



Anti-Infective Therapy

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Newsweek

ANTIBIOTICS

THE END OF MIRACLE DRUGS?

WARNING

**NO LONGER
EFFECTIVE
AGAINST
KILLER
BUGS**

Outline

- Misconceptions about antibiotics
- What you need to know to prescribe
 - Pharmacokinetics
 - Toxicity
 - Spectrum
- Concept of narrow vs. broad-spectrum
- Logical approach to selecting antibiotics

Key points about Anti-Infective Therapy

1. Too often antibiotics are prescribed to fulfill the patient's expectations, rather than to treat a true bacterial infection.
2. A single antibiotic cannot fulfill all infectious disease needs.
3. Physicians ignore the remarkable adaptability of bacteria, fungi and viruses at their patient's peril.
4. Anti-infective therapy is dynamic and requires a basic understanding of microbiology

Key points about Anti-Infective Therapy

5. The “shotgun” approach to infectious diseases must end, or we may truly experience the end of the antibiotic era

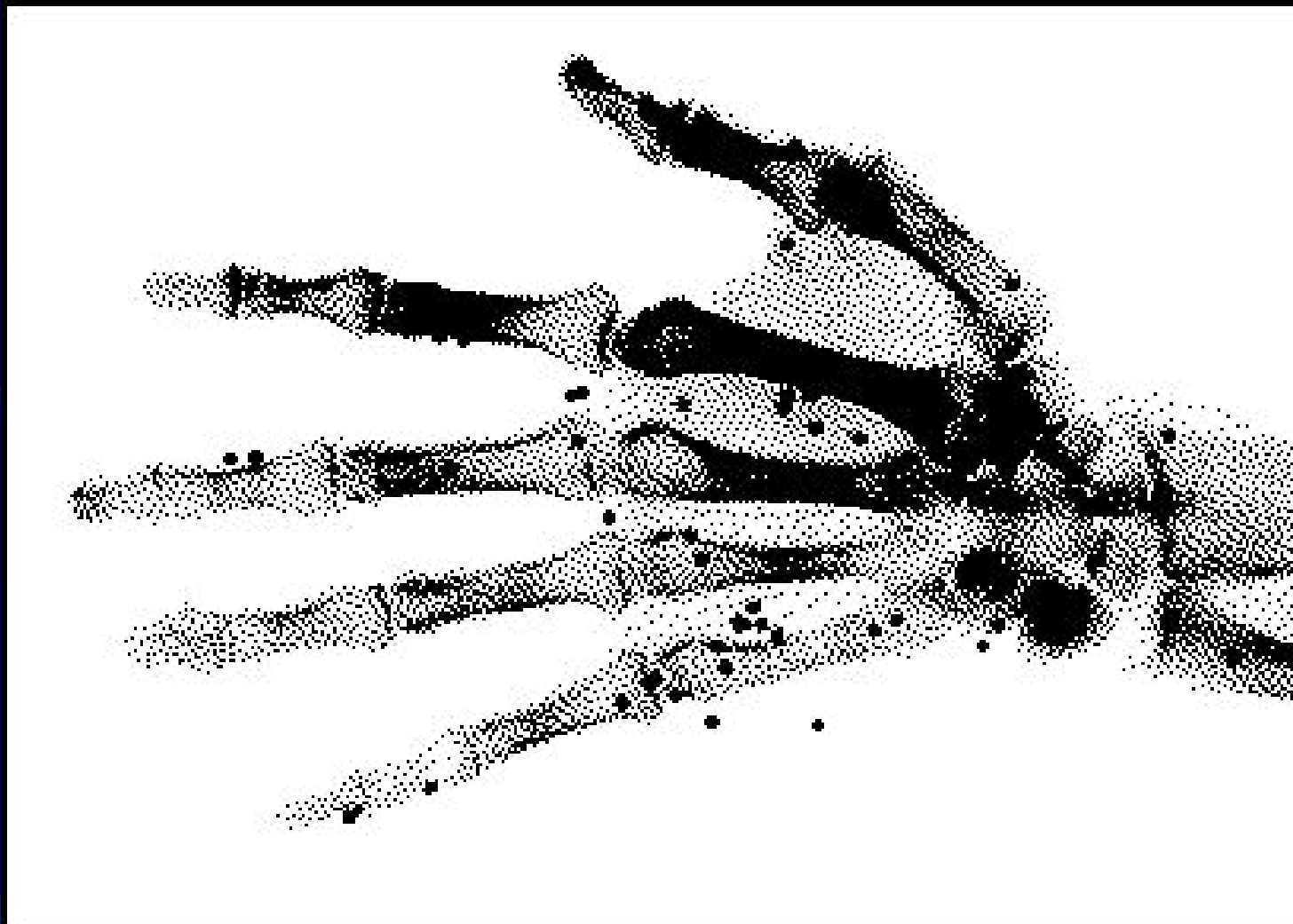


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Question 1

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Problem of Collateral Damage

Key points about antibiotic resistance

Bacteria can quickly alter their genetic makeup by:

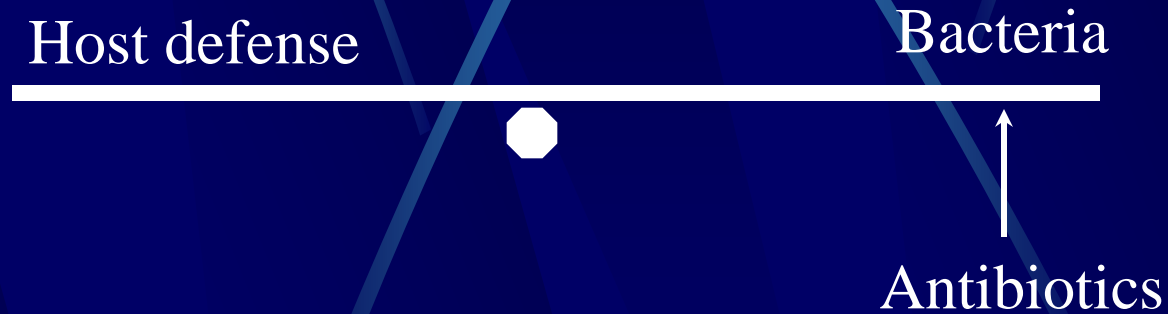
1. Point mutations
2. Transfer of DNA by plasmid **conjugation**
3. Transfer of DNA by bacteriophage **transduction**
4. Transfer of naked DNA transposons by **transformation**

The ability of bacteria to share their DNA provides a survival advantage, allowing them to quickly adapt to antibiotic exposure.

Three Biochemical mechanisms

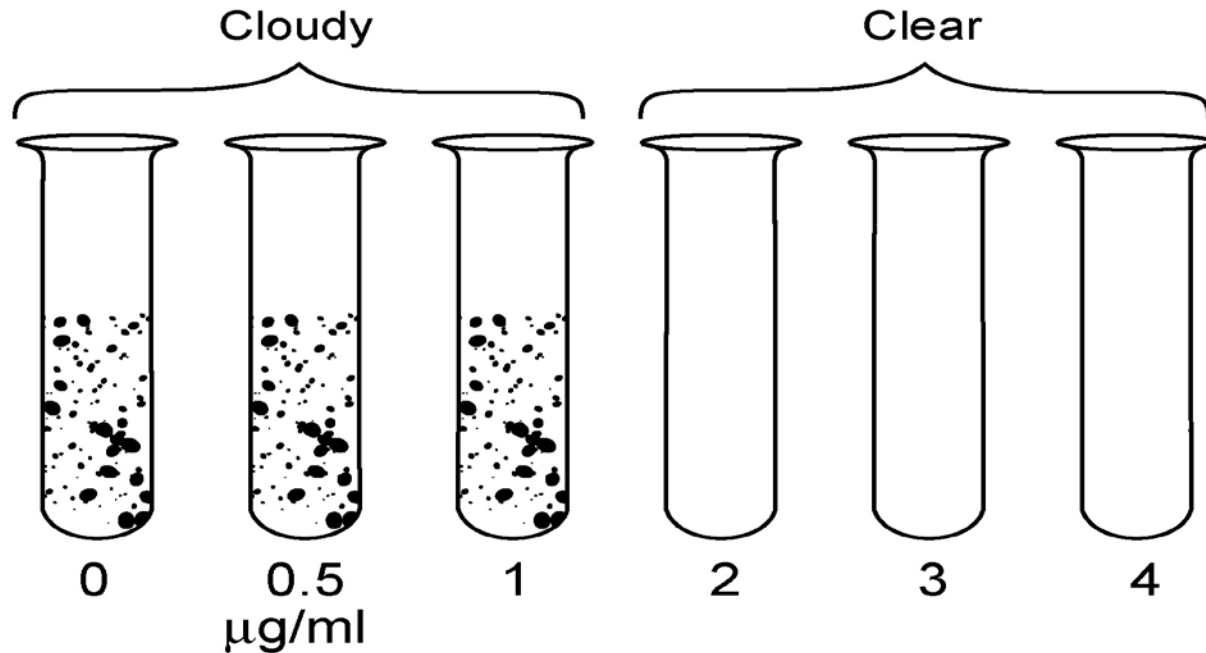
1. Degradation or modification of the antibiotics
 - β -lactamases
 - Esterases
2. Reduction in antibiotic concentration
 - Pumps
 - Porins
3. Modification of the antibiotic target
 - Penicillin binding proteins
 - D-Ala-D-Ala to D-Ala-D-lactate (VRE)
 - Demethylation of ribosomal RNA

Balance between host defense and the bacteria

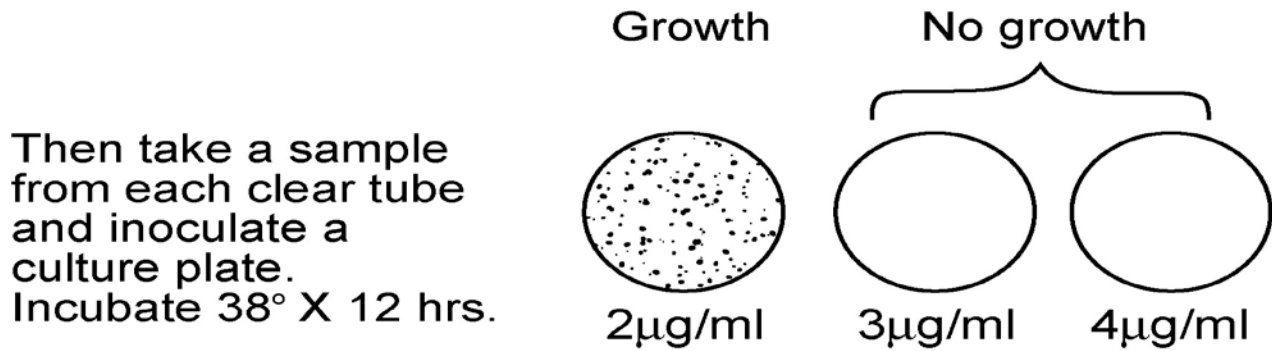


MIC & MBC

Inoculate all tubes with 10^4 bacteria incubate 38°C X 12 hrs



Minimal Inhibitory Concentration (MIC) = $2\mu\text{g/ml}$



Then take a sample from each clear tube and inoculate a culture plate. Incubate 38° X 12 hrs.

Minimal Bacterial concentration (MBC) = $3\mu\text{g/ml}$

- MIC (Minimal Inhibitory Concentration)
 - MIC determined for each pathogen by serially diluting the antibiotic in liquid media containing 10^4 bacteria/ml
 - Then incubate tubes 24 hours
 - MIC read as lowest concentration of antibiotic that prevents bacterial growth (clear media)
- MBC (Minimal Bactericidal Concentration)
 - Take the clear tubes from above, plate on solid media
 - Lowest concentration of antibiotic that blocks all growth is MBC
- Automated systems used in lab (Microscan, uses breakpoints)

“The material on specific antibiotics is overwhelming”

Should know:

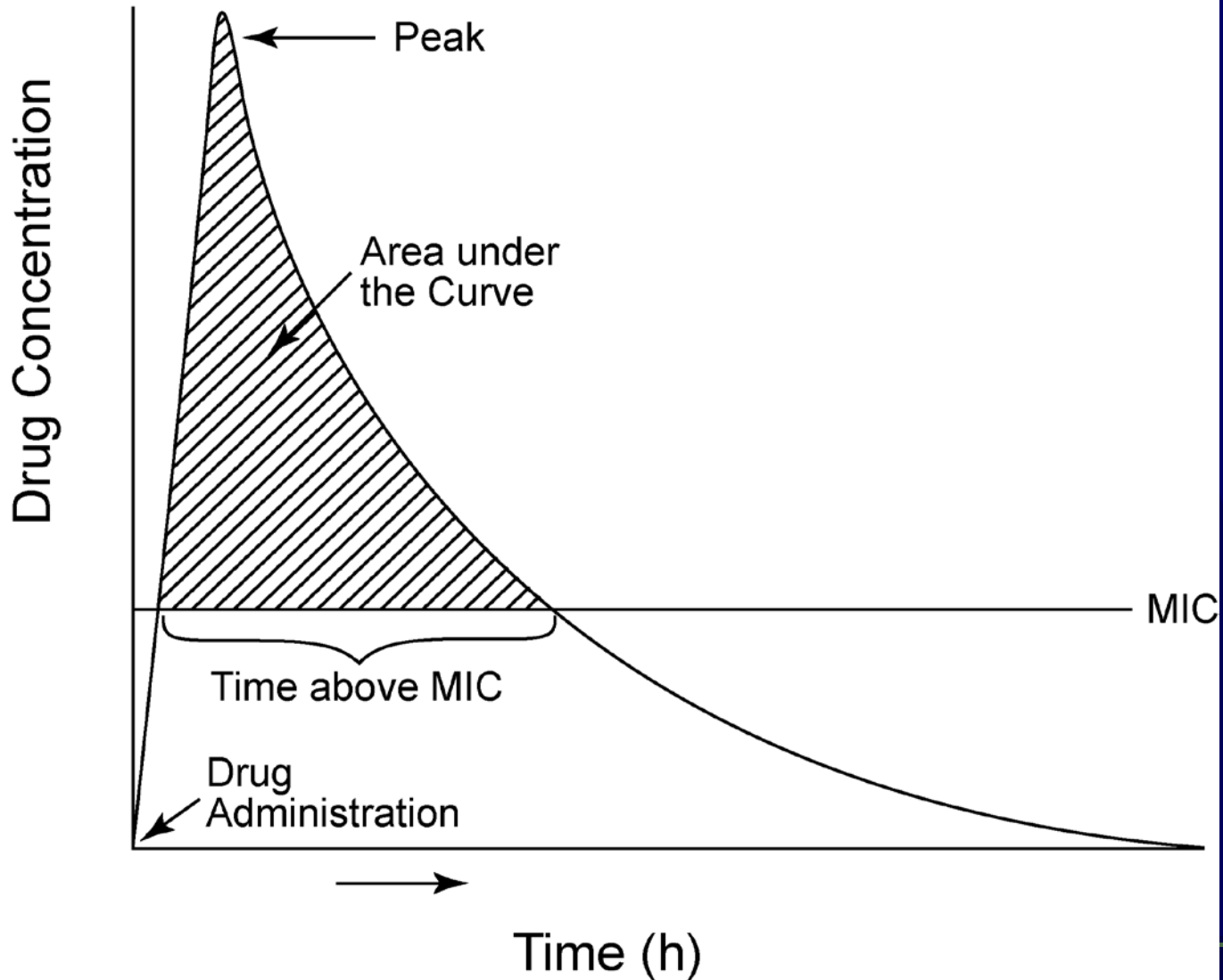
Different classes of antibiotics

- Mechanisms of action
- Major toxicities
- How they are primarily metabolized
- What bacteria they kill (only roughly, ie. Gram-positive, Gram-negative)
- Which types of infections they primarily used for treatment

Factors that affect serum antibiotic levels

- Absorption (when have po antibiotic)
- Volume of distribution
- Metabolism/ Excretion

Pharmaco Kinetics of a Typical Antibiotic



For effective treatment

- Cell wall agents: Need to maintain antibiotic level above the MIC for at least 50% of time interval
 - PCNs
 - Cephalosporins
 - Carbapenem
 - Vancomycin
 - Concentration dependent killing, high peak is important
 - Quinolones
 - Aminoglycosides
- (Also see a post-antibiotic effect)
- “I didn’ t fully understand what post-antibiotic effect meant”

Question 2

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In order to dose antibiotics

- Need to know how the drug is cleared
 - Most antibiotics, renal clearance
 - Penicillins (short half-life)
 - Most cephalosporins (half-life depends on agent)
 - Carbapenems (half-life depends on agent)
 - Aminoglycosides (short-intermediate half-life)
 - Vancomycin (intermediate half-life)
 - Quinolones (intermediate to long half-life)
 - Sulfonamides ((half-life depends on agent)
 - Some hepatic clearance
 - Ceftriaxone (long half-life)
 - Macrolides (half-life depends on agent)
 - Tetracyclines (long half-life)
 - Clindamycin (short half-life)
 - Chloramphenicol (intermediate half-life)
 - Linezolid (intermediate half-life)
- (short = 30 min-2 h, intermediate 3-6 hr, long >7 h)



Question 3

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Must be familiar with toxicities

- Penicillins -allergic reactions
 - Immediate IgE-mediated (hives, wheezing)
 - Delayed hypersensitivity (skin rash)
- Cephalosporins -few allergic reactions, **safest drug class** (5% cross-reactivity with PCN)
- Macrolides - GI toxicity
- Fluoroquinolones - cartilage effects
- Aminoglycosides - **most toxic class**
 - Renal failure
 - Ototoxicity (hair cells)
 - Neuromuscular blockade
- Tetracyclines - photosensitivity, dental enamel
- Sulfonamides - allergic reactions
- Clindamycin - C. difficile colitis
- Chloramphenicol - bone marrow toxicity, Grey baby
- Linezolid - bone marrow toxicity

Classic Maculo-papular Drug Rash

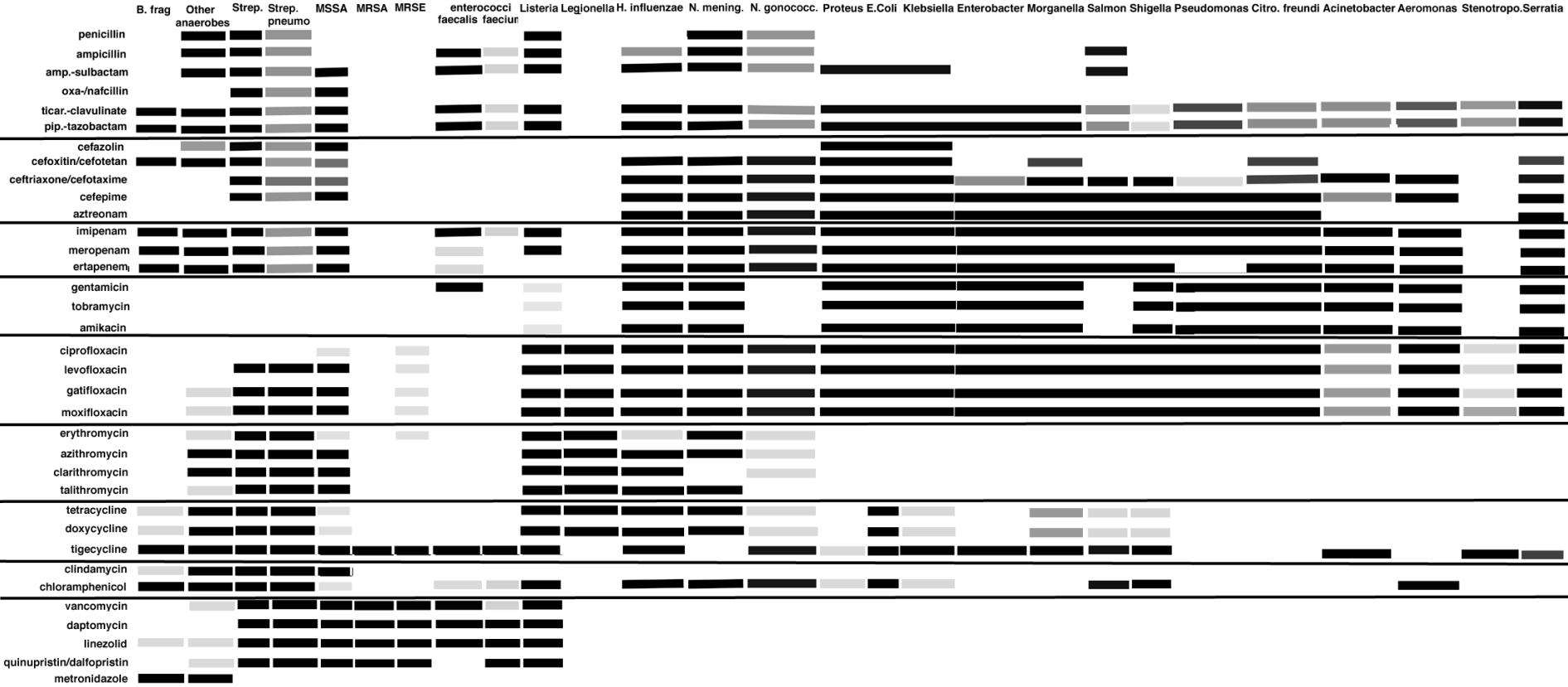


Hives



Must know the bacterial spectrum

Antibiogram of all Major Antibiotics (prepared by Frederick Southwick)

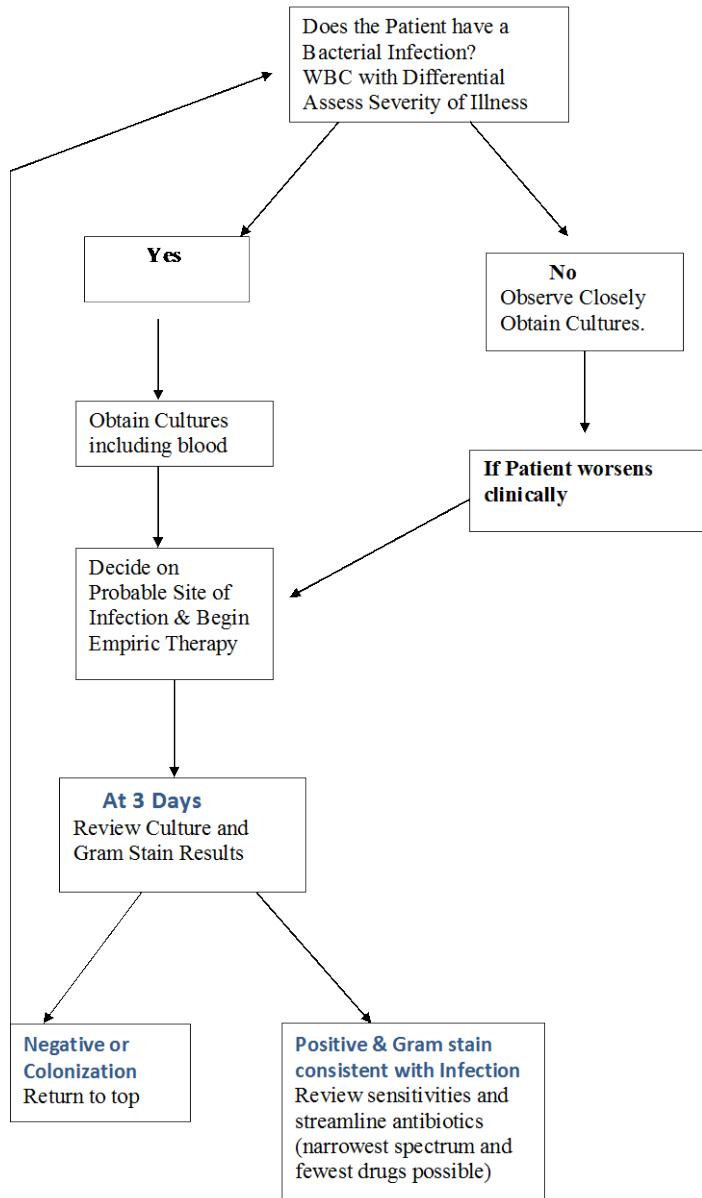


Blank = not recommended
 Light gray = < 30% susceptibility
 Darker gray = 30-60% susceptibility
 Black = 61-95% susceptibility

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Antibiotics Classified by Spectrum

Narrow	Moderately Broad	Broad	Very Broad
Penicillin	Ampicillin	Ampicillin-sulbactam Amoxicillin-clavulinate	Ticarcillin-clavulinate Piperacillin-tazobactam
Oxacillin/ Nafcillin	Ticarcillin Piperacillin	Ceftriaxone, Cefotaxime Ceftizoxime, Ceftazidime	Imipenem Meropenem
Cefazolin Cephalexin	Cefoxitin Cefotetan	Cefixime Cefpodoxime proxetil	Gatifloxacin Moxifloxacin
Aztreonam	Cefuroxime-axitel Cefaclor	Cefepime	
Aminoglycosides	Ciprofloxacin	Tetracycline Doxycycline	
Vancomycin	Trimethoprim- sulfamethoxazole	Chloramphenicol	
Macrolides		Levofloxacin	
Clindamycin			
Lanazolid			
Synercid™			
Metronidazole			



Key points about the steps required to design an antibiotic regimen

1. Assess the probability of bacterial infection
(antibiotics should be avoided in viral infections)
 - WBC count is helpful (Procalcitonin?)
 - History is helpful
 - Cannot always differentiate

Key points about the steps required to design an antibiotic regimen

2. Be familiar with the primary pathogens responsible for infection at each anatomic site
 - Symptoms often localize the site of infection as can diagnostic tests
 - You will be learning these facts during the systemic section of our course.

Key points about the steps required to design an antibiotic regimen

3. Be familiar with the bacterial flora in your hospital
 - Our hospital has MRSA everywhere
 - Gainesville has MRSA in the community
 - Resistant Gram-negative rods in SICU
4. Take into account previous antibiotic treatment
 - If had Abx within 2 weeks highly likely to be due to a resistant organism

Key points about the steps required to design an antibiotic regimen

5. Take into account the specific host factors
 - age
 - immune status
 - hepatic and renal function
 - duration of hospitalization
 - severity of illness

Key points about the steps required to design an antibiotic regimen

6. Use the minimum number and narrowest spectrum antibiotics possible
7. Switch to a narrower spectrum antibiotic regimen based on culture results (**Streamline**)
8. Take into account acquisition cost and the costs of toxicity (example aminoglycosides)

Question 4

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Obey the 3-Day Rule –

Continuing broad-spectrum antibiotics beyond 3 days drastically alters the host's normal flora selecting for resistant organisms (Primarily an inpatient issue).

After 3 days streamline your antibiotics. Use narrower spectrum antibiotics to specifically treat the pathogens identified by culture and Gram stain.

Key points about Colonization

- 1) Growth of resistant organisms is the **rule** in the patient on antibiotics.
- 2) Antibiotics should be switched only if there is evidence for a **new infection**

To be discussed in our Respiratory Lecture and CMC

Conclusions

- Antibiotics can do harm and must be used judiciously
- Must know their toxicities, pharmacokinetics, and spectrum to properly use
- Must know the basics of infectious diseases to make the best guess
- Use the narrowest spectrum possible.
- Don't use the "shotgun" approach

