Principles of Antibiotic Therapy - Handout

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1 Introduction

1.1 Antibiotics - The Medical Miracle

Antibiotics have revolutionized medicine and dramatically reduced mortality from bacterial infections.

1.2 Medicine Pre-Antibiotics

Before antibiotics, doctors relied on limited treatments including alcohol prescriptions and herbal remedies.

1.3 Dawn of Antibiotic Discovery

Key discoveries:

- **Paul Ehrlich** - Salvarsan (1909)
- **Alexander Fleming** - Penicillin (1929), purified by Florey, Chain, Heatley (1940)
- **Gerhard Domagk** - Sulfanilamides (1931)

1.4 Mortality Reduction with Antibiotic Therapy

Disease	Pre-antibiotic era	Antibiotic era	Change
Community-acquired pneumonia	~35%	~10%	-25%
Nosocomial pneumonia	~60%	~30%	-30%
Bacterial endocarditis	~100%	~25%	-75%
Gram-negative bacteremia	~70%	~10%	-60%
Bacterial meningitis	>80%	<20%	-60%
Cellulitis	~11%	<0.5%	-10%

(Spellberg, 2025a)

2 Current Challenges

2.1 Antibiotic Resistance

Antibiotic resistance is a growing global health threat. The WHO has identified priority pathogens including:

- **Critical Priority**: Carbapenem-resistant Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacteriaceae
- **High Priority**: MRSA, vancomycin-resistant Enterococcus, etc.

2.2 Slowing Antibiotic Discovery

New antibiotic development has dramatically slowed while resistance continues to increase.

2.3 Antibiotics as a Societal Trust

- Antibiotic overprescription represents a “tragedy of the commons”
- Individual prescriptions may seem harmless, but collective impact is catastrophic
- Physicians must serve as experts in use and protection of antimicrobial agents

3 The 10 Principles of Effective Antibiotic Therapy

3.1 Principle #1: Accurate Differential Diagnosis

Medical history is the most important diagnostic tool

Key elements: - Current symptoms (8 cardinal descriptors: Timing, Location, Character, Aggravating Factors, Alleviating Factors, Associated Symptoms, Severity, Setting) - Fever patterns - Risk factors for infection - Travel and exposure history - Sexual history - Vaccination status - Past medical/surgical history - Social history

3.1.1 Case Example: Brucellosis Spondylitis

A 34-year-old sheep and cattle farmer from Sicily with back pain. Detailed history revealed occupational exposure leading to diagnosis of Brucellosis, requiring specialized treatment with Gentamicin + Doxycycline + Rifampin.

3.1.2 Antibiotics Are Usually Started Empirically

The typical timeline: - 0h: Suspect infection - 1h: Culture suspected sites, **begin empiric therapy** - 24h: Gram stain results - 36-48h: Identification - 72-96h: Susceptibilities available, **change to definitive therapy**

Important: 90-98% of upper respiratory tract infections are caused by viruses and do not require antibiotics.

3.2 Principle #2: Only Use Antibiotics When They Alter Clinical Course

- Antibiotics should be part of a rational therapeutic plan, not a reflexive response
- Patients without bacterial infections cannot benefit from antibiotics
- Consider ethical dilemmas: end-of-life care, non-adherent patients

3.2.1 Risks of Antibiotic Therapy

> **Warning**
>
> - 1 in 5 patients given antibiotics are harmed by adverse events or superinfection
> - Every additional 10 days of therapy = 3% increased risk of adverse effects

3.2.2 Positive Cultures Proof of Infection

Without symptoms, positive cultures often represent colonization or contamination: - Wound swabs - Urine cultures (asymptomatic bacteriuria) - Respiratory samples - Stool cultures

3.3 Principle #3: Empirically Target Microbes in Differential Diagnosis

3.3.1 Know the Spectrum of Activity

Use resources like the Sanford Guide to understand antibiotic coverage.

3.3.2 Community vs. Nosocomial Infections

Community infections: - Infrequently caused by MDR gram-negative bacteria - Avoid routine MRSA coverage unless risk factors present - Reserve last-line agents (e.g., fluoroquinolones) for appropriate cases

Nosocomial infections: - More likely caused by resistant pathogens - May require coverage for Pseudomonas or non-fermenting gram-negatives - Greater MRSA risk, especially with recent antibiotic use

3.4 Principle #4: Lower Threshold for Empirical Therapy in Critically-Ill Patients

3.4.1 Antibiotic Timing is Critical in Septic Shock

Early appropriate antibiotic therapy dramatically improves survival in septic shock. Each hour of delay in appropriate therapy increases mortality. (Kumar et al., 2006)

3.5 Principle #5: Host Factors Affect Spectrum of Empirical Therapy

3.5.1 Common Immunocompromised Conditions

1. Chronic diseases (diabetes, COPD)
2. Autoimmune diseases
3. Genetic diseases
4. Cancer/chemotherapy
5. HIV
6. Transplant recipients
7. Advanced age
8. Malnutrition

9. **Chronic corticosteroid use** (>10 mg prednisone equivalents for 2-4 weeks)
10. Chronic infections
11. Smoking

3.5.2 Special Consideration: PCP vs. CAP

Immunocompromised patients on corticosteroids may develop Pneumocystis jirovecii pneumonia (PCP) rather than typical community-acquired pneumonia.

3.6 Principle #6: Use PK/PD Principles to Optimize Treatment

3.6.1 Key Pharmacokinetic Variables

Volume of Distribution (Vd): - Volume that appears to hold the drug at plasma concentration - Average plasma volume: ~3L - Higher Vd = lower serum concentrations - Important for loading dose calculations

Clearance (CL): - Drug elimination from body (mL/min or L/hr) - CL total = CL renal + CL hepatic + CL other - Important for maintenance dose calculations - Affected by organ function

3.6.2 Important Distinctions

- Vd and CL are physiologically-based but do not interact
- **Vd determines loading dose**
- **CL determines maintenance dose**
- Most antibiotics eliminated via kidneys - adjust for renal function

3.6.3 Renal Function Estimation

Cockcroft-Gault formula:

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}) \times \text{weight (kg)}}{72 \times \text{SCr (mg/dL)}} \times 0.85 \text{ (if female)}$$

Problems with creatinine-based dosing: - Based on chronic kidney disease, not acute - Delayed decrease in creatinine with injury resolution - May lead to unnecessary underdosing in first 48 hours

3.6.4 PK/PD Indices

Three main patterns: - **Concentration-dependent**: Peak/MIC ratio (aminoglycosides, fluoroquinolones) - **Time-dependent**: %T>MIC (-lactams) - **AUC-dependent**: AUC/MIC ratio (vancomycin, linezolid)

3.6.5 Site-Specific Considerations

- Match antibiotic penetration to infection site
- Anatomically-privileged sites (CNS, eye, prostate) require special consideration
- Urinary concentrations often much higher than serum
- Daptomycin inactivated in lung (don't use for pneumonia)
- Aminoglycosides bound by purulent material (emphasizes need for source control)

3.7 Principle #7: De-escalate Based on Microbiology and Clinical Response

3.7.1 De-escalation Strategies

- Stop unnecessary coverage when pathogen identified
- Clinical improvement (reduced fever, leukocytosis)
- Stop empiric therapy for resistant pathogens if not isolated
- Use biomarkers appropriately (procalcitonin)

3.7.2 Gram Stain-Guided Therapy

Gram stain results can guide early de-escalation, reducing use of anti-pseudomonal agents by 30% and MRSA agents by 40%. (Yoshimura et al., 2022)

3.7.3 Susceptibility Testing

Mean Inhibitory Concentration (MIC) determines which antibiotics are appropriate for documented infections.

3.8 Principle #8: If Therapy Not Working, Consider Source Control or Alternative Diagnosis

3.8.1 Treatment Failure Indicators

- Persistent fever
- Elevated white blood cell count
- Continued purulent secretions
- Ongoing signs of inflammation
- Biomarker elevation

3.8.2 Source Control Issues

Common problems: - Occult abscess formation - Empyema - Biofilm on indwelling devices - Failure to remove infected foreign material

3.8.3 Remember: Antibiotic FAIL

- **F**alse diagnosis
- **A**llergies
- **I**ntercurrent infections
- **L**ocalized process requiring drainage

3.9 Principle #9: Distinguish New Infection from Failure of Initial Therapy

- New symptoms after resolution suggest new infection, not persistence
- Rarely, emergence of resistance from initial pathogens
- Reculture and image if necessary
- Reasonable to broaden therapy in patients with recent antibiotic exposure
- Change one antibiotic at a time when possible

3.10 Principle #10: Duration Should Be As Short As Possible

3.10.1 Evidence for Shorter Courses

Disease	Short course	Long course	Outcome
Bacteremia, gram-negative	7 days	14 days	Equivalent
COPD exacerbation	5 days	7 days	Equivalent
Intra-abdominal infection	4 days	10 days	Equivalent
Neutropenic fever	Until stable	Until non-neutropenic	Equivalent
Osteomyelitis, chronic	42 days	84 days	Equivalent
Pneumonia, CAP	3-5 days	7-10 days	Equivalent
Pneumonia, VAP	8 days	10-15 days	Equivalent
Pyelonephritis	5-7 days	10-14 days	Equivalent
Skin infections	5-6 days	10-14 days	Equivalent
Sinusitis, acute	5 days	10 days	Equivalent

(Spellberg, 2025b)

4 Common Myths of Antibiotic Therapy

4.1 Myth #1: "Bactericidal" Antibiotics Are More Effective Than "Bacteriostatic"

4.1.1 Evidence Against This Myth

- 56 randomized controlled trials reviewed
- 49/56 found no difference in clinical outcomes
- 6 trials showed linezolid (bacteriostatic) superior to bactericidal agents
- Examples of failed superiority:
  - Daptomycin vs. vancomycin for S. aureus bacteremia

  - Adding aminoglycosides to -lactams (no benefit, more toxicity)

(Wald-Dickler et al., 2017)

4.2 Myth #2: Oral Antibiotics Are Less Effective Than IV

4.2.1 Modern Evidence

Osteomyelitis: Historical poor outcomes with drugs having low bone concentrations (sulfanilamide, erythromycin, tetracycline). Modern antibiotics achieve excellent bone levels.

Meta-analyses show equivalence for: - Osteomyelitis - Bacteremia
- Endocarditis

(Wald-Dickler et al., 2022)

4.2.2 Transition to Oral Therapy Checklist

- Patient hemodynamically stable?
- Functioning GI tract?
- Can take drugs by mouth?
- Antibiotic option with good bioavailability available?

Key: Many modern antibiotics have excellent oral bioavailability (fluoroquinolones, linezolid, metronidazole, etc.)

4.3 Myth #3: Combination Therapy Is Always Better

4.3.1 The Good: When Combination Helps

Broader spectrum needed: - Adding macrolide/doxycycline for atypicals in pneumonia - High MDR prevalence requiring broader coverage

Preventing resistance: - Tuberculosis (slow growth, persisters, high bacterial density) - HIV and hepatitis C (resistance = fatal outcome)

Superior outcomes with two agents: - Rifampin combinations for bone/joint infections (reduces relapse) - Cryptococcal meningitis (amphotericin B + 5-FC) - Necrotizing fasciitis (add clindamycin/linezolid to stop toxin production)

Eukaryotic infections: - Multiple life cycle stages require different agents - Pharmacokinetic interactions enhance penetration

4.3.2 The Bad: Redundant Definitive Therapy

- Few data supporting two active agents for acute pyogenic bacterial infections
- Organisms in planktonic growth, not multiple life phases
- Single agent pharmacology and killing is good

Pseudomonas aeruginosa: Meta-analysis shows no benefit of combination therapy, with increased toxicity risk. (Hu et al., 2013)

4.3.3 The Ugly: Imperfect Data

- Fungal infections outside cryptococcosis: unclear benefit (except possible Aspergillus with echinocandins + triazoles)
- Theoretical benefit in test tubes may not translate clinically
- Greater selection for resistance
- Greater microbiome impact

5 Conclusions

- Antibiotics are miracle cures that fundamentally altered medical practice
- Their power to treat infections is fleeting due to resistance
- Physicians bear responsibility for:
  - Using antibiotics effectively to heal patients
  - Preserving antibiotic effectiveness through stewardship
  - Serving as experts in antimicrobial use and protection

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