*Enterobacter*	*P. aeruginosa*
Ampicillin			
Amp/sulb	Amp/sulb		
Piperacillin	Piperacillin	Piperacillin	Piperacillin
Pip/Tazo	Pip/Tazo	Pip/Tazo	Pip/Tazo
Cephalosporins	Cephalosporins	3rd, 4th, 5th gen.	Ceftaz/Cefepime
Carbapenems	Carbapenems	Carbapenems	Imip, Mero, Dori
Aztreonam	Aztreonam	Aztreonam	Aztreonam
Aminoglycosides	Aminoglycosides	Aminoglycosides	Amino-glycosides
Fluoroquinolone	Fluoroquinolone	Fluoroquinolone	Cipro and Levo
Trimeth/Sulf	Trimeth/Sulf	Trimeth/Sulf	

Antibiotics with Anti-anaerobic Activity

- ß-lactams
  - » Ampicillin/Sulbactam*, Piperacillin/Tazobactam*
  - » Carbapenems (imipenem, meropenem, doripenem, ertapenem)*
  - » Cefoxitin
  - » Cefotetan

- Chloramphenicol
- Metronidazole*
- Clindamycin
- Tigecycline*

* Highly active

Comparison of Antimicrobials[1]

Organism	Vancomycin	Daptomycin	Linezolid	Ceftaroline	Telavancin	Tedizolid	Oritavancin	Dalbavancin
Streptococcus Grp A,B,C,G	+	+	+	+	+	+	+	+
Streptococcus pneumoniae	+	+[2]	+	+	+	+	+	+
Enterococcus faecalis	+	+	+	+	+	+	+	+
Enterococcus faecium	±	+	+	-	+	+	+	+
MSSA	+	+	+	+	+	+	+	+
Coagulase-negative Staph.	+	+	+	+	+	+	+	+
VRE	-	+	+	±[3]	±	+	+	±
MRSA	+	+	+	+	+	+	+	+
VISA	-	±	±	±	+	-	+	+
VRSA	-	±	±	±	-	-	+	-

MRSA, methicillin-resistant *S. aureus;* MSSA, methicillin-resistant *S. aureus;* VRE, vancomycin-resistant *Enterococcus;* VRSA, vancomycin-resistant *S. aureus*

1: Cefolozane/tazobactam has activity against some *Streptococcus* species, but not *Staphylococcus* species and is not included.

2: Not appropriate for respiratory tract infections (e.g., pneumonia); 3: Not active against *E. faecium*

Comparison of Antimicrobials

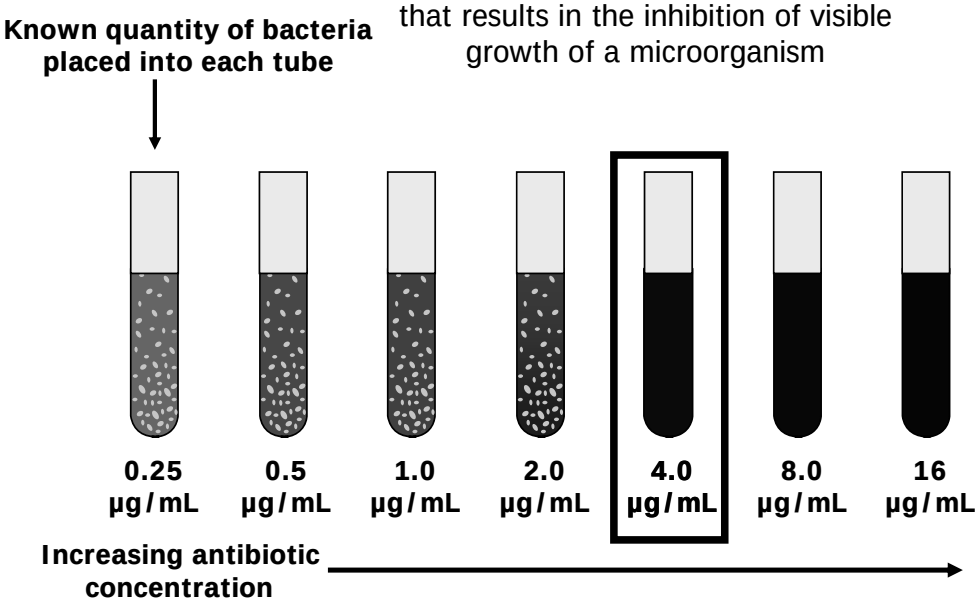
Organism	Meropenem	Piperacillin/ tazobactam	Ceftriaxone	Cefepime	Ceftaroline	Cefolozane/ tazobactam
E.coli	+	+	+	+	+	+
H. influenzae	+	+	+	+	+	-
Klebsiella sp.	+	+	+	+	+	+
Enterobacter sp.	+	+	+	+	+	+
Proteus mirabilis	+	+	+	+	+	+
Pseudomonas aeruginosa	+	+	-	+	-	+
Acinetobacter sp.	±	±	-	±	-	-
ESBL-GNR	+	±	-	-	-	±
CRE	-	-	-	-	-	-

- CRE, carbapenemase resistant Enterobacteriaceae
- ESBL, extend β-lactamase producing Gram negative rods (*E. coli, Klebsiella* spp., *Enterobacter* spp.)
- GNR, Gram negative rods

Methods for Testing Resistance and Efficacy

Methods for Testing Resistance: Minimal Inhibitory Concentration

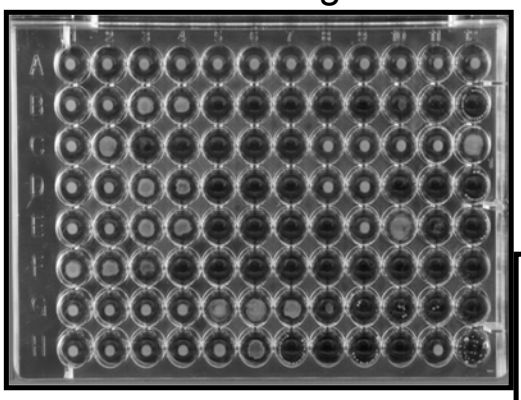
Lowest concentration of an antimicrobial that results in the inhibition of visible growth of a microorganism



Sinus and Allergy Health Partnership. *Otolaryngol Head Neck Surg*. 2000;123(1 Pt 2):S1.

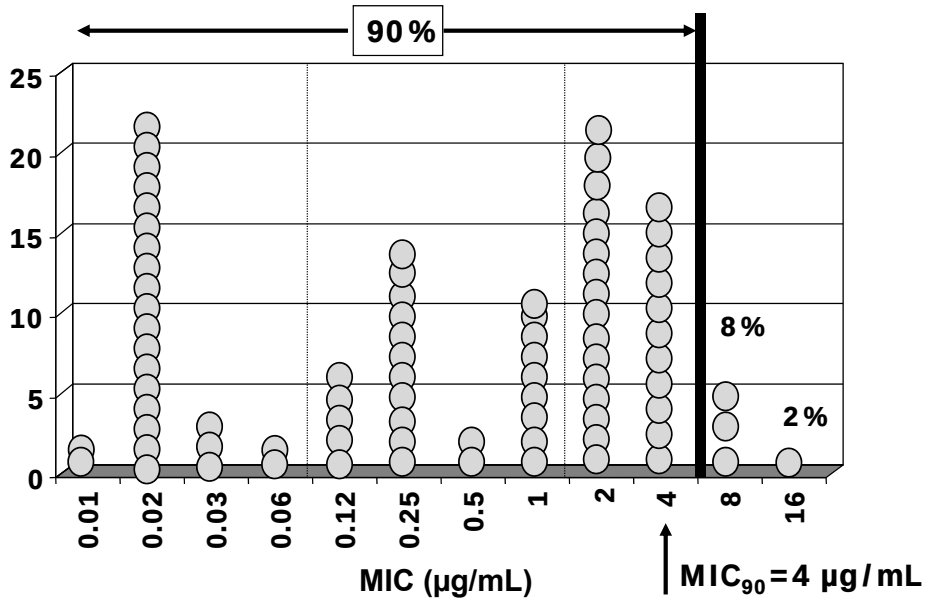
Methods for Testing Resistance: Automated Minimal Inhibitory Concentration

Well Plate for MIC Testing

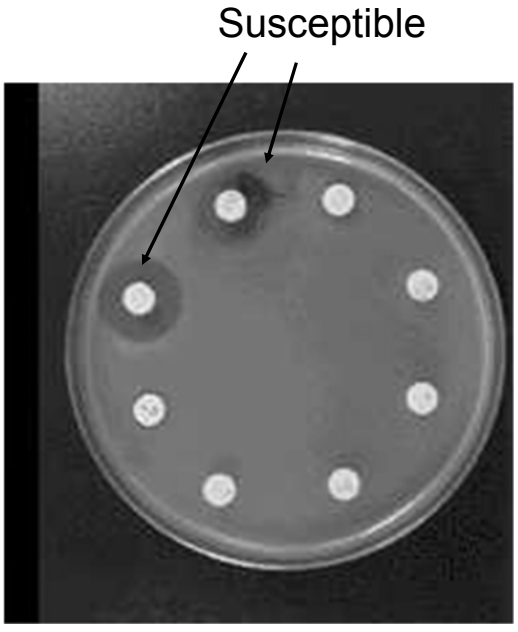


Many Labs Use Automated Testing

MIC_{90}: Lowest Concentration That Inhibits Growth of 90% of Isolates

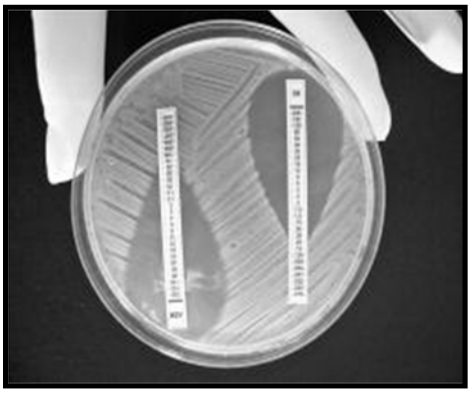


Methods for Testing Resistance: Kirby-Bauer Disc Diffusion Test



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.

Methods for Testing Resistance: E-test Strip



E-test®

Concept of Breakpoint to Determine Susceptibility

EXAMPLE:
Susceptibility testing for a single isolate of *Pseudomonas aeruginosa*

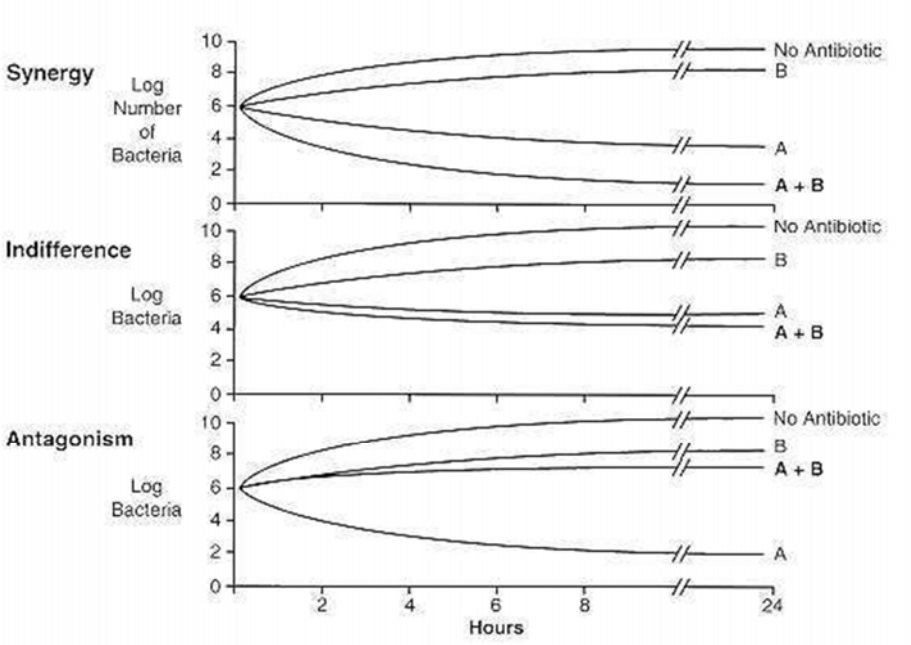
-Breakpoint for intermediate resistance for meropenem is 4 and for piperacillin/tazobactam (pip/tazo) 32

-Pip/tazo is the better choice between the two

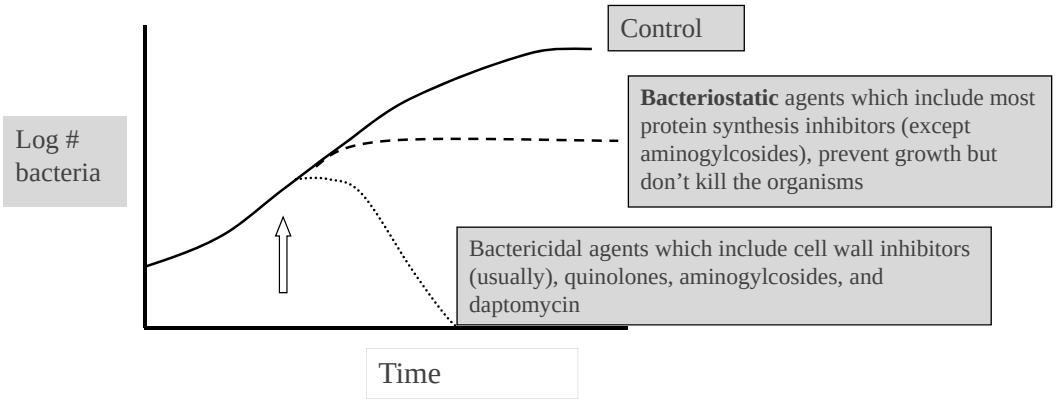
-Ciprofloxacin is a poor choice even though the MIC is lowest of the three

Antibiotic	MIC	Breakpoint	Susceptibility
Ampicillin	>16	8	Resistant
Gentamicin	2	4	Susceptible
Cephalothin	>16	N/A	Resistant
Cefepime	8	32	Susceptible
Cefotaxime	16	16/32	Intermediate
Ceftazidime	2	32	Susceptible
Aztreonam	4	16	Susceptible
Ciprofloxacin	2	2	Resistant
Amp/Sulbactam	>16	8	Resistant
Meropenem	4	4/8	Intermediate
Pip/tazo	8	32-64/128	Susceptible

Principles of Antibacterial Therapy: Synergy and Antagonism of Antibiotics



Principles of Antibacterial Therapy: Bacteriostatic or Bactericidal



Bactericidal agents required for meningitis, endocarditis and infections in neutropenic hosts

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**
- **Use early IV to PO switch**

Acknowledgements

- David Weber (slides)
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