Introduction and General Principles of Infectious Diseases

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Introduction

• Pharmacotherapy II (PHCL 430; PHCL 503)
  – Continuation of 416; 501 & 502
  – Integration:
    • 430 with Pharmaceutical Care 429
    • 503 with case presentation for lab
  – Emphasis is on application to patient care and drug therapy
  – Uses current medical literature (guidelines & studies)
Introduction 2

• Syllabus
  – Overview
  – Objectives
  – Course materials
    • Emphasis is on faculty’s lectures & handouts
    • Articles are usually source documents for recommendations and are for review / reference
    • Book chapters are to help learn material from lecture if you need more explanation.
Introduction 3

• Course documents
  – Available on the internet
    • http://sites.google.com/site/drtedmorton/
      – Syllabus
      – Links to faculty’s presentations etc.
      – Articles & references
• Studying
  – This class will be challenging!
    • Lots of material and requires both critical thinking skills and recall of facts
  – How to pass
    • Study, Study, Study
      – Read course materials before each lecture
      – Review your notes from class immediately
      – Use the objectives to focus your learning
      – Make tables of bugs vs drugs etc.
Introduction 5

• Examinations
  – Multiple choice & short answer
  – Average of 5 per lecture hour
  – Based on objectives / pharmacotherapy

• Attendance & Conduct = Professionalism
  – Welcome to the Profession of Pharmacy
  – Respect for yourself and others (patients, faculty)
Overview

• Objectives
• Review of key concepts from pre-required classes
  – Microbiology
  – Pharmacology
  – Pathophysiology & Immunology
Overview 2

• Diagnosis and treatment of infection
• Clinical use of antibiotics
  – Empiric
  – Definitive
  – Prophylaxis
• Pharmacists Role
  – Patient
  – Institution
Objectives

- Recall foundational principles of microbiology, pharmacology, pathophysiology, & immunology in the treatment of infectious diseases
- Recognize predisposing conditions leading to the development of infection and preventative measures
Objectives 2

• Describe physical findings, lab etc used in the diagnosis of infection and monitoring of response to therapy
• Name and differentiate the 3 primary uses of antibiotics
• Explain the use of patient data to optimize initial and subsequent antibiotic therapy
Background Reading & References


• 430 & 503:
  – Chapter 69
    • Antimicrobial Regimen Selection

• 503 Only:
  – Case # 109
  – Assigned readings
Microbiology

• Structure & function of organisms different than eukaryotes
  – Allows them to invade and cause harm
  – Serves as targets for safe and effective therapy
  – Rapidly mutate, change

• Pathogenesis
  – Exposure to virulent pathogen
  – Compromised innate or adaptive immune system
Microbiology 2

Bacteria

• Gram Positive Cocci
  – Staphylococcus aureus, S. epidermidis
  – Streptococcus viridans, pyogenes; Enterococcus

• Gram Positive Rods
  – Clostridium, Bacillus, Listeria
Microbiology 3

Bacteria

• Gram Negative Rods
  – Enterobacteriaceae (E. coli, Proteus, Klebsiella)
  – Pseudomonas; Haemophilus

• Gram Negative Cocci
  – Neisseria Meningtidis

• Anaerobes
  – Peptostreptococcus, Bacteroides
Microbiology 4

• Atypicals
  – Mycoplasma & Chlamydia

• Acid-Fast Bacilli
  – Mycobacterium tuberculosis

• Protozoa

• Viruses (Hepatitis, Influenza, HIV)

• Fungus (Candida, Aspergillus)
Microbiology 5

• What you need to know about the bugs:
  – General taxonomy & names
    • gram-positive vs negative, aerobic vs anaerobic
  – Disease states they cause
    • Lungs, skin, central nervous system etc.
  – What antibiotics work, drugs of choice
  – What are key resistance mechanisms and how common are they (percent susceptible)
Microbiology 6

• Identification
  – Culture, PCR etc
  – Quantitative thresholds for diagnosis

• Susceptibility testing
  – Minimum Inhibitory Concentration
    • Microtube vs Etest etc
  – Zone of inhibition
    • Kirby-Bauer
  – Interpretation (relative to drug concentrations)
    • Susceptible, Intermediate & Resistant
Susceptibility

• Concentration at the site of infection relative to MIC predicts clinical success but is difficult to measure directly!
  – Measure in vitro MIC or KB zone
    +/- bloodstream levels etc.

• Interpretation of MIC or KB zone result is Bug - Drug combination specific using standards
  – Cannot just pick the drug with the lowest MIC
1) Serially dilute antibiotic

2) Innoculate with fixed concentration of organisms

3) Incubate for fixed time frame

4) Interpret MIC = 1 mcg/mL
Susceptibility 2

• Susceptible (S)
  – Clinical success can be expected if treated with usual doses

• Intermediate (I)
  – Clinical success may be possible if
    • High doses of antibiotic are used
    • Antibiotic concentrates at the site of infection
    • Combination of synergistic agents are used

• Resistant (R)
  – Treatment failure is expected
Pharmacology

- To be effective, antibiotics must reach the site of infection at adequate concentrations to inhibit or kill the bacteria without harming the patient
Pharmacology 2

• Efficacy & Safety
  – Mechanism of action & resistance
  – Spectrum of activity
  – Pharmacokinetics & Pharmacodynamics
  – Adverse effects, Drug Interactions, Cost & Compliance
Mechanism of Action

- Cell wall synthesis
  - Cycloserine
  - Vancomycin
  - Bacitracin
  - Fosfomycin
  - Penicillins
  - Cephalosporins
  - Monobactams
  - Carbapenems

- DNA replication (DNA gyrase)
  - Nalidixic acid
  - Quinolones

- DNA-dependent RNA polymerase
  - Rifampin

- Protein synthesis (50S inhibitors)
  - Erythromycin
  - Chloramphenicol
  - Clindamycin

- Protein synthesis (30S inhibitors)
  - Tetracycline
  - Spectinomycin
  - Streptomycin
  - Gentamicin, tobramycin
  - Amikacin

- Folic acid metabolism
  - Trimethoprim
  - Sulfonamides

- PABA

- THF A
  - DHF A

- Ribosomes
  - mRNA
  - DNA

- Cell membrane
  - Polymyxins
Mechanism of Resistance

• Prevent from reaching target
  – Altered porin channel (pseudomonas)
  – Efflux pumps (tetracyclines)

• Inactivate antibiotic
  – Beta – lactamase (hundreds)
  – AME’s (aminoglycosides)

• Change Target
  – Absolute (PBP 2a in MRSA)
  – Relative (PBP’s in Streptococcus pneumoniae)
Pharmacodynamics

• Bacteriostatic
  – Inhibits growth at all concentrations above MIC
  – Requires intact immune system for killing
  – Avoid in life-threatening diseases states
  – Still may be a drug of choice if no other options
Pharmacodynamics 2

- **Bacteriocidal:**
  - Inhibits growth above MIC, Kills above MBC
    - Dose Dependent Killing (Peak to MIC)
      - Aminoglycosides and Quinolones
      - 10:1 ratio usually best
      - “once daily” aminoglycosides
    - Exposure Dependent Killing (Time Above MIC)
      - Beta-Lactams
      - Depends on organism and host immune status
      - Neutropenic: need 100% T > MIC
Pharmacokinetics (ADME)

• Absorption
  – Many antibiotics are IV only or PO only
  – Others have excellent oral bioavailability
    • safer / outpatient treatment

• Distribution
  – Many sights of infection are not easily reached by antibiotics
    • Central nervous system, lung, bone
Pharmacokinetics (ADME) 2

• Metabolism / Eliminations
  – Hepatic: drug interactions via CYP 450
    • Inhibitors: Macrolides, Azoles
    • Inducers: Rifampin
    • Both: Protease inhibitors
  – Renal: dose adjustment with dysfunction
    • Elderly, critically ill
Rational combination regimens

- Expand spectrum $\beta$-Lactam & macrolide in CAP
- Prevent resistance INH & Rifampin for TB
- Enhance Killing (Synergy)
  - $1 + 1 = 3$
    - $\beta$-Lactam + Aminoglycoside vs Gram Negative Rod
  - $1 + 0 = 2$
    - ($\beta$-Lactam + Aminoglycoside) vs S. aureus, S. viridans & Enterococcus sps
- Avoid Antagonism
  - Static with cidal
  - (Penicillin & Tetracyclines)
Pathophysiology & Immunology

• Host Defense / immune system
  – Innate (skin etc.) & Adaptive (cellular & humeral)
  – How it can be compromised
    • Surgery, immuno-suppression

• Manifestations of infection
  – Diagnosis and assessment of response
  – Local (pain, purulence, inflammation)
  – Systemic (fever, leukocytosis)
Changing Timeline of Infection after Organ Transplantation

Innate Immunity: The Acute Inflammatory Response
Summary from pre-requisites

• Serves as the foundation for this class
  – You should have learned (or are currently learning) this information
  – If you don’t remember or recall it, go back and review
  – Read the recommended book chapters as well if you are having trouble
Pharmacotherapy of Infectious Diseases
General Principles

• Why do we care?
  – Major cause of morbidity & mortality
  – Accounts for billions $ a year world wide
  – Inpatient & Outpatient prescriptions
    • 1/3 of hospital budgets
    • 14 of the top 100 hospital drugs
    • Major % of outpatient prescriptions
Why does it happen?

We share the world with potential pathogens

• Exposure to a virulent pathogen
  – Brucella, Malaria, HIV, Tb, STD’s, H1N1
  – Protect against with public health measures
    • Hand washing
    • Vaccination
    • Vector control
    • Avoiding contact
      – drinking unpasteurized milk
      – Isolation precautions / masks for respiratory
Why does it happen? 2

• Compromised immune function
  – Innate
    • Skin: surgery, cuts, catheters
    • Respiratory tract: smoking, intubation
  – Adaptive
    • Cellular:
      – Neutrophils (after chemotherapy)
      – Lymphocytes (HIV)
      – Both: immunosuppressive drugs (transplant)
    • Humeral: inherited etc.
What happens to the patient?

• The inflammatory response:
  – Localized
    • Redness, swelling, purulence, pain
  – Systemic
    • Fever (also hypothermia) & Chills
      – Single oral temp >38.3 C or 38.0 C over at least 1 hour
      – Rectal Temp - subtract 0.4 C (0.8 F)
      – Axillary - add 1 C (1.8 F)
    • ‪Heart Rate, Blood Pressure
    • Increased WBC (also decreased) & % Neutrophils
      – Normal 4.8 - 10 x 10^3 cells/mm^3
How is an infection diagnosed?

- **History & Physical Examination**
  - Signs & symptoms

- **Laboratory Studies**
  - WBC, serology

- **Imaging**
  - X-Rays

- **Culture collection**
  - from suspected site of infection (blood, urine...
How do we pick initial antibiotics?

• From the initial diagnosis – likely pathogens
  – Past epidemiologic studies of similar patients

• Picking initial empiric antibiotics
  – Active against likely pathogens
    • May require combination of drugs
  – Effective in clinical trials for empiric therapy
  – Optimal for the individual patient
    • Severity of illness
    • Available routes of administration
    • Allergies, drug interactions, cost, organ dysfunction.
How do we optimize therapy?

• Assess clinical response & lab, cultures
  – Converting to definitive therapy (next slide)
  – De-escalation or escalation
  – Dose, frequency, route & duration
  – Serum drug levels and MIC to optimize PK & PD
  – IV to PO conversion
  – Managing drug interactions, side effects
What is the best (definitive) therapy?

- Cultures & sensitivity confirm microbiologic diagnosis and susceptibility
  - Minimum significant colony count for urine, sputum to distinguish infection vs contamination
- Pick the “drug of choice”
  - Most effective, narrow spectrum, least toxic & least expensive regimen (may be a combination)
    - Based on guidelines, clinical trials etc.
    - Individualized to each patient
When are antibiotics justified to prevent infection?

• Prophylaxis for specific at-risk patients
  – Surgical:
    • Need depends on the risk of post-operative infections
    • Agent depends on likely pathogens (Staph & Strep)
    • Given just before incision & continued < 24 hours
  – Medical:
    • Specific defined risk due to immune deficit or exposure
      – Travel to malaria area
      – Low CD4 cell count (< 200) for PCP
      – Asplenia
Summary:
Use of antibiotics in infection

• Empiric
  – Treat likely / suspected pathogens

• Definitive
  – Treat known / confirmed susceptible pathogen

• Prophylaxis: prevent infection in at-risk patient
  – Surgical & Medical
Pharmacists Role

• Patient Care
  – Empiric treatment selection
  – Optimization of therapy
    • Agent selection & dosing regimen
  – Drug Interactions (prevent & manage)
  – Adverse Drug Events (prevent, detect & manage)
Pharmacists Role

• Organizational
  – P&T
    • Formulary management
      – Committee and Day to Day monitoring
    • Medication Use Evaluation
      – Appropriateness...
  – ADE/MSV (including drug interactions)
  – Infection Control
    • Tracking resistance outbreaks and trends
    • Prevention (surgical prophylaxis and vaccines)